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The Efficacy and Safety of Creatine Supplementation in the General Population

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THE EFFICACY AND SAFETY OF CREATINE SUPPLEMENTATION IN THE GENERAL
POPULATION

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ABSTRACT

The purpose of this study was to determine whether supplementation with creatine monohydrate is efficacious beyond the realm of its most popular use, which is in athletics. This study investigated the safety of creatine supplementation in the general population. References were collected through a review of PubMed and Scopus databases. Initial keywords searched were creatine supplementation and creatine safety. Where possible, trials with human subjects were utilized. Studies focused on creatine's effects in athletes or weightlifting parameters were eliminated. Topics were further narrowed down by conditions with the most amount of research and medical concerns recognized as common to primary care. Creatine supplementation showed potential benefits in treatment for major depressive disorder, diabetes, bone density, and osteoarthritis. Mild weight gain due to the osmotic effect of creatine was the only side effect noted in the evidence. Kidney function is not affected by creatine supplementation. Creatine supplementation has potential benefits for many different patient populations, with the only side effect of creatine supplementation being mild weight gain due to the osmotic effect of increased creatine saturation in the body. Clinicians should consider creatine supplementation without fear of potential serious adverse effects based on the available evidence.

INTRODUCTION

Creatine is a naturally occurring compound composed of three amino acids: glycine, arginine, and methionine. Approximately 95% of creatine is found within skeletal muscle, with the remainder being found in the brain and testes (in males). About two-thirds of creatine is stored as phosphocreatine, with the rest available as free creatine. The average person requires about 2g of creatine daily to maintain normal stores within the body. For most people (except those following vegan diets), about half of the daily creatine requirement is fulfilled by foods, with the other half being synthesized by the liver and kidneys (Kreider et al., 2017).

Creatine works through various and complex pathways. One mechanism of action involves the hydrolysis of phosphocreatine into creatine and a phosphoryl group, which can be used to resynthesize adenosine triphosphate (ATP). This is critical for energy production, particularly during maximal effort exercise such as sprinting or heavy weightlifting. Creatine also works within the mitochondria to facilitate energy metabolism (Kreider et al., 2017).

According to the International Society of Sports Nutrition, the most effective way to supplement creatine is to ingest 20g split between four doses for a period of five days (Kreider et al., 2017). This is the fastest way to fully saturate the body's creatine stores. From there, a daily dose of 3-5g will maintain stores in most adults. Some people may experience mild gastrointestinal distress with the 20g loading dose. An alternative dosing strategy would be to just start at the 3-5g daily maintenance dose. This dosing protocol may mitigate side effects, but will delay the full effects of supplementation because saturation may take up to 30 days to be reached rather than five to seven days with the loading protocol.

Creatine supplementation increases muscle phosphocreatine concentration, reduces muscle acidosis and oxidative metabolism, and increases lean body mass. For all these reasons, creatine has been extensively studied for its use as an ergogenic aid in athletes of all sports, particularly those involving short bursts of activity. These benefits are well known and discussed in the realm of athletics (Kreider et al., 2017).

Statement of the Problem

Creatine is used by athletes worldwide; however, creatine has also been studied for numerous other potential benefits in both general and disease-specific populations. These results are not nearly as well known, and creatine is not widely used outside of the athlete population. Clinicians may be missing opportunities to utilize creatine, which is a cheap, over-the-counter nutritional aid. Additionally, there is often concern voiced over the safety of creatine supplementation, often citing deleterious effects on hydration, kidney function, or overall health. These concerns may not be founded in actual scientific evidence.

Research Questions

1. Does creatine supplementation provide benefit in any patient populations besides athletes?
2. Is creatine supplementation safe?

Creatine has been studied as a potential treatment for many diseases with varying degrees of success. This study will focus on some of the areas where creatine shows potential for benefit to the largest population of patients. Diseases that are exceedingly rare or where creatine was altogether not beneficial will be spared in the interest of brevity.

REVIEW OF LITERATURE

Methodology

References were collected through a review of PubMed and Scopus databases. In PubMed, the following MeSH terms were used: “creatine monohydrate AND supplementation”, “creatine monohydrate AND safety”, “creatine AND depression”, “creatine AND diabetes”, “creatine AND glycemic control”, “creatine AND osteoarthritis”, “creatine AND kidney function”, “creatine AND adverse effects”, “creatine AND therapeutic uses”. Scopus was searched with “creatine monohydrate”, “creatine uses”, and “creatine safety”. Where possible, trials with human subjects were utilized. Studies that focused on creatine’s effects in athletes or weightlifting parameters were eliminated. Topics were further narrowed down by conditions with the most amount of research and medical concerns recognized as commonly seen in primary care.

Psychological Disorders

Major depressive disorder (MDD) is treated most commonly with selective serotonin reuptake inhibitor (SSRI) pharmacotherapy. One of the major drawbacks to this class of medication is the delayed onset of therapeutic relief of depression symptoms. According Lyoo et al. (2012), this may take several weeks. Of the studies utilizing creatine supplementation in patients with depression, the two most prevalent were earlier treatment response and increased brain phosphocreatine (PCr).

Lyoo et al. (2012) reported patients with MDD have been found to have lower brain levels of phosphocreatine. Additionally, patients who responded positively to depression treatment have shown subsequent normalization (increase) of their phosphocreatine levels.

Kondo et al. (2011) utilized magnetic resonance spectroscopy, the only in vivo method able to quantify brain levels of phosphocreatine, in order to measure the effects of creatine supplementation in female adolescents with MDD resistant to traditional SSRI therapy. Five adolescent females with SSRI-resistant MDD currently treated with fluoxetine were recruited. Utilizing the Children's Depression Rating Scale-Revised (CDRS-R), patients' raw scores were greater than or equal to 40, despite treatment. The patients had 31-phosphorus magnetic resonance spectroscopy performed at baseline and after eight weeks of supplementation with a daily dose of 4g creatine. For comparison, a group of six healthy females were imaged eight weeks apart. The creatine group saw a significant increase in PCr after 8 weeks (.151 vs. .161, $p=.02$), while the healthy controls saw no change. Additionally, average CDRS-R score went from 69 (SD 9.69) to 30.6 (SD 8.50) during that same time, a drop of 56%. Though a small sample size, this study demonstrated that increased PCr levels in depression can be correlated to a reduction in depressive symptoms.

Hellem et al. (2015) also utilized magnetic resonance spectroscopy to monitor PCr concentration. They studied 14 females with depression and comorbid methamphetamine addiction. After eight weeks of treatment with a 5g daily dose of creatine, brain PCr levels increased from 0.223 to 0.233 ($p= <.01$).

The Hamilton Depression Rating Scale (HAM-D) is a common tool used to rate the severity of depressive symptoms. Numerous studies have used this tool to evaluate the response of patients supplemented with creatine. Lyoo et al. (2012) and Hellem et al. (2015) were among the studies achieving positive results with adjunctive creatine supplementation, while Nemets and Levine (2013) did not have such definite success.

Lyoo et al. (2012) studied females diagnosed with MDD. It was a double-blind placebo-controlled clinical trial and participants were randomly assigned. The first group received escitalopram plus placebo and the second group received escitalopram plus 3g/day creatine for the first week and 5g/day thereafter. The primary outcome was measured via HAM-D. Secondary outcomes were the Montgomery-Asberg Depression Rating Scale (MADRS), and the Clinical Global Impressions Scale (CGI). Measures were taken initially and weekly thereafter. Treatment response was defined as a 50% reduction from baseline HAM-D score. Remission was defined as a HAM-D score of 7 or less.

Participants receiving creatine augmentation showed greater mean improvement on the HAM-D (-44.9% vs. -24.1%, $z = -4.89$) as early as week 2. Similar improvements by week 2 were seen on MADRS ($z = 4.87$, $p < 0.001$) and CGI ($z = -2.84$, $p = 0.005$). By conclusion of the study at week 8, participants receiving creatine reduced HAM-D score by 79.7% vs. 62.5% for placebo ($z = -3.84$, $p < 0.001$). Regarding treatment response, the creatine group showed a favorable and significant difference at week 2 (odds ratio=16.05, $p = 0.02$) week 4 (OR=16.54, $p = 0.001$), but not at week 8 (OR=5.01, $p = 0.17$). By week 8, remission was achieved by 13 (52%) of the creatine group but only 7 (25.9%) in the placebo group (OR=6.92, $p = 0.008$). There were no statistically different frequencies of adverse events in the two treatment groups, and no serious adverse events in either group. This study, according to Lyoo et al. (2012), suggests depression may improve to a greater extent in patients treated with escitalopram receiving creatine than those receiving placebo as early as two weeks after the initiation of treatment. The creatine group also demonstrated earlier treatment response and a higher remission rate without any difference in adverse effects.

Hellem et al. (2015), as previously mentioned, demonstrated increased PCr levels with creatine supplementation. Consequently, depression symptoms, measured with the HAM-D scale, decreased. This study used females with co-morbid methamphetamine addiction. Positive drug screens for methamphetamine decreased from 50% of participants at baseline to 21.4% by week 6, though no statistical significance to this decrease was detailed by researchers.

As helpful as creatine appears to be in MDD, it showed no benefit and was potentially even harmful in other mental health studies. Nemets and Levine (2013) utilized a pilot, dose finding, 4-week double-blind parallel augmentation study testing eighteen patients with MDD not responsive to three weeks of antidepressant treatment. The patients were placed into groups receiving placebo, 5g creatine, or 10g creatine daily in combination with their current antidepressant medication. After four weeks, there was no difference in HAM-D rating between the three groups. However, two female patients responded well (>50% reduction in HAM-D score after two weeks) to creatine augmentation. Overall, the authors concluded creatine augmentation showed no advantage compared to placebo, although certain subsets of patients may see a more rapid response.

Levental et al. (2015) studied creatine supplementation in patients with chronic schizophrenia. Treatment with creatine only mildly improved schizophrenia symptomology and did not improve cognitive functions. With a sample size of only seven participants, and no control group, this study did not give convincing evidence to support creatine in patients with schizophrenia. Toniolo, Fernandes, Silva, da Silva Dias, and Lafer (2016) studied effects of creatine as adjunctive therapy in bipolar depression. While creatine supplementation showed mild, but significant improvement in verbal fluency, it also activated hypomania in one patient and mania in another. Lastly, Roitman, Green, Osher, Karni, and Levine (2007) completed a

small pilot study of creatine supplementation in patients with unipolar or bipolar depression. While results were promising for unipolar depression, both participants with bipolar depression withdrew from the study after developing hypomania or mania. Based on these studies, the evidence shows creatine only has potential benefit in MDD, and should especially be avoided in bipolar depression.

Type 2 Diabetes Mellitus

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease characterized by an initial state of insulin resistance in the liver and muscle tissue which progresses to impaired insulin secretion and persistent hyperglycemia (Pinto, Botelho, Pimentel, Campos-Ferraz, & Mota, 2016). There are many pathophysiological mechanisms which can be involved in the development of this disease process. Two of them are the glucose transporter (GLUT) and adenosine monophosphate-activated protein kinase (AMPK). GLUT4 is an insulin-regulated glucose transporter, most commonly found in muscle and adipose. When glucose is ingested, the pancreas releases insulin, which binds to the insulin receptor of muscle cells. This sets off a cascade which moves GLUT4 transporters from within the intracellular space to the plasma membrane. Once incorporated in the plasma membrane, GLUT4 transporters allow glucose to move within the cell to be used for energy. In T2DM, insulin resistance and/or subsequent low circulating insulin means GLUT4 transporters are increasingly sequestered within the intracellular space, leading to hyperglycemia and the inability for cells to produce energy.

AMPK phosphorylates many target proteins, which in turn stimulate such processes as stimulation of hepatic fatty acid oxidation, muscle glucose uptake, and modulation of insulin secretion by pancreatic beta-cells. (Pinto et al. 2016). One way the AMPK signaling system is

stimulated is via exercise, so it stands to reason control of T2DM may be affected by the level AMPK stimulation.

Much of the research involving creatine and diabetes or glycemic control has been completed in different animal studies. A systematic review by Pinto et al (2016) noted the results were largely divergent, which proves species-specific responses do exist in creatine studies. Given this analysis, animal studies were not highly weighted or extrapolated to hypothesize human results.

There are however, two double-blind, randomized trials that examined the effects of creatine in patients diagnosed with T2DM. Gualano et al. (2011a) and Alves et al. (2012) both compared creatine supplementation against placebo, with participants in both studies also undergoing an exercise regimen of both cardiovascular and strength training.

Gualano et al. (2011a) treated patients with T2DM with either a 5g daily dose of creatine, while the control group was given dextrose. Treatment was blinded to both participants and researchers until completion of the study. Participants in both groups underwent an exercise program with three sessions per week. Sessions consisted of 25 minutes of strength training followed by 30 minutes of cardiovascular exercise. The primary outcome was glycemic control as assessed by hemoglobin A1c (HbA1c). Secondary outcomes included glucose, insulin, and C-peptide measured in intervals following a standardized meal tolerance test (MTT). The two groups had no significant difference in baseline HbA1c ($p=0.92$). After 12 weeks, only the creatine group showed a mean reduction HbA1c, and the difference between groups was statistically significant (-1.1% , 95% CI -1.9% to -0.4% , $p=.008$). There was a significant reduction in postprandial glycemia in the creatine group at 0 (-48 mg/dl, $p=0.001$), 30 (-48 mg/dl, $p=0.004$), and 60 min (-68 mg/dl, $p=0.003$) compared to the placebo group. Insulin and C-

peptide measurements showed no significant differences between groups. Muscle GLUT-4 membrane content was also measured, though not as a primary or secondary outcome. At baseline, there was no significant difference between the creatine and placebo groups. Both groups increased GLUT-4 content after intervention to the point there was no difference between each group and the control group ($p=0.92$). However, the creatine group increased GLUT-4 significantly more than the placebo group ($p=0.03$). Based on this data, Gualano et al. (2011a) concluded creatine supplementation, when paired with an exercise regimen, improved glycemic control in patients with T2DM. This improvement in glycemic control was attributed primarily to increased muscle GLUT-4 recruitment, resulting in improved cellular energy utilization.

Following the results of Gualano et al. (2011a), another study by Alves et al. (2012) sought to build on those results and further investigate the link of increased GLUT-4 and improved glycemic control in patients with T2DM supplemented with creatine. They followed a similar protocol, dividing groups of patients with T2DM into creatine 5g/day or placebo. This was paired with a twice-weekly exercise program. Subjects were followed for 12 weeks. A subset of 10 individuals (4 from placebo group, 6 from creatine group) were selected to have muscle biopsies performed at baseline and post-intervention. Researchers selected four “master-regulators” of insulin and muscle contraction to be measured. Insulin receptor (IR-B), AMPK alpha (AMPK- α), Akt/protein kinase B (AKT-1), and p42/44 mitogen-activated kinase (MAPK p42/44) were the regulators chosen.

Results of GLUT-4 were in line with the work of Gualano et al. (2011a), showing an increase post-intervention. Amongst the regulating proteins, expression of IR-B, AKT-1, and MAPK p42/44 were unchanged. AMPK- α , however, showed an increase positive correlated with GLUT-4 ($p<0.001$), and was higher in the creatine group vs. placebo, though not quite reaching

statistical significance ($p=.06$). AMPK- α was inversely correlated with HbA1c levels ($r= -0.68$, $p<0.001$). GLUT-4 was inversely correlated to HbA1c levels ($r= -0.89$, $p<0.001$).

The results from Alves et al. (2012) drilled further down on the work of Gualano et al. (2011a), attributing the increase in GLUT-4 and subsequent improvement in HbA1c to increased expression of AMPK- α . Additionally, results suggested this improvement was increased with creatine supplementation.

While the safety of creatine supplementation will be addressed a topic on its own, it is important to point out none of the studies involving creatine and diabetes or glycemic control noted any serious adverse events with creatine usage, and there were no significant differences in adverse effects between placebo and treatment groups. Gualano et al. (2011b) studied kidney function with creatine use in patients with T2DM. Since these patients are at higher risk for kidney complications, the authors felt it was important to study to potential side effects of creatine usage on kidney function. Using the same participant data from Gualano et al. (2011a) which studied glycemic control, estimated creatine clearance, serum and urinary urea, electrolytes, proteinuria, and albuminuria were measured. After 12 weeks of intervention, there were no significant differences in any of these parameters between groups. While it was a small sample size, it was an important finding, especially with the pre-disposition for those with T2DM to have kidney problems. This study suggested the safety of creatine supplementation in patients with T2DM but without chronic kidney disease.

Musculoskeletal Health and Disorders

Given creatine's well-established effects on muscle strength and function (Neves et al. 2011), it is worth investigating if creatine has additional musculoskeletal benefits. Candow and

Chilibeck (2010) explored creatine's potential benefits in regards to bone density in the elderly. Neves et al. (2011) studied use of creatine in knee osteoarthritis (OA). Lastly, Roy, de Beer, Harvey, and Tarnopolsky (2005) studied its use in recovery from total knee replacement.

Candow and Chilibeck (2010) noted, "aging is associated with a reduction in bone mass (i.e. 0.5% per year after the age of 40)." The authors also report physical activity is the only current proven strategy to increase bone mass and bone strength while reducing risks of falls in the elderly. The mechanism by which resistance training improves bone formation is mechanical strain applied to bone via muscle hypertrophy (Candow & Chilibeck, 2010). Despite these benefits, even those who continue resistance training with advancing age are prone to experiencing bone loss. Since creatine supplementation is associated with increased muscle mass, and muscle mass is a predictor of bone mass, it was hypothesized creatine may be associated with increased bone mass. The authors also pointed out creatine, when added to a culture medium, increased metabolic activity of osteoblast-like cells and production of osteoprotegerin, which inhibits osteoclast differentiation. If creatine behaved similarly within the human body, the results would be increased bone mass and density. One common marker of bone resorption used in studies is N-telopeptides, which are inversely related to bone density.

Candow and Chilibeck (2010) reviewed nine studies related to bone density and creatine supplementation. The studies varied in parameters such as subject age, creatine dosage, duration, exercise program (or not), and outcomes to measure bone density and/or mass. Of the nine studies compiled, five showed an improvement in either bone density or resorption, including four studies showing decreased N-telopeptides.

Conversely, four studies of those compiled did not show any improvement between groups in bone density or resorption, though it is worth noting that only one study measured N-

teloptides. Given these equivocal results, the authors determined they were unsure if creatine supplementation improved bone density or mass via increased production. They were, however, more positive on the potential for creatine to improve bone maintenance via decreased resorption. Further research was suggested to investigate creatine's benefits on bone in humans.

Another potentially useful effect for creatine is in OA. Neves et al. (2011) sought to investigate whether creatine's positive effects on muscle would lead to improvement in arthritis symptoms. The authors reported previous research had proven quadriceps weakness is associated with functional impairment in OA, and muscle strength may prevent further progression of existing OA. The authors also pointed to the evidence of strengthening exercises in knee OA and hypothesized any treatment enhancing exercise's muscle strengthening effect could be therapeutic for patients with knee OA. A 12 week, double-blind, randomized control trial with 26 participants diagnosed with knee OA was performed. Participants in the creatine group received a loading dose of 20g for the first 7 days, and 5g daily thereafter. The placebo group received equal doses of dextrose. A structured exercise program was performed three times per week by both groups. The primary outcome was a timed-stands test evaluating how many times the participant could stand-up from a chair in 30 seconds. Secondary outcome included a function, pain, and stiffness assessment validated by the Osteoarthritis Research Society, a 10 question quality of assessment, and muscle strength and body composition measurements. Only the creatine group improved on the primary outcome (creatine: pre= 15.7, post= 18.1, placebo: pre= 15.0, post 15.2, $p=0.04$). Both groups showed significant reductions in pain, but only the creatine group improved in stiffness and physical function ($p= 0.024$ and $p= 0.005$, respectively). The creatine group improved on quality of life assessment while the placebo group did not ($p= 0.01$).

No significant differences were noted in muscle strength ($p = .081$), however, the creatine group did show a significant increase in lower limb lean mass ($p = 0.04$). No adverse effects or differences in kidney function were discovered in either group ($p = 0.72$). This study demonstrated creatine's potential benefits in physical function and quality of life parameters in patients with OA.

With creatine showing promise in reducing bone resorption in the elderly as well as function in those with OA, another avenue to explore was its role in patients undergoing knee surgery, particularly total knee arthroplasty (TKA). Roy, Beer, Harvey, and Tarnopolsky (2005) selected 37 adults undergoing TKA and supplemented them with either 10g creatine/day pre-surgery and 5g/day for 30 days post-surgery or placebo. Primary outcomes measured were body composition via DEXA scan and quadriceps, ankle, and handgrip strength. Results no statistical difference between groups for any of the primary outcomes. Creatine does not appear to be useful for patients undergoing TKA.

Safety of creatine supplementation

For years, creatine has been best known for its use in athletes. However, creatine has acquired a dubious reputation thanks in part to what Kim, Kim, Carpentier, and Poortmans (2011) say are “doubtful allegations of adverse effects of creatine supplementation...released through the press media and through scientific publications.” While anecdotal reports exist detailing muscle cramps, gastrointestinal complaints, liver or kidney damage with creatine supplementation, little research exists proving harmful effects. As previously mentioned, Gualano et al. (2011b) found no effects on kidney function in patients with T2DM who supplemented with creatine. Genc et al. (2014) also studied effects of creatine and kidney function, though in rats. The researchers in this study induced kidney damage in two groups with

cisplatin, a nephrotoxic substance. One group was given cisplatin only, the other group was given cisplatin and 300 mg/kg of creatine for 30 days after the cisplatin injection. A third group of healthy rats was used as control. BUN and creatinine levels, histopathology evaluation, and body weights were outcomes measured. The cisplatin only group showed decreased weight, impaired BUN and creatinine levels, and histopathological changes. The cisplatin and creatine group, when compared to the cisplatin only group, had less weight loss and better BUN, creatinine, and histopathology scores ($p < .05$). Despite this, both groups fared worse than the healthy control group. This study demonstrated creatine was not just neutral, but rather nephroprotective against the toxic effect of cisplatin.

Kim et al. (2011) reviewed research tied to many anecdotal complaints of creatine's adverse effects. The authors found five total studies looking at muscle cramping with creatine use. None of the studies found muscle cramping was caused by creatine supplementation. The authors suggested the intensity of the exercise being performed may be the culprit rather than creatine. As for gastrointestinal (GI) complaints, two small studies reported some side effects of GI distress. The first study had subjects consuming 40g of creatine per day, a higher than normal dosing load, in addition to 400mg of caffeine. The other study had athletes consuming 6-8mg creatine per day for up to 3-5 months, which is again a slightly higher dosing strategy than other studies. Three other studies reported no GI side effects, even with doses as high as 20g per day. The authors concluded there was insufficient evidence to support the notion of creatine causing GI problems. Liver dysfunction was studied next, looking at alkaline phosphatase, aspartate transaminase, alanine transaminase, and gamma glutamyl transpeptidase markers in numerous studies. Dosing protocols ranged from 20g daily for 5 days up to 10g daily for 5 years. No evidence of detrimental effects of liver function were discovered. Lastly, complaints of kidney

impairment were investigated. After thorough review, the authors concluded kidney function was not affected by creatine supplementation using short-term doses up to 20g daily or by long-term doses of 10g/day or less thereafter. (Kim et al., 2011)

The International Society of Sports Nutrition (ISSN) offered a position stand on the safety and efficacy of creatine supplementation authored by Kreider et al. (2017). The position stand offers many possible therapeutic roles of creatine supplementation, but for purposes of this literature review, the focus will be on the ISSN's position on the safety of creatine. The ISSN reports the only consistent side effect reported in over 1,000 studies reviewed in weight gain. This weight gain is explained by creatine's osmotic effect. As creatine's concentration within the body increases, the body maintains more water, usually in the range of 0.5-1.0 liters (Kreider et al. 2017). Beyond this side effect, the ISSN reports studies as involving at least 30g per day for up to 5 years have been conducted without any additional side effects reported. Beyond that, the authors not only refute the claims that creatine may cause dehydration, muscle injuries, renal injury, or liver dysfunction, but point out that creatine may reduce the incidence of many of these side effects. Going back to the osmotic effect of creatine, Kreider et al. (2017) note creatine has shown potential benefit in enhancing tolerance to heat as well as preventing muscle injury or cramping.

Lastly, the ISSN's position stand also acknowledges many manufacturer's age recommendations (18 and older) are not founded in evidence, but rather in liability management. They state there is no scientific evidence showing harm of creatine supplementation in infants, children or adolescents. Furthermore, there are some rare conditions involving inborn errors of creatine metabolism in which creatine supplementation is vital for survival. Kreider et al. even go as far to point out creatine supplementation may have some benefits in pregnancy, especially

when there is hypoxic insult to the fetus. While it is admitted that further research must be done, the authors believe creatine supplementation may be beneficial for fetal growth and development.

DISCUSSION

Creatine supplementation increased phosphocreatine saturation in the brain, reduced time to efficacy when used as an SSRI adjuvant, and ameliorated symptoms of depression in numerous studies. Creatine supplementation showed improved glycemic control as measured by HbA1c and glucose area under the curve when combined with exercise in patients with T2DM. Creatine supplementation showed improved muscle function and decreased pain in patients with knee OA. There is also evidence that shows creatine may reduce the rate of bone resorption in the elderly. Creatine does not offer functional benefits in recovery from total knee arthroplasty. Creatine is safe for use in all tested dosage ranges and for use up to several years. At typical doses, it is safe for use in virtually all patient populations.

Does creatine supplementation provide benefit in any patient populations besides athletes?

Psychological Disorders.

Creatine's presence in the brain, as phosphocreatine, has been established via studies using magnetic resonance spectroscopy. Creatine supplementation has shown to increase brain phosphocreatine concentrations, and increased phosphocreatine concentrations have been associated with amelioration of depression symptoms (Kondo et al., 2011). In patients with MDD who have achieved treatment success, a normalization (increase) of phosphocreatine levels has occurred (Lyo et al., 2012). The studies conducted to this point regarding creatine supplementation and MDD have either been small sample sizes or even pilot studies. In order for

creatine to gain a foothold amongst other plausible depression treatments, larger studies are needed. In addition, almost all studies were 12 weeks or less in duration. A longer-term study would be beneficial in determining if the positive effects of creatine supplementation continue with further treatment.

While creatine's effects for MDD (a unipolar depression) are positive in nature, its effects on bipolar depression are quite the opposite. MDD is defined by a patient's persistent feelings on one end of the emotional spectrum, and an increase of cerebral phosphocreatine brings the patient back towards a euthymic state. What was seen in bipolar depression, however, was that creatine supplementation does stabilize mood regardless where it falls on the spectrum. Instead, it may be a mood activating substance (Roitman et al. 2007), which is not conducive for bipolar patients who are prone to manic or hypomanic states. This is an important distinction for clinicians to make.

Creatine was not shown to be beneficial for primary outcomes in patients with negative symptom schizophrenia (Levental et al., 2015). There were small improvements in some secondary outcomes, but conclusions were limited by small sample size of the study. No adverse or negative effects were seen in treatment of schizophrenia with creatine.

In patients with comorbid methamphetamine addiction and depression, creatine supplementation showed improved depression symptoms as well as reduced methamphetamine use (Hellem et al., 2015). Other studies have proven benefits of creatine supplementation in treatment of depression (Lyoo et al., 2012) without co-morbidities, so the next logical step would be to trial creatine supplementation in methamphetamine users without comorbid depression. It is plausible methamphetamine use affects phosphocreatine stores in the brain, but the magnitude of this effect is still uncertain.

Type 2 Diabetes Mellitus.

Perhaps the most promising and consistent benefit of creatine supplementation is that of improved glycemic control when paired with exercise. Gualano et al. (2011a) and Alves et al. (2012) came to the same conclusion that creatine supplementation and a structured exercise program significantly improved glycemic control as measured by HbA1c. Furthermore, Gualano et al. (2011) identified increased muscle GLUT-4 membrane content as the mechanism by which this improved glycemic control was achieved. Alves et al. (2012) built on this research by identifying APMK-a as the signaling protein responsible for bringing GLUT-4 receptors from the intracellular space into the membrane.

Gualano et al. (2011b) showed creatine did not impair kidney function in patients with T2DM. This is an important distinction due to the end-organ damage T2DM can cause, including on the kidneys. Given that diabetes is a chronic, usually lifelong disease, another means by which to improve glycemic control that comes without serious cost or side effects, it is important for further research to be conducted to maximize the potential of creatine as a treatment for T2DM.

Musculoskeletal Disorders.

The majority of evidence supporting benefits of creatine supplementation is related to increased athletic performance, lean muscle mass, and recovery from short, intense exercise (Kreider et al., 2017). It is also established that creatine supplementation has a synergistic effect when combined with exercise. Therefore, the results seen with patients with knee OA can be explained by creatine supplementation synergistically working with an exercise program to increase lower limb lean mass, muscle strength, and physical function (Neves et al., 2011).

Further research would be needed to confirm this effect in OA of other joints. Neves et al. (2011) also commented muscle weakness and/or atrophy is often a precursor to OA. Reduced support from the surrounding musculature results in increased stress on the joint itself, which leads to deterioration and eventually OA. The authors went to speculate creatine supplementation, paired with a structure exercise program, could be used in a prophylactic manner to either prevent OA or stop the progression of symptoms.

Besides OA, creatine also showed potential as a treatment to decrease bone resorption in the elderly. This effect was most commonly seen when paired with exercise (Candow & Chilibeck, 2010), with increased lean mass leading to increased mechanical tension and subsequent decrease in excretion of osteoclastic biomarkers. OA and decreased bone density are two very common problems in the elderly population, making this research important for geriatric patients.

In regards to musculoskeletal health, one area creatine did not show benefit was in knee strength or recovery when used in the peri-surgery window for total knee arthroplasty (Roy et al., 2005). The authors speculated patients need to exceed a minimum threshold of activity to increase uptake of creatine into the muscle.

Is creatine supplementation safe?

The evidence regarding creatine supplementation consistently shows it is safe for use in almost any population, at any dose, for any duration. Certainly there are limitations, but doses far above what was used in the themes discussed in this study have been studied without serious or long-term adverse effects. Duration of studies go at least 5 years in length (Kreider et al., 2017), again without adverse effects noted. The only potential side effect consistently noted was weight

gain, which was directly attributed to increases in lean mass, whether it be water retention from the osmotic effect of creatine or increased muscle mass. Kim et al. (2011) found no conclusive evidence of liver or kidney dysfunction, even in studies lasting up to 5 years. Muscle cramping and gastrointestinal distress were also determined to be unfounded anecdotal evidence or inconclusive at very least. Lastly, Kreider et al. (2017) stated age requirements on creatine packaging are manufacturers recommendations only and not based on any clinical evidence. Creatine, to this point, has been found to be safe in adolescents, infants, and even pregnancy. Furthermore, there are possible further benefits in specific disease states in these populations which would be worthy of additional study.

APPLICABILITY TO CLINICAL PRACTICE

Depression, diabetes, osteoarthritis, and reduced bone density are very common problems seen in primary care. Virtually all primary care providers seeing and treating many patients affected by these chronic conditions. It is reasonable to think many of these patients would possibly benefit from creatine supplementation. There are multiple areas of resistance that might be met when trying to implement what has been learned in this project into practice. First and foremost, creatine is an over-the-counter supplement, which poses problems of product quality and purity. Patients can be given advice about reputable brands with reputation of good manufacturing practices, but ultimately supplements are not subject to FDA standards prescription drugs are manufactured under. Secondly, patients may not be familiar with or know anyone who takes creatine, or worse yet, may have a very negative feeling based on the aforementioned case studies or anecdotes questioning its safety. Try as one might to educate, it may be futile if the patient is not open to believing the evidence with which they are presented.

Those challenges being noted, the evidence to date overwhelmingly shows creatine is a safe supplement for essentially anyone to use. It has been studied in many dosage ranges and for many years of long-term use. After completing this study, practitioners should feel comfortable prescribing creatine to almost any patient without hesitation in regards to its safety.

Beyond its safety, creatine shows good potential for benefit in many circumstances. Having a tool to potentially shorten the all-too-problematic waiting period between initiation of SSRIs and the actual onset of relief is very enticing. Furthermore, there is a stigma associated with antidepressants that turns many patients off from using them. A naturally occurring substance may be more amenable to their treatment plan. It is imperative, however, for the clinician to have a proper diagnosis prior to initiating treatment with creatine, especially when differentiating between a unipolar or bipolar depression. As beneficial as creatine may be in MDD, it can be mania-inducing in bipolar depression.

In many patients, especially the elderly, the potential benefits of decreased bone resorption and improvement of OA symptoms has the potential to really impact quality of life. Bone and joint problems are becoming increasingly prevalent as obesity continues to increase in the United States.

Patients with diabetes might be interested to try a nonpharmacological option that shows promise of being almost as potent as some pharmacological agents, but without the side effect profile or associated cost. Furthermore, the synergistic effect between creatine and exercise is yet another reason to encourage positive lifestyle habits in T2DM.

Further research is likely needed before creatine becomes a staple of treatment plans. However, the potential benefits and lack of adverse effects make creatine worth trying,

especially if other traditional therapies fail and the clinician is struggling with treating one of the previously listed conditions.

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