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Creatine Supplementation as an Adjunct to Exercise in Type 2 Diabetes: Effects on Muscle Metabolism and Glycemic Control – A Literature-Based Review

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ABSTRACT

Introduction and aim of the study. This study aimed to evaluate the role of creatine supplementation, particularly in combination with physical activity, in the management of type 2 diabetes mellitus, with emphasis on muscle metabolism and glycemic control.

Research materials and methods: A literature-based review was conducted using major scientific databases, including PubMed, Scopus, and Web of Science. The analysis included randomized controlled trials, systematic reviews, and mechanistic studies investigating creatine supplementation and its metabolic effects in diabetic and non-diabetic populations.

Basic results: Creatine plays a central role in cellular energy metabolism through the phosphocreatine system. Evidence suggests that supplementation may enhance glucose uptake via increased GLUT-4 translocation, improve insulin sensitivity, and support skeletal muscle function. When combined with exercise, creatine may exert synergistic effects on glycemic control. However, available clinical evidence remains limited and heterogeneous.

Conclusions: Creatine supplementation may be a promising adjunct strategy in the management of type 2 diabetes, particularly when combined with regular physical activity. Further high-quality clinical trials are required to establish clear clinical recommendations.

Keywords: creatine; type 2 diabetes; glucose metabolism; skeletal muscle; exercise; supplementation

1. Introduction

Type 2 Diabetes Mellitus (T2DM) is a chronic, progressive metabolic disorder characterized by insulin resistance, impaired insulin secretion, and persistent hyperglycemia. It represents one of the leading global health threats — with estimates ranging from 529 to 828 million affected people worldwide — and is associated with cardiovascular disease, neuropathy, nephropathy, and retinopathy, all of which lead to increased morbidity and mortality.(1-3)

A key feature of T2DM is impaired glucose uptake in skeletal muscle, which accounts for approximately 80% of insulin-mediated glucose disposal under normal physiological conditions.(4, 5) Insulin resistance leads to decreased translocation of glucose transporter type 4 (GLUT-4) to the cell membrane, resulting in reduced glucose uptake and elevated blood glucose levels. (6, 7) The molecular basis of this impairment involves multiple defects in the insulin signaling cascade, including reduced insulin receptor substrate-1 (IRS-1) tyrosine phosphorylation, impaired phosphatidylinositol 3-kinase

(PI3K) activation, and defective GLUT-4 translocation. (6, 8, 9) Consequently, interventions targeting skeletal muscle metabolism are critical for improving glycemic control.

Physical activity has an important role in T2DM management, enhancing insulin sensitivity and promoting glucose uptake through both insulin-dependent and insulin-independent mechanisms. (1, 10) Exercise stimulates AMP-activated protein kinase (AMPK) signaling, leading to increased GLUT-4 translocation that remains fully functional even in the presence of severe insulin resistance.(7, 11) AMPK phosphorylates downstream targets, including TBC1D1 and TBC1D4 (AS160), facilitating GLUT-4 vesicle trafficking through pathways at least partially distinct from insulin signaling. (11-13) Chronic exercise training additionally induces favorable adaptations, including increased GLUT-4 expression, enhanced mitochondrial biogenesis via PGC-1α activation, and improved oxidative enzyme capacity. (10, 14)

Creatine is a naturally existing compound involved in cellular energy homeostasis, primarily stored in skeletal muscle as phosphocreatine, where it is essential in rapid adenosine triphosphate (ATP) regeneration through the creatine kinase reaction. (15, 16) While traditionally associated with improvements in strength and power performance, emerging evidence suggests that creatine may also affect glucose metabolism and insulin sensitivity by modulating GLUT-4 expression, activating AMPK, and altering glycogen storage capacity. (17-19)

Although these promising mechanisms, the clinical evidence supporting creatine supplementation in T2DM remains limited and inconsistent. This literature-based review aims to evaluate the role of creatine supplementation, particularly in combination with physical activity, in patients with type 2 diabetes, with emphasis on muscle metabolism, glucose regulation, and potential synergistic mechanisms.

2. Research Materials and Methods

2.1 Search Strategy

A comprehensive literature search was performed across PubMed, MEDLINE, Scopus, Web of Science, Google Scholar, and The Cochrane Library. The search employed combinations of keywords and MeSH terms including: "creatine," "creatine supplementation," "creatine monohydrate," "type 2 diabetes," "glucose metabolism," "glycemic control," "insulin sensitivity," "GLUT-4," "skeletal muscle," "exercise," "physical activity," "resistance training," and "aerobic training."

The screening process involved stepwise evaluation of titles, abstracts, and full-text articles. Reference lists of all included studies were manually screened using the snowballing method to minimize the risk of omitting relevant publications.

2.2 Inclusion Criteria

Studies were included if they met the following criteria:

- Articles published in English

- Studies involving human participants or relevant animal models investigating creatine supplementation in the context of glucose metabolism, insulin sensitivity, or skeletal muscle function

- Original research articles, including randomized controlled trials (RCTs), cohort studies, and cross-sectional studies, as well as systematic reviews and meta-analyses

- Studies investigating the relationship between creatine supplementation, with or without physical activity, and metabolic outcomes relevant to type 2 diabetes (e.g., glycemic control, GLUT-4 expression, AMPK signaling, glycogen storage, insulin sensitivity, or muscle energetics)

- Publications published between 1998 and 2026, ensuring inclusion of both foundational and recent scientific evidence

2.3 Exclusion Criteria

Studies were excluded if they met any of the following criteria:

- Studies examining creatine supplementation exclusively in the context of athletic performance without any assessment of metabolic or glycemic outcomes

- Studies focused on other metabolic disorders (e.g., type 1 diabetes, metabolic syndrome) without specific relevance to type 2 diabetes or glucose homeostasis mechanisms

- Case reports, editorials, letters to the editor, conference abstracts without full-text availability, or opinion pieces without original data

- Studies lacking sufficient methodological detail to assess quality and validity (e.g., absence of control groups, unclear intervention protocols, or unreported outcome measures)

- Studies conducted exclusively in pediatric populations (age<18 years), given the distinct pathophysiology of metabolic disease in this group

- Duplicate publications or secondary analyses of previously included datasets that did not provide additional applicable information

- Studies published in languages other than English for which verified translations were not available

2.4 Data Extraction and Synthesis

Data were extracted using a standardized approach. For clinical trials: study design, sample size, participant characteristics, intervention details, exercise protocol, outcomes, and adverse events were recorded. For mechanistic studies: molecular targets (GLUT-4, AMPK, glycogen content), signaling pathways, and proposed mechanisms were extracted.

Given the heterogeneity of study designs, a narrative synthesis approach was used rather than quantitative meta-analysis. Evidence was synthesized thematically into the following categories: creatine metabolism and energy homeostasis; skeletal muscle glucose uptake mechanisms; effects of creatine on glycemic control; creatine-exercise synergy and clinical evidence; and safety concerns.

3. Creatine, Energy Metabolism, and Skeletal Muscle Glucose Uptake in Type 2 Diabetes

3.1 The Phosphocreatine System and Muscle Energetics

The creatine kinase-phosphocreatine (CK-PCr) system is one of the most important energy-buffering mechanisms in skeletal muscle, functioning via the reversible reaction: PCr + ADP + H^+ ↔ Cr + ATP. (16, 20) During periods of high ATP utilization, phosphocreatine donates its high-energy phosphate group to ADP, rapidly regenerating ATP at approximately 10-fold the rate of oxidative phosphorylation. (20, 21) The spatial organization of creatine kinase isoforms — mitochondrial CK near ATP production sites and cytosolic CK near myofibrillar ATPases — creates an energy shuttle that enables efficient energy transfer throughout the cell. (16, 22)

Oral creatine monohydrate supplementation increases skeletal muscle total creatine content by approximately **20-30%**. (23, 24) Standard protocols involve either a loading phase (20 g/day for 5-7 days) followed by maintenance (3-5 g/day), or chronic low-dose supplementation (3-5 g/day for 4-6 weeks). (23, 25, 26) The enhanced energy buffering capacity improves performance during high-intensity activities and might facilitate greater training volumes, leading to superior adaptations in muscle mass and metabolic capacity. (23)

3.2 AMPK as a Convergence Point Between Energy Sensing and Glucose Uptake

The CK-PCr system interfaces directly with AMP-activated protein kinase (AMPK), a heterotrimeric kinase activated by increases in the AMP: ATP ratio via upstream kinases LKB1 and CaMKKβ. (27, 28) Early studies reported that phosphocreatine acts as an allosteric inhibitor of AMPK, with its consumption during contraction contributing to AMPK activation.(29) However, subsequent work using

purified AMPK preparations found this inhibition was greatly reduced, suggesting phosphocreatine may modulate AMPK indirectly rather than through direct allosteric inhibition. (30)

Paradoxically, creatine supplementation can increase AMPK phosphorylation even without changes in ATP or phosphocreatine concentrations. In rat skeletal muscle, creatine feeding increased AMPK phosphorylation by **50%** with unchanged high-energy phosphate levels. (18) In cultured L6 muscle cells, creatine increased phosphorylation of both α1 and α2 AMPK isoforms by approximately **2-fold**. (31) However, one human study found no effect of creatine on AMPK expression or phosphorylation, suggesting these effects may be context-dependent. (32) In contrast, in patients with type 2 diabetes receiving creatine (5 g/day for 12 weeks), changes in AMPK-α protein content correlated significantly with changes in GLUT-4 translocation ($r=0.78$, $p<0.001$) and HbA1c ($r=-0.68$, $p<0.001$), suggesting that AMPK signaling may be more relevant in the insulin-resistant state.(33)

AMPK activation is a key regulator of glucose uptake in skeletal muscle, particularly in maintaining enhanced glucose permeability in the period after contraction and mediating exercise-induced insulin sensitization — pathways that remain functional even in severe insulin resistance. (11, 12, 28) This convergence — where creatine influences the same AMPK pathway that exercise uses to bypass insulin resistance — provides the mechanistic explanation for investigating creatine-exercise combinations in T2DM.

3.3 Insulin Resistance, GLUT-4 Defects, and the Therapeutic Opportunity

Skeletal muscle insulin resistance is a primary defect in the pathogenesis of T2DM. Accumulation of intramyocellular lipid metabolites (diacylglycerols, ceramides) activates serine/threonine kinase cascades that impair IRS-1/PI3K/Akt signaling, causing diminished GLUT-4 translocation. (34, 35) Reduced mitochondrial oxidative capacity may predispose to this lipid accumulation. (36)

In T2DM, both GLUT-4 protein expression and insulin-stimulated translocation are impaired. (18, 37) GLUT-4 gene expression is regulated by myocyte enhancer factor 2 (MEF2) transcription factors; in diabetic states, MEF2A is selectively downregulated, directly resulting in decrease of GLUT-4 transcription. (37, 38) Exercise counteracts these defects by increasing MEF2-dependent GLUT-4 transcription. (39) Creatine feeding in rats increased nuclear MEF2A, MEF2C, and MEF2D protein levels by **60-90%** and MEF2 DNA binding activity by **~40%**, concomitant with increased GLUT-4 expression. (18) This evidence positions creatine as a potential modulator of the transcriptional machinery governing GLUT-4 expression, as detailed in the following section.

4. Effects of Creatine Supplementation on Glycemic Control

4.1 GLUT-4 Translocation and Expression

Multiple lines of evidence demonstrate that creatine supplementation influences GLUT-4 expression and function in skeletal muscle through separate mechanisms at both the transcriptional and post-translational levels.

In animal studies, the intake of creatine boosts GLUT-4 protein expression in skeletal muscle by 40-100%, which corresponds with similar increases in GLUT-4 mRNA levels. Investigations into the mechanisms revealed that creatine consumption enhances the nuclear presence and DNA-binding activity of MEF2 transcription factors that control GLUT-4 gene expression. Specifically, supplementation with creatine raised the levels of MEF2A, MEF2C, and MEF2D proteins in nuclear extracts by 60-90%, along with a roughly 40% increase in MEF2 DNA-binding activity. These alterations were linked to improved insulin-stimulated glucose transport rates and an increase in muscle glycogen content, establishing a clear mechanistic link from creatine consumption to enhanced glucose disposal capacity. (18)

In human studies, creatine supplementation combined with resistance training increases GLUT-4 protein content in muscle by 24-33% compared with placebo. Critically, these effects appear to require concurrent changes in muscle activity level. In a controlled study examining the effects of creatine during muscle immobilization and subsequent rehabilitation training, creatine supplementation prevented the decline in GLUT-4 that occurred during immobilization and enhanced GLUT-4 recovery during retraining, but did not affect GLUT-4 expression in contralateral control legs with stable activity patterns. This activity-dependence is an important finding, suggesting that creatine functions primarily as an amplifier of exercise-induced adaptations rather than as an independent stimulus for metabolic remodeling. (40, 41)

In patients with type 2 diabetes specifically, creatine supplementation (5 g/day for 12 weeks) combined with exercise training significantly increases GLUT-4 translocation to the sarcolemma—the functional step required for glucose uptake. This enhanced translocation occurs alongside improvements in glycemic control, and the correlation between GLUT-4 translocation and HbA1c reduction provides direct mechanistic support for creatine's glucose-lowering effects in this population. (33, 42)

4.2 AMPK Signaling Pathway

AMPK activation represents a second key mechanism linking creatine supplementation to improved glucose metabolism. In cultured L6 rat skeletal muscle cells, creatine supplementation increases phosphorylation of both α1 and α2 AMPK isoforms by approximately 2-fold, indicating high enzyme

activation. Notably, this activation occurs even in the absence of changes in ATP, AMP, or phosphocreatine concentrations. It suggests that creatine influences AMPK through mechanisms beyond simple energy stress—possibly through creatinine accumulation, changes in creatine kinase activity, or effects on upstream AMPK kinases such as LKB1 or CaMKKβ (31).

The clinical relevance of this pathway is supported by data from patients with type 2 diabetes. Changes in AMPK-α protein content following creatine supplementation correlate closely with changes in GLUT-4 translocation ($r=0.78$, $p<0.001$) and HbA1c levels ($r=-0.68$, $p<0.001$). These robust correlations suggest that AMPK signaling acts as a critical mediating pathway between creatine supplementation and improved glycemic outcomes, and that the magnitude of the AMPK response may predict the degree of clinical benefit (33).

4.3 Glucose Oxidation, Glycogen Storage, and Metabolic Flexibility

Beyond its effects on glucose uptake, creatine supplementation influences intracellular glucose fate in ways directly relevant to T2DM pathophysiology. In cultured muscle cells, creatine supplementation increases basal glucose oxidation by approximately 40% and reduces basal lactate production by 42%, consistent with a shift from anaerobic glycolysis toward oxidative glucose metabolism. This metabolic shift is accompanied by increased citrate synthase activity, a marker of mitochondrial oxidative capacity, suggesting that creatine may enhance mitochondrial function and improve metabolic flexibility—the ability to switch between fuel sources based on availability, which is characteristically impaired in T2DM. (31)

Creatine supplementation also enhances muscle glycogen storage capacity. In human studies combining creatine with resistance training, muscle glycogen content was significantly higher compared to placebo. This is clinically relevant because impaired muscle glycogen synthesis represents one of the earliest and most prominent defects in T2DM insulin resistance, contributing to postprandial hyperglycemia. The mechanism may involve increased glucose uptake, providing greater substrate availability; enhanced glycogen synthase activity; or improved insulin sensitivity of the glycogen synthesis pathway. (41, 43)

4.4 Effects on Insulin Secretion

While most research has focused on creatine's effects on peripheral glucose uptake, some evidence suggests effects on pancreatic function. In rodent studies, prolonged creatine supplementation (2% of diet for 4-8 weeks) increased pancreatic creatine content and was associated with 2- to 3-fold elevated insulin secretion in response to glucose challenge. However, these changes were accompanied by impaired glucose tolerance at 8 weeks, suggesting compensatory hyperinsulinemia rather than a beneficial effect.(44) In vitro studies in pancreatic β-cells confirmed that creatine potentiates glucose-stimulated insulin secretion, acting as a potentiator rather than an initiator of secretion.(45)

Importantly, these rodent findings have not been replicated in human studies. Clinical trials in type 2 diabetes patients show no significant changes in fasting insulin, C-peptide, or insulin sensitivity indices following creatine supplementation, indicating that creatine's glucose-lowering effects in humans are mediated primarily through enhanced peripheral glucose disposal rather than altered insulin secretion. (42)

5. Creatine-Exercise Synergy and Clinical Evidence

5.1 Complementary Mechanisms and Activity-Dependence

Exercise and creatine exert complementary effects through different yet aligning mechanisms: exercise activates AMPK via energy stress, enhances mitochondrial biogenesis, and upregulates GLUT-4 expression, while creatine augments energy buffering capacity, activates AMPK through alternative mechanisms, and amplifies training-induced metabolic adaptations. The activity-dependence of creatine's effects on GLUT-4—occurring only in exercised muscle, with no effect in non-exercised contralateral limbs—strongly suggests that the combination is essential for metabolic benefit. (40, 41)

The ergogenic effects of creatine may further enhance this synergy by facilitating greater training volumes and intensities. By improving the capacity for rapid ATP regeneration during high-intensity contraction, creatine supplementation enables more repetitions, heavier loads, and higher training intensities, potentially amplifying the metabolic stimulus for chronic adaptations, including increased muscle mass, enhanced oxidative capacity, and improved insulin sensitivity. (23) Recent evidence further supports this synergy: mitochondrial creatine kinase 2 (CKMT2) expression is reduced in T2DM skeletal muscle and is upregulated by exercise training, with CKMT2 overexpression improving mitochondrial respiration independently of creatine availability.(46)

5.2 Clinical Trial Evidence in Type 2 Diabetes

The clinical evidence base remains limited but promising. A systematic review identified only three randomized controlled trials totaling 87 participants with T2DM, with low certainty of evidence per GRADE criteria. (47)

The most methodologically rigorous trial randomized 25 T2DM patients to creatine (5 g/day) or placebo for 12 weeks, with both groups participating in supervised exercise training three times per week. The creatine group demonstrated significant reductions in HbA1c from 7.4±0.7% to 6.4±0.4%, whereas the placebo group showed no change (7.5±0.6% to 7.6±0.7%), resulting in a between-group difference of **-1.1%** (95% CI -1.9% to -0.4%, p=0.004). (33, 42) This magnitude of reduction is clinically meaningful, as each 1% decrease in HbA1c is associated with approximately 20% reduction in diabetes-related microvascular complications. (48) The creatine group also demonstrated significantly lower glucose area under the curve during meal tolerance testing (delta AUC: -7790±4600 vs. +2008±7614, p=0.05)

and reduced glycemia at 0, 30, and 60 minutes. Insulin and C-peptide concentrations were comparable between groups, confirming that improved glycemic control was mediated by enhanced peripheral glucose disposal. Muscle biopsies confirmed increased GLUT-4 translocation and correlated AMPK-α changes. (33, 42)

In healthy sedentary males undergoing aerobic training, creatine supplementation (~10 g/day for 12 weeks) significantly decreased glucose AUC during oral glucose tolerance testing compared to placebo ($p=0.034$). (49) Similarly, combined creatine and protein supplementation with resistance training decreased glucose AUC from 232±23 to 170±23 $mmol \cdot L^{-1} \cdot min^{-1}$, whereas placebo with training showed no significant change. (41)

In limited comparisons with metformin and glibenclamide, no significant differences in glucose-lowering efficacy were observed, though small sample sizes preclude definitive conclusions. No trials have examined creatine as an adjunct to standard pharmacotherapy, representing an important evidence gap. Notably, creatine supplementation without concurrent exercise training has not demonstrated glycemic benefits in healthy populations, with one study reporting no effect on glucose tolerance or insulin sensitivity, and another reporting worsened glucose homeostasis in sedentary vegetarians.(50, 51)

5.3 Limitations of Current Evidence

Key limitations constrain the interpretation and generalizability of existing findings. Sample sizes have been small (the largest trial, n=25), limiting statistical power and precluding meaningful subgroup analyses. Trial durations have been short (typically 12 weeks), insufficient to assess long-term efficacy, durability of effects, or impact on diabetes complications. Existing trials enrolled relatively select populations—younger patients (mean age 50-60 years) with moderate glycemic control (HbA1c 7-8%) on oral hypoglycemic agents—and the efficacy in older patients, those with poorer glycemic control, or sedentary individuals remains uncertain. Given creatine's activity-dependent effects, benefits in physically inactive patients may be substantially attenuated. No trials have examined patient-centered outcomes such as cardiovascular events, diabetes complications, quality of life, or mortality. (17, 47)

6. Safety, Limitations, and Conclusions

6.1 Kidney Function

In T2DM patients specifically, a 12-week RCT found no adverse effects of creatine (5 g/day) on GFR measured by ^{51}Cr-EDTA clearance (creatine: 90.4±16.9 to 96.1±15.0 mL/min/1.73m²; placebo: 97.9±21.6 to 96.4±26.8; $p=0.58$), with unchanged creatinine clearance, urea, electrolytes, proteinuria, and albuminuria.(52) Meta-analyses across diverse populations confirm that creatine produces a small

increase in serum creatinine (MD 0.07-0.13 mg/dL) reflecting increased creatine-to-creatinine conversion rather than impaired kidney function, with no significant changes in GFR. Caution is advised in individuals with pre-existing renal disease; pre-supplementation kidney function assessment may be prudent in high-risk populations. (53-55)

6.2 Other Adverse Effects

Systematic reviews report no major adverse effects in T2DM populations.(47) In healthy populations, long-term supplementation (up to 30 g/day for 5 years) has been reported as safe and well-tolerated. (23) Minor side effects (gastrointestinal discomfort, nausea, muscle cramping) are uncommon at maintenance doses of 3-5 g/day and are more frequently associated with high-dose loading protocols.(23, 56) Weight gain due to water retention during the loading phase is generally modest (1-2 kg) and stabilizes during maintenance.(23) Long-term safety data in diabetic populations remain limited, representing an important knowledge gap. (17, 47)

6.3 Conclusions

Creatine supplementation, particularly when combined with regular physical activity, may be a promising adjunctive strategy for the management of type 2 diabetes mellitus. The available evidence supports several converging mechanisms: enhanced GLUT-4 translocation via MEF2 transcription factor activation(18), AMPK-mediated glucose uptake(31, 33), increased glucose oxidation(31), and augmented muscle glycogen storage capacity(41). The synergistic interaction between creatine and exercise appears to be a critical determinant of metabolic benefit, as creatine's effects on GLUT-4 expression and glucose metabolism are largely activity-dependent(40, 41). Clinical trial evidence, though limited, demonstrates clinically meaningful HbA1c reductions of -1.1% when creatine is combined with structured exercise training(42). Safety data are reassuring, with no evidence of adverse renal effects at standard doses. (52-54)

However, the current evidence base consists of a small number of trials with limited sample sizes, short intervention durations, and select patient populations. No studies have examined long-term outcomes, patient-centered endpoints, or the interaction between creatine and standard pharmacotherapy. Future research should prioritize large-scale, multicenter RCTs with longer follow-up periods, diverse patient populations, and clinically relevant endpoints. Studies examining creatine as an adjunct to both exercise and pharmacological therapy, dose-response relationships, and identification of patient subgroups most likely to benefit are particularly warranted. Until such evidence becomes available, creatine supplementation cannot be formally recommended as a standard component of T2DM management, but it represents a biologically plausible and safe intervention deserving of further clinical investigation.(17, 47)

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