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The Potential Role of Creatine Supplementation in Glycemic Control and Insulin Resistance: A Literature Review

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ABSTRACT

Introduction and purpose

Type 2 diabetes mellitus (T2DM) is a severe metabolic disorder characterized by insulin resistance and persistent hyperglycemia, leading to serious cardiometabolic complications. Recent studies suggest that creatine supplementation may influence glucose metabolism and insulin sensitivity. This review aims to summarize the current knowledge on the effects of creatine on glucose regulation and its potential therapeutic implications for metabolic disorders.

Description of the state of knowledge

Creatine is a non-protein amino acid primarily stored in muscle cells as phosphocreatine, which is essential for ATP resynthesis. Beyond its role in energy metabolism, creatine exhibits pleiotropic effects, including modulation of glycogen stores, oxidative stress, inflammatory responses, and insulin signaling. Studies indicate that creatine supplementation can enhance glucose uptake by increasing GLUT-4 translocation and activating AMPK, mimicking the

mechanisms induced by exercise. Moreover, some findings suggest that creatine may improve glycemic control, particularly when combined with physical activity. However, while animal studies demonstrate a reduction in hyperglycemia, clinical studies report inconsistent results regarding insulin secretion and overall metabolic effects.

Conclusions

Creatine supplementation appears promising as an adjunct therapy for improving insulin sensitivity and glucose homeostasis, particularly in combination with exercise. However, the exact mechanisms and long-term metabolic outcomes remain to be fully elucidated. Further randomized controlled trials are needed to determine its clinical applicability in T2DM and other metabolic disorders.

KEY WORDS

creatine; type 2 diabetes; insulin resistance; glucose metabolism

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is one of the most prevalent chronic diseases in the modern world [1]. It is a metabolic disorder that causes chronic hyperglycemia due to insulin resistance and impaired insulin secretion by pancreatic β-cells. Prolonged hyperglycemia increases the risk of cardiometabolic complications, including hypertension, atherosclerosis, dyslipidemia, and abdominal obesity [2].

Insulin resistance is a condition in which tissue sensitivity to insulin decreases, playing a key role in the pathogenesis of metabolic syndrome, non-alcoholic fatty liver disease (NAFLD), atherosclerosis, and T2DM [3]. Before T2DM develops, insulin resistance raises blood glucose levels. In response, the body increases insulin secretion, leading to chronic hyperinsulinemia. Persistent hyperglycemia eventually causes β-cell dysfunction, accelerating the progression of diabetes [4].

Creatine is a non-proteinogenic amino acid synthesized in the body from arginine, glycine, and methionine [5, 6]. Approximately 66% of its cellular stores exist in the form of phosphocreatine (PCr), which plays a crucial role in ATP resynthesis [6, 7]. Creatine naturally breaks down into creatinine, requiring continuous replenishment through endogenous synthesis—mainly in the liver and kidneys—and through dietary sources, including red meat, seafood, and supplements. [8, 9]. Beyond its role in energy metabolism, creatine exhibits pleiotropic effects, such as

influencing glycogen storage, protein metabolism, insulin-like growth factor-1 (IGF-1), calcium homeostasis, oxidative stress, inflammatory responses, and myogenic factors [7].

Creatine supplementation is widely used to enhance physical performance, particularly in sports requiring short bursts of high-intensity effort [10, 11]. However, there is growing interest in its potential therapeutic benefits for various conditions, including neurodegenerative diseases, muscle disorders, and metabolic disturbances such as insulin resistance and T2DM [12]. Preliminary studies suggest that creatine may play a role in glucose metabolism regulation by improving insulin sensitivity and increasing muscle glycogen accumulation, especially when combined with carbohydrate intake [13, 14]. This mechanism may be attributed to the involvement of insulin-dependent transporters in creatine and glucose uptake by muscle cells. Although in vitro studies indicate that creatine may stimulate insulin secretion [15, 16], clinical trials have not yet provided conclusive evidence supporting this effect [17, 18]. Furthermore, creatine supplementation has been shown to reduce hyperglycemia in animal models [19] and improve glycemic control in sedentary individuals and patients with T2DM, particularly when combined with physical activity [20, 21]. These findings suggest that creatine may serve as an adjunct therapy for diabetes management. The aim of this review is to summarize the current knowledge on the effects of creatine supplementation on glycemic regulation and to identify areas requiring further research.

DESCRIPTION OF THE STATE OF KNOWLEDGE

EPIDEMIOLOGY

Diabetes remains one of the greatest global health challenges, ranking among the leading causes of morbidity, disability, and mortality. In 2019, it was the eighth leading cause of death and disability worldwide [22, 23]. The global healthcare expenditures related to diabetes in individuals aged 20–79 years were estimated at $966 billion USD in 2021, with projections indicating an increase to over $1,054 billion USD by 2045 [24]. In 2021, the global number of people with diabetes reached 529 million, with an age-standardized prevalence of 6.1%, representing a 90.5% increase compared to 1990. Projections indicate that by 2045, this prevalence will rise to 9.8%, affecting approximately 1.31 billion people. Type 2 diabetes mellitus (T2DM) accounts for over 96% of all diabetes cases and is a multifactorial disorder, with excess body weight being the primary risk factor [22]. The prevalence of diabetes also varies by sex—in 2021, the age-standardized prevalence was higher in men than in women,

with a male-to-female ratio of 1.14 [25, 22]. The risk of developing diabetes increases with age, peaking at 24.4% in the 75–79 age group, whereas it remains below 1% in individuals under 20 years old [22]. In addition to metabolic and demographic factors, environmental and lifestyle factors such as physical inactivity, high-calorie diets, alcohol consumption, and smoking also contribute to T2DM development. The genetic component of T2DM susceptibility is estimated to range from 30% to 70%, depending on age at onset and the severity of glycemic disturbances [22, 26]. To date, over 100 genes have been identified as being associated with T2DM susceptibility, including TCF7L2, GCK, KCNJ11, and PPARG [26]. Diabetes-related complications include both macrovascular and microvascular diseases, such as chronic kidney disease (CKD), retinopathy, neuropathy, and diabetic foot ulcers (DFU), all of which pose significant health burdens [27]. CKD is recognized as a major contributor to increased mortality and disability-adjusted life years (DALYs) in diabetic patients, with a prevalence estimated at 20–40% and rising [28]. It is projected that diabetic neuropathy (DN) and DFU will develop in 50% and 34% of individuals with diabetes, respectively [29, 30]. Approximately 20% of patients with DFU require lower limb amputation, and the five-year mortality rate in this group exceeds 70% [29]. Diabetic retinopathy (DR) affects 22% of individuals with diabetes, with 6% developing vision-threatening forms that can lead to permanent vision loss or blindness [31]. Insulin resistance, a key factor in the pathogenesis of T2DM, is frequently assessed in the context of metabolic syndrome. Analysis of NHANES data from 2003 indicated that insulin resistance affected approximately 22% of American adults over the age of 20. By 2021, this prevalence had risen to 40% among individuals aged 18–44 years, based on the HOMA-IR index. While the rise in insulin resistance is partially correlated with increasing obesity rates, other factors, including hypertension, dyslipidemia, and physical inactivity, also contribute to its progression. This condition is observed across all ethnic groups; however, available data on demographic differences remain limited [32, 33].

MECHANISMS OF CREATINE'S IMPACT ON GLUCOSE METABOLISM

GLUT-4 Translocation and Glucose Uptake

Creatine supplementation may enhance GLUT-4 translocation to the cell membrane, resulting in increased glucose uptake in a manner similar to that induced by physical exercise [34, 21, 35]. Glucose transporter type 4 (GLUT-4) is a key protein responsible for glucose uptake in muscle cells [36]. Increased levels of GLUT-4 on the cell membrane may contribute to

improved insulin sensitivity and glucose tolerance [34]. Animal studies have shown that creatine promotes the expression of the SLC2A4 gene, which encodes GLUT-4, and increases the content of this protein in muscles [37]. Similar effects have been observed in humans when creatine supplementation was combined with a training program following a period of limb immobilization [34], although not all studies confirm these findings [38, 39]. Notably, in patients with T2DM, creatine-induced improvements in glycemic control were primarily associated with increased GLUT-4 translocation to the sarcolemma, whereas no changes were observed in the total GLUT-4 content in muscles [21]. The increase in GLUT-4 translocation was also correlated with elevated expression of AMP-activated protein kinase (AMPK-α), a protein that facilitates GLUT-4 translocation [35]. Similar results were noted in healthy young men, where short-term creatine supplementation increased the levels of protein kinase Bα (PKBα/Akt1), a key player in insulin-stimulated GLUT-4 translocation and glycogen synthesis [39].

Interaction with Physical Activity

Physical activity is a strong stimulus for glucose uptake in muscles by enhancing (1) glucose delivery from the blood to muscles, (2) glucose transport across the muscle cell membrane, and (3) intracellular glucose phosphorylation and insulin sensitivity [40]. Importantly, patients with T2DM retain the ability to translocate GLUT-4 to the sarcolemma in response to physical exercise [41], making it an effective means for increasing glucose uptake. Exercise-induced GLUT-4 translocation appears to occur through the AMPK pathway via an insulin-independent mechanism [42]. This means that, regardless of circulating insulin levels and their peripheral effects (which are supported by muscle contractions through improved insulin signaling), exercise can directly stimulate GLUT-4 translocation to the sarcolemma, resulting in better glycemic control [43].

Preliminary studies suggest that creatine supplementation may amplify the beneficial effects of exercise on glucose metabolism. The role of creatine, both as a standalone intervention and in combination with physical activity, in regulating carbohydrate metabolism is further discussed in the following subsections.

Osmoregulatory Properties of Creatine

Creatine can increase water retention in muscle tissue, thereby altering cellular osmolarity [39]. An increase in intracellular osmolarity causes cell swelling. Numerous studies have demonstrated that cell swelling serves as a strong stimulus for glycogen synthesis in both muscles [44] and the liver [45]. Consequently, creatine, by inducing cellular swelling, may enhance muscle glycogen stores [39]. Additionally, increased intracellular osmolarity has been associated with elevated circulating insulin-like growth factor 1 (IGF-1) levels, which exhibit insulin-like effects and suppress the activity of counter-regulatory hormones involved in glycogen catabolism [46].

Impact on Insulin Secretion

Under physiological conditions, pancreatic β-cells secrete insulin in response to various energy substrates, including glucose, fatty acids, and amino acids, as well as hormonal and metabolic signals. Insulin regulates blood glucose levels by activating the phosphoinositide 3-kinase (PI3K) pathway, which facilitates the translocation of the GLUT-4 transporter to the cell membrane, thereby increasing glucose uptake by skeletal muscles [47, 48]. Additionally, insulin initiates the mitogen-activated protein kinase (MAPK) pathway, which plays a crucial role in cell proliferation and nuclear processes [49]. As previously mentioned, insulin resistance is a precursor to type 2 diabetes (T2DM) and, in combination with genetic and environmental factors, can lead to β-cell dysfunction, ultimately resulting in a progressive decline in insulin secretion [50, 51]. This mechanism is typically associated with PI3K signaling pathway impairments, increased serine phosphorylation of insulin receptor substrates (IRS), and inhibition of tyrosine phosphorylation [52]. In some cases, IRS protein degradation has also been observed [53]. Moreover, in T2DM, insulin resistance may be linked to abnormal GLUT-4 translocation, independent of its reduced skeletal muscle levels [21]. Recent studies indicate disruptions in creatine metabolism in individuals with T2DM. A prospective cohort study found that elevated plasma creatine levels correlated with an increased risk of developing the disease, possibly due to mitochondrial dysfunction and impaired energy homeostasis [54, 55]. It remains unclear whether creatine merely serves as a biomarker of this process or actively contributes to its development. Potential mechanisms through which creatine supplementation may influence glucose metabolism include: (a) stimulation of insulin secretion, (b) effects on osmoregulation,

and (c) enhancement of GLUT-4 expression and translocation. There is also evidence suggesting that creatine and physical activity act synergistically to improve glycemic regulation [56].

In vitro and ex vivo studies have demonstrated that high creatine concentrations can moderately stimulate insulin secretion in isolated rat pancreas and mouse pancreatic islets [57, 58]. In animal models, creatine supplementation led to increased insulin levels in the blood and an improvement in the insulinogenic index [59, 60]. However, clinical studies have not confirmed this effect in humans, either in healthy individuals or in patients with T2DM, regardless of whether creatine was taken alone or in combination with physical activity [20, 21, 38].

Mitochondrial Function and Reduction of Oxidative Stress

Research suggests that creatine may exhibit antioxidant properties, thereby protecting mitochondria from oxidative stress. Preliminary evidence indicates that creatine supplementation may mitigate mitochondrial damage induced by toxins in animal and cellular models, including studies involving rats exposed to nitropropionic acid and Drosophila melanogaster exposed to rotenone [61, 62]. The exact mechanism behind this effect is not fully understood, but creatine may enhance the activity of antioxidant enzymes and facilitate the elimination of reactive oxygen and nitrogen species (ROS, RONS) [61, 63, 64]. Given that skeletal muscles store approximately 90% of total creatine, and mitochondria are the primary source of ROS, its protective effects may have significant metabolic implications [65].

Creatine plays a crucial role in protecting mitochondrial DNA (mtDNA) and RNA from oxidative stress, which helps maintain cellular integrity, particularly under conditions of increased oxidative burden [66]. This mechanism includes mitochondrial stabilization and the regulation of mitochondriogenesis, potentially preventing mtDNA mutations associated with neurodegenerative and cardiovascular diseases [67, 68]. The antioxidant activity of creatine reduces the negative consequences of mitochondrial mutations, such as decreased ATP production and reduced mitochondrial membrane potential [66, 69, 70]. Beyond mitochondrial protection, creatine may stabilize RNA, which is essential for muscle homeostasis and protein synthesis. RNA damage leads to impaired regeneration and protein synthesis, negatively affecting muscle mass [70]. Studies have shown that creatine supports ATP regeneration and reduces RNA damage induced by xenobiotics such as doxorubicin [71]. Additionally, it may modulate the expression of factors regulating muscle development, such as IGF-1 mRNA and myogenic regulatory factors (MRFs), thereby promoting anabolic processes [72, 73]. Research

also suggests that creatine influences neuronal function, including the regulation of GABA receptors and exocytosis mechanisms [74, 75, 76]. Moreover, it increases the expression of antioxidant enzymes, such as peroxiredoxins, which enhance antioxidant defenses [70, 77]. It is also possible that creatine's antioxidant properties are related to the presence of arginine, which affects nitric oxide (NO) synthesis—a key factor in metabolic regulation and glucose uptake by muscles [78]. Additionally, other amino acids, such as glycine and methionine, may participate in antioxidant processes, further strengthening creatine's protective effects [79].

CREATINE SUPPLEMENTATION AND METABOLIC DISORDERS – LITERATURE REVIEW

The Effect of Creatine Supplementation Alone on Glycemic Control

Creatine supplementation increases intramuscular creatine stores by 10–30%, which supports improvements in lean body mass, muscle strength, and endurance, particularly among older adults [10, 39, 80, 81, 82, 83]. Additionally, creatine may modulate the expression of genes involved in glycogen metabolism and cellular signaling, potentially inducing metabolic adaptations that occur independently of physical activity [39].

Animal model studies have shown that creatine supplementation may enhance GLUT-4 expression and AMPK phosphorylation, contributing to increased glycogen storage [37]. Furthermore, some evidence suggests that creatine accumulation in the pancreas may stimulate insulin secretion [59]. However, research findings remain inconclusive—some studies have reported no significant changes in glucose metabolism or insulin sensitivity [34, 84].

In animal models of insulin resistance, creatine supplementation has shown varied metabolic effects, highlighting both potential benefits and risks. While it may offer therapeutic advantages, it can also worsen hyperglycemia and hyperinsulinemia, emphasizing the significant variability in physiological responses to this compound [19, 60, 85]. In human glucose tolerance tests, creatine supplementation raised blood glucose levels but also increased muscle glycogen content [38, 86]. However, other studies found no significant changes in glucose metabolism or insulin response [18].

There is also evidence that creatine may enhance glycogen synthesis without significantly altering GLUT-4 expression, while also preventing its decline under conditions of muscle immobilization. Preliminary clinical studies suggest that creatine may be effective in glycemic regulation, potentially matching metformin in short-term blood sugar reduction [87].

Nonetheless, the inconsistency of findings underscores the need for further research on creatine's role in metabolic disorders [38, 39].

The Effect of Creatine Supplementation Combined with Physical Exercise on Glycemic Control

Regular physical activity is a key component of diabetes therapy, contributing to improved insulin sensitivity and increased glucose uptake by muscles [36, 88]. Creatine supplementation may further support these processes, although study results remain inconsistent [21, 56].

Animal studies have shown that creatine may lower glucose levels and improve glucose tolerance in exercised rats, while other analyses did not confirm these effects. Variations in findings may be attributed to different supplementation protocols and exercise types [89, 90].

In human studies, Op't Eijnde et al. demonstrated that creatine supplementation prevented a decline in GLUT-4 transporter expression in muscles during immobilization, and promoted its increased expression during rehabilitation, but only in combination with training [34]. Similar effects were observed in the study by Derave et al. [90].

In the context of long-term supplementation, Gualano et al. found that combining creatine with aerobic training resulted in a greater reduction in glucose levels in response to an oral glucose tolerance test compared to individuals who did not receive creatine supplementation [20]. In a subsequent study on patients with type 2 diabetes, the same intervention led to a significant reduction in glycated hemoglobin (HbA1c) levels and improved GLUT-4 translocation to the sarcolemma, suggesting a mechanism responsible for better glycemic control [21, 35]. Notably, creatine did not significantly affect insulin levels or the HOMA-IR index [18, 38]. From a clinical perspective, creatine appears to be safe, with no significant adverse effects reported [21, 35]. However, not all studies confirm its efficacy in improving glucose metabolism. In a pilot study involving older adults, creatine supplementation combined with resistance training did not provide benefits in terms of insulin resistance [91].

In summary, available data suggest that creatine supplementation may aid in glucose regulation, particularly when combined with physical exercise. However, study results remain inconsistent. Further research is needed to determine optimal supplementation protocols and identify patient groups that may benefit the most.

CONCLUSIONS

Available scientific evidence suggests that creatine supplementation may positively influence glucose metabolism, potentially improving insulin sensitivity through mechanisms primarily involving GLUT-4 translocation and AMPK activation. While preclinical data and some clinical studies indicate a beneficial effect on glycemic control, overall findings remain inconclusive. Creatine supplementation, particularly in combination with physical exercise, may serve as a supportive strategy in managing insulin resistance and type 2 diabetes mellitus (T2DM).

Further research is needed to clarify the long-term metabolic effects of creatine supplementation, especially in individuals with T2DM. Well-designed, randomized controlled trials should assess optimal dosing strategies and the interaction between creatine and physical exercise in glycemic regulation. Understanding these mechanisms could facilitate the integration of creatine into therapeutic strategies for metabolic disorders.

DISCLOSURE

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