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Therapeutic effects of creatine supplementation in patients with type II diabetes

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Abstract

Background: Type 2 diabetes mellitus (T2DM) prevalence is disturbingly increasing all over the world. Clinicians and patients need new ways of improving T2DM therapy.

Aim of this study: The aim of this study is to present the current scientific literature on the potential hypoglycemic effects of creatine in patients with type 2 diabetes.

Material and methods: A systematic review of the scientific and medical literature from the PubMed and Google Scholar databases was carried out. This was achieved according to the keywords: type 2 diabetes and creatine supplementation. 25 items of literature were qualified for analysis.

Results and conclusions:

Creatine supplementation, when combined with physical activity, improves glycemic control in type 2 diabetic patients. Increased glucose transfer into muscle cells by type 4 glucose transporter (GLUT-4) translocation to the sarcolemma is one of the potential mechanisms explaining these hypoglycemic effects. Creatine has a big potential to become a nutritional therapy adjuvant for type 2 diabetes. However, in order to draw firm conclusions about the efficacy and safety of creatine as a diabetic intervention, larger, longer-term, controlled trials involving type 2 diabetes with variable disease severity and different pharmacological treatments are required.

Keywords: type 2 diabetes, creatine supplementation

Introduction

Type 2 diabetes mellitus (T2DM) is a metabolic chronic disease. Its popularity is increasing year by year all over the world [1]. The estimated prevalence of diabetes worldwide in 2019 is 9.3% (463 million people), and it is expected to increase to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045 [2].

Type 2 diabetes can be effectively managed with lifestyle modifications, such as dietary interventions and physical activity, and pharmacologic interventions based on guidelines from worldwide diabetes societies [3], [4].

A possible nutritional therapy adjuvant is creatine, especially when it is combined with exercise due to its hypoglycemic effects and potentially alleviating insulin resistance condition. The therapeutic role of creatine in diabetes is becoming more and more popular [5],[6],[7].

Creatine is a natural amine, that is both synthesized by the kidneys, pancreas and liver and ingested from food [8]. It has become one of the most consumed and thoroughly described ergogenic agents [9]. Many years of research have shown that it has a fair number of benefits among athletes to increase muscle strength, endurance [10], [11], [12], [13] and improve muscle recovery [14].

Aim of this study

The aim of this study is to present the current scientific literature on the potential hypoglycemic effects of creatine in patients with type 2 diabetes.

Material and methods

A systematic review of the scientific and medical literature regarding the metabolism, safety and potential benefits of creatine use in people with type 2 diabetes was carried out. This was achieved by searching in PubMed and Google Scholar for keywords such as: type 2 diabetes and creatine supplementation.

Results

A study on the effect of creatine supplementation on people with diabetes [15] showed that the administration of creatine for 12 weeks had a significant beneficial effect on this group. 25 people with previously diagnosed type 2 diabetes, physically inactive for at least a year, were analyzed and divided into a group receiving creatine (CR) or a placebo (PL). Both groups of patients followed a program of moderate-intensity aerobic training combined with strengthening exercises for 12 weeks. During the study period, measurements of glycosylated hemoglobin (Hb A1c), area under the curve of glucose, insulin and C-peptide as well as insulin sensitivity indices were made. Physical performance, lipid profile, and GLUT-4 protein expression and translocation were also assessed. Hb A1c was significantly lowered in the creatine group compared to the placebo group Fig.1 (CR: PRE = 7.4 ± 0.7, POST = 6.4 ± 0.4; PL: PRE = 7.5 ± 0.6 POST = 7.6 ± 0.7, P = 0.004, difference = −1.1%, 95% confidence interval = −1.9% to −0.4%). The delta area under the glucose curve was significantly lower in the CR group than in the PL group Tab.2 (CR = −7790 ± 4600, PL = 2008 ± 7614; P = 0.05). The CR group also showed reduced glycemia at 0, 30 and 60 min during the meal tolerance test and increased GLUT-4 translocation. Insulin and C-peptide concentrations, surrogates insulin sensitivity, exercise capacity, lipid profile, and side effects were comparable between the groups. The CR group experienced no serious adverse effects. Several patients reported experiencing cramps, nausea, and diarrhea. However, there was no significant difference in these occurrences between the groups.

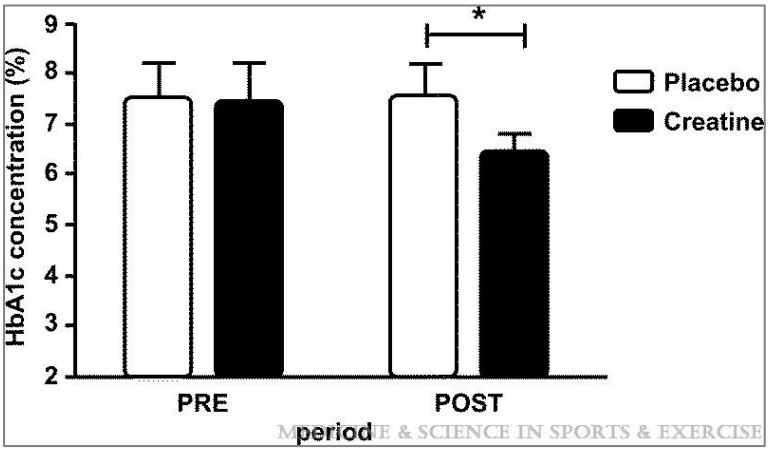

Fig. 1. Effects of creatine supplementation combined with exercise training in type 2 diabetic patients on HbA1c concentrations. *Interaction effect (P = 0.004; estimated difference of means = −1.1%, 95% CI= −1.9% to −0.4%). Data are means ± SD. Mixed model for repeated measures was used to compare placebo (n = 12) versus creatine (n = 13) [15].

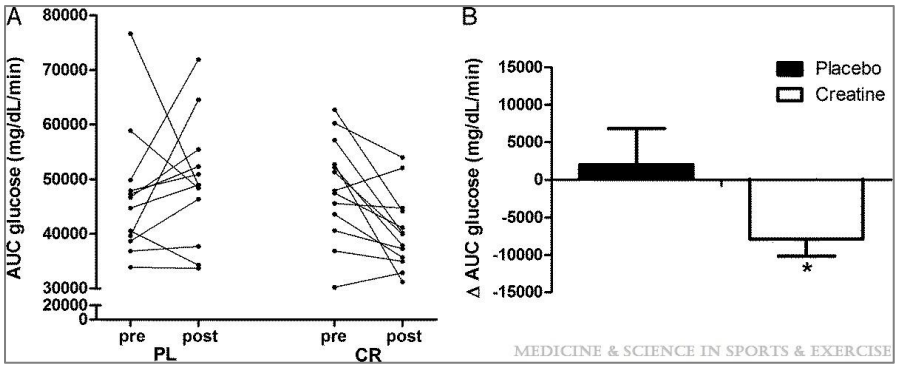

Fig. 2. Effects of creatine supplementation combined with exercise training in type 2 diabetic patients on the area under the curve of glucose concentration. A, Individual data for AUC. B, Means ± SD for the delta area under the curve of glucose concentration. *Significant treatment effect compared with placebo (P = 0.05). Student's t-test was used to compare placebo (n = 12) versus creatine (n = 13) [15].

Research has shown that creatine supplementation in type 2 diabetes causes improvement in glycemic control (as assessed by the glycated hemoglobin - Hb1Ac) and possible mechanisms of that results involve: (1) increased beta-cell insulin secretion; (2) creatine-induced changes in osmoregulation (3) increased glucose uptake via type 4 glucose transporter (GLUT-4) content and activity. Additionally, (4) creatine supplementation could enhance the known benefits of exercise on glucose uptake/insulin sensitivity. However, there is currently insufficient clinical data to support all of these mechanisms [16] (Fig.3).

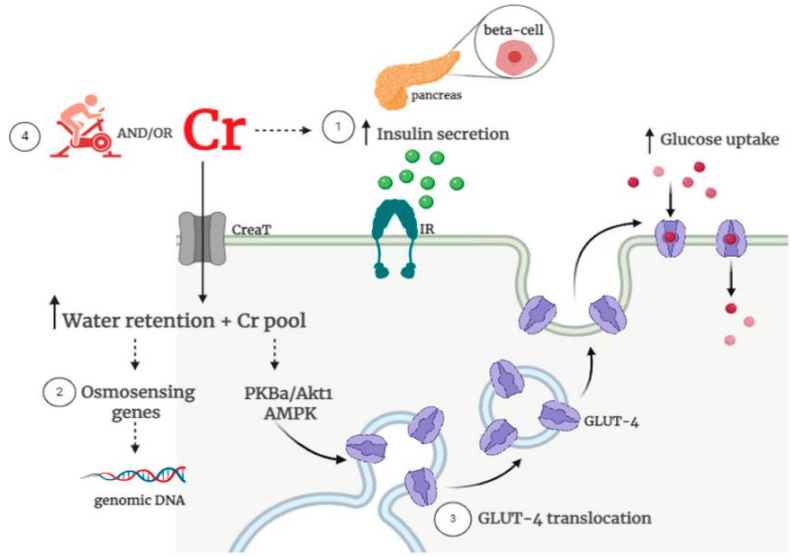

Fig. 3. Note: Cr: creatine; CreaT: creatine transporter; IR: insulin receptor; GLUT-4: glucose transporter; PKBa/Akt1: protein kinase Bα; AMPK: Adenosine Monophosphate-activated protein kinase [16].

On the other hand, the studies that required only oral creatine supplementation without exercise failed to improve glucose tolerance and insulin sensitivity, based on the results of fasting glucose and insulin concentrations [17] and the oral glucose tolerance test (OGTT) [18]. That effect could have been related to a modest insulinotropic creatine capacity [18].

AMPK-α protein content presented a tendency to be higher ($p = 0.06$) after Cr supplementation (5 g/d for 12w). The changes in AMPK-α protein content were significantly related ($p < 0.001$) to the changes in GLUT-4 translocation ($r = 0.78$) and Hb1Ac levels ($r = -0.68$), suggesting that AMPK-α may play an important role in facilitating Cr-induced glucose uptake in diabetic patients. [19] It has also been reported that creatine supplementation prevents the decline of GLUT-4 transporters during fixation while increasing GLUT-4 by 40% during recovery after atrophy [20]. Long term creatine supplementation, combined with aerobic training improves glucose tolerance in humans to a greater extent than aerobic training alone, but it does not alter insulin sensitivity [21]. In regard to concerns about safety of creatine supplementation, mostly related to kidney function

[22], [23], [24] it was demonstrated, that creatine supplementation does not impair kidney function in type 2 diabetic patients based on: creatinine clearance, serum and urinary urea, electrolytes, proteinuria, and albuminuria [25].

In summary, creatine has a big potential to become a nutritional therapy adjuvant, but large, longer-term, controlled trials involving type 2 diabetes with variable disease severity and different pharmacological treatments are necessary to draw firm conclusions on the efficacy and safety of creatine as an anti-diabetic intervention. It is equally important to develop new investigations aimed at unraveling the mechanisms by which creatine, combined or not with training, could regulate glucose control, as basic research is indeed useful to better target the potentially most benefited populations for testing creatine in next clinical trials [16].

Conclusions

1. Creatine supplementation, particularly when combined with training, may potentially affect glucose uptake.
2. Increased GLUT-4 recruitment to the sarcolemma appears to be the underlying mechanism.
3. In order to draw firm conclusions about the efficacy and safety of creatine as a diabetic intervention, larger, longer-term, controlled trials involving type 2 diabetes with variable disease severity and different pharmacological treatments are required.

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