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INVITED REVIEW

Creatine supplementation and glycemic control: a systematic review

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Abstract The focus of this review is the effects of creatine supplementation with or without exercise on glucose metabolism. A comprehensive examination of the past 16 years of study within the field provided a distillation of key data. Both in animal and human studies, creatine supplementation together with exercise training demonstrated greater beneficial effects on glucose metabolism; creatine supplementation itself demonstrated positive results in only a few of the studies. In the animal studies, the effects of creatine supplementation on glucose metabolism were even more distinct, and caution is needed in extrapolating these data to different species, especially to humans. Regarding human studies, considering the samples characteristics, the findings cannot be extrapolated to patients who have poorer glycemic control, are older, are on a different pharmacological treatment (e.g., exogenous insulin therapy) or are physically inactive. Thus, creatine supplementation is a possible nutritional therapy adjuvant with hypoglycemic effects, particularly when used in conjunction with exercise.

Keywords Creatine · Type 2 diabetes · Exercise · Insulin · Glucose

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Introduction

Type 2 diabetes mellitus (T2DM) is a metabolic chronic disease that is major public health problem leading to increased morbility, mortality, and poor quality-of-life (IDF 2013; DeFronzo et al. 2015). In 2013, 382 million people worldwide were estimated to have diabetes, among whom 80 % live in low- and middle-income countries; following this trend until 2035, it is expected that the prevalence will rise to 592 million people (IDF 2013). T2DM is mainly characterized by a state of insulin resistance in muscle and the liver, which can progress to impaired insulin secretion, and, ultimately, sustained hyperglycemia (DeFronzo et al. 2015).

In healthy individuals, insulin signaling starts with insulin binding to the insulin receptor tyrosine kinase (IR), which phosphorylates a family of insulin receptor substrates (IRSs), namely IRS1 and IRS2. This leads to activation of phosphatidylinositol 3-kinase (PI3K), which promotes glucose transporter (GLUT) translocation to the plasma membrane, where it takes up glucose into the cell (DeFronzo 2009). In contrast, when there is increased serine phosphorylation of IRS, tyrosine phosphorylation is inhibited and/or IRS is degraded, leading to insulin resistance (Hiratani et al. 2005; Bouzakri et al. 2006; Copps and White 2012). To adapt to the insulin resistance, β-cells augment insulin secretion to maintain normal blood glucose concentrations. However, as time goes by, β-cells start to fail and blood glucose levels start to rise, resulting in the onset of T2DM (DeFronzo 2009).

T2DM can be effectively managed with lifestyle modifications, such as dietary interventions and physical activity, and the use of some medications (Knowler et al. 2002; Ramachandran et al. 2006; Pan et al. 1997). Creatine supplementation has been pointed out as a novel promising

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strategy to modulate glucose metabolism, potentially alleviating insulin resistance condition.

Creatine (α-methyl guanidine-acetic acid), a guanidine-derived compound, is a natural amine found in the cells of the human body in a free and phosphorylated form (phosphorylcreatine) (Gualano et al. 2010; Wallimann et al. 2011; Guzun et al. 2011). It is synthesized endogenously by the liver, kidney, and pancreas (~1–2 g/day) from arginine, glycine, and methionine, or it can be consumed in the diet mainly from meats (~1–5 g/day) (Wyss and Kaddurah-Daouk 2000) Approximately 95 % of the creatine content is found in the skeletal muscle, and a small portion can be found in the brain, testicles, and bones (Gualano et al. 2010; Wallimann et al. 2011; Harris 2011).

Professor Roger Harris et al. 1992 demonstrated that creatine supplementation was able to augment muscle creatine, and phosphorylcreatine content. Since then, supplementation has been largely used by healthy individuals and athletes to improve performance, enhance gains in strength, and attenuate atrophy, muscle weakness, and metabolic dysfunction, such as T2DM (Branch 2003; Gualano et al. 2010; Pinto et al. 2016).

In the 70s, Alsever et al. (1970) and Marco et al. (1976) demonstrated that creatine can modestly increase insulin secretion in vitro. In 2000, Ferrante et al. observed that creatine ingestion improved hyperglycemia and delayed the onset of diabetes in a transgenic mice mimicking Huntington's disease. Furthermore, Op't Eijnde et al. (2001) demonstrated that creatine supplementation was able to attenuate the decline of muscle GLUT4 expression after 2 weeks of immobilization in healthy individuals. Improvements in glycemia were also showed in sedentary and T2DM patients following creatine supplementation along with an exercise training program (Gualano et al. 2011). The aim of this systematic review was to compile the experimental and clinical evidence regarding the effects of creatine supplementation in glucose metabolism, covering a commonly overlooked effect of creatine in literature, that could be potentially relevant to clinicians, dietitians, and scientists interested in T2DM.

We used the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) method to systematically review the articles that assessed the effects of creatine supplementation with or without exercise training on glucose metabolism. This systematic review was registered in PROSPERO with the number CRD42015016578. We searched PubMed and Scopus for articles published from 2000 up to June 2015 to identify all single- and double-blind-controlled clinical trials and animal studies that investigated the effects of creatine supplementation with or without exercise training on glucose metabolism.

As shown in Table 1, the search terms used for creatine supplementation and glucose metabolism were linked using "OR" as a Boolean function, and the results of the two searches were combined by utilizing the "AND" Boolean. The search results from different databases were combined and any duplicates were removed. Article titles and abstracts were screened to exclude irrelevant studies. After screening, papers were excluded based on the inclusion and exclusion criteria. Finally, we manually searched the references of the selected papers.

Inclusion criteria were as follows: (a) double- and single-blind-controlled clinical trials investigating the effect of creatine supplementation with or without exercise training on any parameters related to glucose metabolism in healthy individuals and diabetic patients; and (b) controlled animal studies investigating the effect of creatine supplementation with or without exercise training on any parameters related to glucose metabolism in healthy and experimentally induced diabetic animals.

Exclusion criteria were as follows: (a) non-controlled or non-prospective-controlled studies (case studies, cross-sectional studies, case–control, cohort or any other type of other retrospective studies), study protocols, pilot studies, letters-to-the editors, editorials, literature reviews, systematic reviews, screening or diagnostic studies, and qualitative research; (b) in vitro studies; (c) studies with animal samples other than rats or mice; (d) studies involving vegetarian; and e) studies in languages other than English and Portuguese.

Figure 1 shows a flow chart of the literature selection. Our database search yielded 170 records, of which 74 were duplicates. Following the analysis of titles and abstracts, we selected 96 studies for examination, 70 of which were not relevant and related to the objective. After reading the full text of 26 articles to screen for inclusion and exclusion criteria, 12 articles were selected. From these selected articles, we manually searched the references, and included seven more articles in the analysis. The final sample consisted of 19 articles included for analysis; 11 articles involved animals, and 8 involved humans. Information on the animal and human studies is summarized in Tables 2 and 3, respectively.

Animal studies

The results of the animal studies are shown in Table 2. A total of 11 studies, including approximately 382 animals, evaluated the effects of creatine supplementation with or without exercise training on glucose metabolism. One study did not mention the sample size (Eijnde et al. 2001). Six studies were controlled (Ferrante et al. 2000; Eijnde et al. 2001; Ju et al. 2005; Souza et al. 2006; Op't Eijnde et al. 2006; Araújo et al. 2013), and 5 were randomized and controlled (Young and Young 2002; Rooney et al. 2002;

Table 1 Search strategy

Search engines	Components	Search keywords	Number of search results
PubMed	Component 1: creatine supplementation	((“creatine”[Title]) OR “creatine supplementation”[Title])	$n = 8758$
	Component 2: glucose metabolism	(((((((((((“diabetes”[Title]) OR “diabetic”[Title]) OR “glycemia”[Title]) OR “fasting blood glucose”[Title]) OR “fasting blood sugar”[Title]) OR “blood glucose”[Title]) OR “insulin”[Title]) OR “insulin resistance”[Title]) OR “serum insulin”[Title]) OR “impaired glucose tolerance”[Title]) OR “impaired fasting glucose”[Title]) OR “glucose homeostasis”[Title]	$n = 348{,}675$
	Component 1 and component 2: creatine supplementation and glucose metabolism	(((((((((((((“diabetes”[Title]) OR “diabetic”[Title]) OR “glycemia”[Title]) OR “fasting blood glucose”[Title]) OR “fasting blood sugar”[Title]) OR “blood glucose”[Title]) OR “insulin”[Title]) OR “insulin resistance”[Title]) OR “serum insulin”[Title]) OR “impaired glucose tolerance”[Title]) OR “impaired fasting glucose”[Title]) OR “glucose homeostasis”[Title])) AND ((“creatine”[Title]) OR “creatine supplementation”[Title])	$n = 77$
Scopus	Component 1: creatine supplementation	((“creatine”[Title]) OR “creatine supplementation”[Title])	$n = 9775$
	Component 2: glucose metabolism	((((((((((“diabetes”[Title]) OR “diabetic”[Title]) OR “glycemia”[Title]) OR “fasting blood glucose”[Title]) OR “fasting blood sugar”[Title]) OR “blood glucose”[Title]) OR “insulin”[Title]) OR “insulin resistance”[Title]) OR “serum insulin”[Title]) OR “impaired glucose tolerance”[Title]) OR “impaired fasting glucose”[Title]) OR “glucose homeostasis”[Title]	$n = 426{,}409$
	Component 1 and component 2: creatine supplementation and glucose metabolism	(((((((((((((“diabetes”[Title]) OR “diabetic”[Title]) OR “glycemia”[Title]) OR “fasting blood glucose”[Title]) OR “fasting blood sugar”[Title]) OR “blood glucose”[Title]) OR “insulin”[Title]) OR “insulin resistance”[Title]) OR “serum insulin”[Title]) OR “impaired glucose tolerance”[Title]) OR “impaired fasting glucose”[Title]) OR “glucose homeostasis”[Title])) AND ((“creatine”[Title]) OR “creatine supplementation”[Title])	$n = 93$

The search strategy consists of two separate components and each component consists of the key words related to “creatine supplementation” and the key words related to “glucose metabolism” individually. The key words in each component were linked using “OR” as a Boolean function, and the results of the two sections were combined by utilizing the “AND” Boolean in final search

Freire et al. 2008; Vaisy et al. 2011; Nicastro et al. 2012). The median sample size was 63 animals (ranging from 8 to 72). Only Ferrante et al. (2000) studied mice; the other studies used rats (Rooney et al. 2002; Young and Young 2002; Ju et al. 2005; Souza et al. 2006; Op't Eijnde et al. 2006; Freire et al. 2008; Vaisy et al. 2011; Eijnde et al. 2001; Nicastro et al. 2012; Araújo et al. 2013). Eight studies investigated healthy animals (Young and Young 2002; Rooney et al. 2002; Ju et al. 2005; Souza et al. 2006; Freire et al. 2008; Eijnde et al. 2001; Vaisy et al. 2011; Araújo et al. 2013), Ferrante et al. (2000) used a transgenic mouse model of Huntington's Disease, Op't Eijnde et al. (2006) studied Goto-Kakizaki rats (a animal model of inherited T2DM), and Nicastro et al. (2012) used rats treated with dexamethasone. Four studies examined the effects of creatine supplementation associated with exercise training on glucose metabolism (Souza et al. 2006; Freire et al. 2008; Vaisy et al. 2011; Araújo et al. 2013), and seven studies

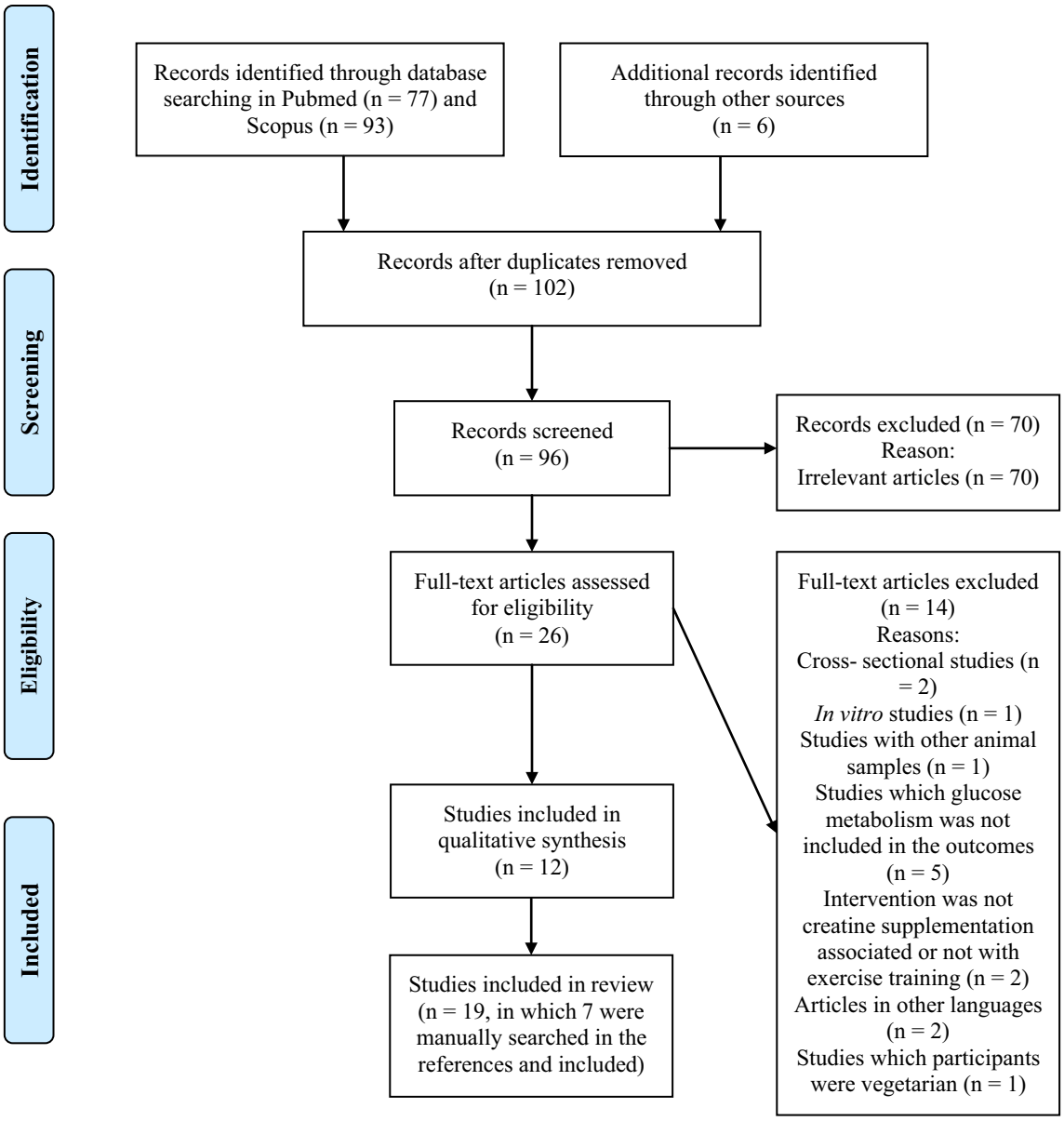

Fig. 1 PRISMA 2009 flow diagram of the structured literature review

adopted creatine supplementation alone (Young and Young 2002; Rooney et al. 2002; Ju et al. 2005; Souza et al. 2006; Op't Eijnde et al. 2006; Eijnde et al. 2001; Nicastro et al. 2012). Studies that involved exercise training employed swimming (Souza et al. 2006; Freire et al. 2008; Vaisy et al. 2011) or treadmill running (Araújo et al. 2013). The dose of creatine supplementation was described as the percentage of the amount of supplement in the diet (from 1 to 13 %) or as the daily dose (ranging from 300 to 5 g/kg). Two studies (Souza et al. 2006; Araújo et al. 2013) used a "loading stage" protocol (i.e., higher dose during 1 week) followed by a "maintenance stage" (i.e., lower dose after "loading" to maintain creatine levels increased), and the remaining studies maintained the same dose protocol during all the experiments (Ferrante et al. 2000; Young and Young 2002; Rooney et al. 2002; Ju et al. 2005; Op't Eijnde et al. 2006; Freire et al. 2008; Eijnde et al. 2001; Vaisy et al. 2011; Nicastro et al. 2012). The duration of the interventions ranged from 5 to 94 days.

The three studies that assessed the effects of creatine supplementation on glucose metabolism in insulin resistant animals (Ferrante et al. 2000; Op't Eijnde et al. 2006; Nicastro et al. 2012) showed conflicting results. Ferrante et al. (2000) and Op't Eijnde et al. 2006 found beneficial effects of creatine, including attenuation of insulin concentration and improved sensitivity to insulin in extrapancreatic

Table 2 Characteristics of the included animal studies

Study (year)	Methods	Target population	*n*	Intervention/ duration of the intervention	Dose	Glucose metabolism outcomes	Results and *p* values	Relevant outcomes	Results and *p* values
Ferrante et al. (2000)	Controlled	Transgenic Huntington's disease R6/2 mice	25(C)/25(Cr)	Oral administration of Cr/21 days of age	Diets supplemented with 1, 2, or 3 % of Cr	Glucose tolerance	[a]Within: NM and [b]Between: S (↑ in 2 %, $p < 0.01$)	Survival	Within: S (↑ in 3 %, $p < 0.0002$) and Between: S (↑ in 1 and 2 %, $p < 0.0001$)
								Rotarod performance	Within: NM and Between: S (↑ in 1, and 2 %, $p < 0.001$)
								Body weight	Within: S (↑ in 2 %, $p < 0.01$) and Between: S (↑ in 1 and 3 %, $p < 0.02$) and S (↑ in 2 %, $p < 0.01$)
Eijnde et al. (2001)	Controlled	Male Wistar rats	NM(C)/NM(Cr)	Oral administration of Cr monohydrate/5 days	Powdered rat chow containing 5 % of Cr monohydrate	Muscle GLUT4 content	Within: NM and Between: NS in either muscle type	Muscle glycogen content	Within: NM and Between: S (↑ in Cr in red gastrocnemius and soleus, $p < 0.05$); NS (white gastrocnemius)
						Glucose transport rate	Within: NM and Between: NS in either muscle type	Muscle Cr and PCr content	Within: NM and Between: S (↑ in Cr in soleus, $p < 0.05$); NS (red gastrocnemius and white gastrocnemius)
						Plasma insulin	Within: NM and Between: NS in either muscle type	Muscle total Cr content	Within: NM and Between: S (↑ in Cr in red gastrocnemius and soleus, $p < 0.05$); NS (white gastrocnemius)
						Blood glucose	Within: NM and Between: NS in either muscle type	Muscle ATP content	Within: NM and Between: S (↓ in Cr in white gastrocnemius, $p < 0.05$); NS (red gastrocnemius and soleus)
								Muscle water content	Within: NM and Between: NS in either muscle type

Table 2 continued

Study (year)	Methods	Target population	*n*	Intervention/ duration of the intervention	Dose	Glucose metabolism outcomes	Results and *p* values	Relevant outcomes	Results and *p* values
						Muscle glucose uptake after insulin perfusion	Within: NM and Between: NS in either muscle type	Glycogen synthase activity	Within: NM and Between: NS in either muscle type
						Muscle glucose uptake after creatine perfusion	Within: NM and Between: NS in either muscle type	Plasma creatine	Within: NM and Between: S (↑ in Cr 1 h after feeding, $p < 0.05$)
								Glycogen synthesis rate	Within: NM and Between: NS in either muscle type
Ju et al. (2005)	Controlled	Female Wistar rats	7(C)/7(Cr)	Oral administration of Cr monohydrate/3 weeks	Chow containing 2 % of Cr monohydrate	Extensor digitorum longus, triceps, and epitrochlearis muscle GLUT4 contents	Within: NM and Between: S (↑ in Cr, $p < 0.05$)	Body weight	Within: NM and Between: NS
						Triceps GLUT4 mRNA	Within: NM and Between: S (↑ in Cr, $p < 0.05$)	Extensor digitorum longus muscle Cr, PCr, total Cr contents, and [PCr]/[total Cr] ratio	Within: NM and Between: NS
						Insulin-stimulated glucose transport in epitrochlearis muscles	Within: NM and Between: S (↑ in Cr, $p < 0.005$)		
						AMPK phosphorylation in extensor digitorum longus muscle	Within: NM and Between: S (↑ in Cr, $p < 0.05$)	Extensor digitorum longus muscle ATP and AMP content	Within: NM and Between: NS
						Acetyl-CoA carboxylase phosphorylation in extensor digitorum longus muscle	Within: NM and Between: S (↑ in Cr, $p < 0.05$)	Extensor digitorum longus muscle creatinine content	Within: NM and Between: S (↑ in Cr, $p < 0.005$)
						Myocyte enhancer factor 2 content	Within: NM and Between: S (↑ in Cr, $p < 0.05$)	Glycogen content of epitrochlearis muscles	Within: NM and Between: S (↑ in Cr, $p < 0.05$)
						Myocyte enhancer factor 2-DNA-binding activity	Within: NM and Between: S (↑ in Cr, $p < 0.05$)		

Table 2 continued

Study (year)	Methods	Target population	*n*	Intervention/ duration of the intervention	Dose	Glucose metabolism outcomes	Results and *p* values	Relevant outcomes	Results and *p* values
Souza et al. (2006)	Controlled	Male Wistar rats	G1: 18(C) G2: 18 (Trained) G3: 18 (Cr) G4: 18 (Trained + Cr)	Oral administration of Cr and/ or Swimming/8 weeks	5 g/kg of body weight of Cr for 7 days (loading phase)/1 g/kg of body weight of Cr for 7 days (maintenance phase)	Plasma glucose levels	Within: NM and Between: S (↓ in G3 during 1–4 week, $p < 0.05$) and (↓ in G4 during 1–8 week, $p < 0.05$)	Body weight	Within: NM and Between: S (↑ in G3 and G4, $p < 0{\cdot}.05$)
								Maximum tolerated load	Within: NM and Between: S (↑ in G4 during 1–8 week, $p < 0.05$)
								Plasma lactate levels	Within: NM and Between: S (↓ in G3 during 1–2 week, $p < 0.05$) and (↓ in G4 during 1–8 week, $p < 0.05$)
Op't Eijnde et al. (2006)	Controlled	Male Goto-Kakizaki rats	G1: 6 (C 6-week age) G2: 6 (C 14-week age) G3: 6 (Cr 6-week age) G4: 6 (Cr 14-week age)	Oral administration of Cr monohydrate/8 weeks	Normal rodent pellets enriched with 2 % Cr	Basal blood D-glucose concentration	Within: NM and Between: NS	Body weight	Within: NM and Between: NS
						Blood D-glucose concentration 5 and 120 min after glucose tolerance test	Within: NM and Between: NS	Muscle Cr content	Within: NM and Between: S (↑ in G3, $p < 0.05$)
						Plasma insulin concentration	Within: NM and Between: S (↓ in G3, and G4, $p < 0.05$)	Muscle glycogen content	Within: NM and Between: NS
						Insulinogenic index before and after administration of exogenous D-glucose	Within: NM and Between: S (↓ in G3, and G4, $p < 0.01$)		

Table 2 continued

Study (year)	Methods	Target population	*n*	Intervention/duration of the intervention	Dose	Glucose metabolism outcomes	Results and *p* values	Relevant outcomes	Results and *p* values
Araújo et al. (2013)	Controlled	Male Wistar rats	G1: 10 (C sedentary) G2: 10 (Cr sedentary) G3: 10 (Trained) G4: 10 (Cr trained)	Oral administration of Cr monohydrate or/and training (treadmill)/8 weeks	Diet supplemented with 13 % Cr for 7 days (loading phase)/diet supplemented with 2 % Cr for 55 days (maintenance phase)	Glucose uptake	Within: NM and Between: NS	Body weight	Within: NM and Between: S (↓ in G3, and G4, $p < 0.05$)
								Food intake	Within: NM and Between: NS
						Glucose oxidation	Within: NM and Between: S (↑ in G2 and G4, $p < 0.05$)	Hydric intake	Within: NM and Between: S (↑ in G4, $p < 0.05$)
								Glycogen synthesis	Within: NM and Between: NS
						Glucose AUC during the OGTT	Within: NM and Between: S (↓ in G4, $p < 0.05$)	Glycogen concentration	Within: NM and Between: NS
								Lactate production by the soleus muscle	Within: NM and Between: S (↓ in G4, $p < 0.05$)
Young and Young (2002)	Random-controlled	Male Sprague–Dawley rats	4(C)/4(Cr)	Oral administration of Cr monohydrate/5 weeks	300 mg/kg body weight in gelatin daily	Insulin-stimulated 2-deoxyglucose uptake	Within: S (↑ in C and Cr, $p < 0.01$) and Between: NS	Body weight	Within: NM and Between: NS
								Epitrochlearis muscle weight	Within: NM and Between: NS
						Basal rates of glucose uptake	Within: NM and Between: NS	Free Cr from plantaris muscle	Within: NM and Between: S (↑ in Cr, $p < 0.01$)
								TCr from plantaris muscle	Within: NM and Between: S (↑ in Cr, $p < 0.05$)
								PCr	Within: NM and Between: NS
						Insulin-stimulated rates of glucose uptake	Within: NM and Between: NS	PCr/TCr ratio	Within: NM and Between: S (↓ in Cr, $p < 0.05$)
								ATP concentration	Within: NM and Between: S (↑ in Cr, $p = 0.05$)

Table 2 continued

Study (year)	Methods	Target population	*n*	Intervention/ duration of the intervention	Dose	Glucose metabolism outcomes	Results and *p* values	Relevant outcomes	Results and *p* values
Rooney et al. (2002)	Random-controlled	Male Wistar rats	8(C)/8(Cr)	Oral administration of Cr hydrate/2, 4, or 8 weeks	20 g of standard chow diet per rat per day of which 2 % by weight was Cr	Fasting plasma glucose levels	Within: NM and Between: NS (2, 4, or 8 weeks)	Body weight	Within: NM and Between: NS (2, 4, or 8 weeks)
						Plasma glucose levels after an oral glucose load	Within: NM and Between: NS (2, 4, or 8 weeks)	Pancreatic Cr content	Within: NM and Between: S (↑ in Cr after 2, 4, and 8 weeks, $p < 0.0001$)
						Fasting plasma insulin levels	Within: NM and Between: NS (2, or 4 weeks) and S (↑ in Cr after 8 weeks, $p = 0.01$)	Quadriceps muscle Cr content	Within: NM and Between: NS (2, 4, or 8 weeks)
								Quadriceps glycogen content	Within: NM and Between: NS (2, 4, or 8 weeks)
						Plasma insulin levels after an oral glucose load	Within: NM and Between: NS (2, 4, or 8 weeks)	Glycogen synthase activity in the quadriceps muscles	Within: NM and Between: NS (2, 4, or 8 weeks)
								Glycogen phosphorylase-α activity in the quadriceps muscles	Within: NM and Between: NS (2, 4, or 8 weeks)

Table 2 continued

Study (year)	Methods	Target population	*n*	Intervention/ duration of the intervention	Dose	Glucose metabolism outcomes	Results and *p* values	Relevant outcomes	Results and *p* values
Freire et al. (2008)	Random-controlled	Male Wistar rats	G1: 9 (C/sedentary/4 weeks of duration) G2: 6 (C/trained/4 weeks of duration) G3: 10 (Cr/sedentary/4 weeks of duration) G4: 8 (Cr/trained/4 weeks of duration) G5: 10 (C/sedentary/8 weeks of duration) G6: 7 (C/trained/8 weeks of duration) G7: 8 (Cr/sedentary/8 weeks of duration) G8: 7 (Cr/trained/8 weeks of duration)	Oral administration of Cr or/and training (swimming)/4 or 8 weeks	Normal rodent pellets enriched with 2 % Cr	OGTT	Within: NS and Between: NS	Body weight	Within: NM and Between: NS
								Liver glycogen content	Within: NS and Between: NS
								Quadriceps glycogen content	Within: NS and Between: NS

Table 2 continued

Study (year)	Methods	Target population	*n*	Intervention/duration of the intervention	Dose	Glucose metabolism outcomes	Results and *p* values	Relevant outcomes	Results and *p* values
Vaisy et al. (2011)	Random-controlled	Male Wistar rats	G1: 10 (C) G2: 16 (Cafeteria diet) G3: 15 (Cafeteria diet + training) G4: 19 (Cr + cafeteria diet) G5: 9 (Cr + cafeteria diet + training)	Cafeteria diet and/or oral administration of Cr monohydrate and/or training (swimming)/12 weeks	Cafeteria diet enriched with 2.5 % Cr	Fasting blood glucose concentration	Within: NM and Between: NS	Body weight	Within: NM and Between: S (↑ in G2, G3, G4, and G5, $p < 0.05$)
						Fasting plasma insulin level	Within: NM and Between: S (↑ in G2, $p < 0.05$) and S (↓ in G3 and G5, $p < 0.05$)	IMLC in soleus and extensor digitorum longus muscles	Within: NM and Between: S (↑ in G2, $p < 0.05$)
								FAT/CD36 protein content in muscle soleus	Within: NM and Between: S (↓ in G3, G4, and G5, $p < 0.05$)
						Whole-body glucose tolerance	Within: NM and Between: S (↓ in G2, G3, G4, and G5, $p < 0.05$)	Fecal fat	Within: NM and Between: S (↑ in G4, $p < 0.05$)
								Triglyceride concentration in blood and liver	Within: NM and Between: S (↑ in G4, $p < 0.05$)
						Insulin-stimulated muscle glucose transport	Within: NM and Between: S (↓ in G2, and G4, $p < 0.05$)	Muscle-free Cr content	Within: NM and Between: NS
								PCr content	Within: NM and Between: NS
								Glycogen content	Within: NM and Between: NS

Table 2 continued

Study (year)	Methods	Target population	*n*	Intervention/ duration of the intervention	Dose	Glucose metabolism outcomes	Results and *p* values	Relevant outcomes	Results and *p* values
Nicastro et al. (2012)	Random-controlled	Male Wistar rats	G1: 6 (DXM) G2: 6 (C) G3: 6 (DXM + Cr) G4: 6 (Cr)	DXM and Cr were given daily via drinking water/7 days	DXM (5 mg/kg/day) and Cr (5 g/kg/day) were given daily via drinking water	Serum glucose concentration	Within: NM and Between: S (↑ in G3, $p < 0.001$)	Body weight	Within: NM and Between: S (↓ in G2 and G4, $p < 0.05$)
								Weight throughout the study	Within: NM and Between: S (↓ in G1 and G3, $p < 0.05$)
						Serum insulin concentration	Within: NM and Between: S (↑ in G3, $p < 0.001$)	Plantaris and extensor digitorum longus muscle mass	Within: NM and Between: S (↓ in G1 and G3, $p < 0.05$)
						GLUT4 translocation	Within: NM and Between: S (↓ in G3, $p < 0.01$)	Muscle dry:wet weight ratio	Within: NM and Between: NS
								Phospho-Ser^{473}-Akt protein levels	Within: NM and Between: S (↓ in G3, $p < 0.001$)
						GLUT4 protein content	Within: NM and Between: NS	Total-FoxO3a protein expression	Within: NM and Between: NS
								Phospho-Ser^{253}-FoxO3a protein expression	Within: NM and Between: S (↓ in G1 and G3, $p < 0.01$)
						HOMA-IR	Within: NM and between: S (↑ in G3, $p < 0.001$)	MuRF-1 protein expression	Within: NM and Between: S (↑ in G1 and G3, $p < 0.001$)

AMPK adenosine monophosphate activated protein kinase, *ATP* adenosine triphosphate, *AUC* area under the curve, *C* control group, *Cr* creatine, *DXM* dexamethasone, *FAT* fatty acid translocase, *G* group, *GLUT* glucose transporter, *HK* hexokinase, *HOMA-IR* insulin resistance index, *IMLC* intramyocellular lipid content, *LDH* lactate dehydrogenase, *mRNA* messenger RNA, *NM* not mentioned, *NS* not significant, *OGTT* oral glucose tolerance test, *PCr* phosphocreatine, *RNA* ribonucleic acid, *S* significant, *TCr* total creatine

[a] "Within", refers to within groups comparisons

[b] "Between" refers to between groups comparisons

Table 3 Characteristics of the included human studies

Study (year)	Methods	Target population	*n*	Intervention/duration of the intervention	Dose	Glucose metabolism outcomes	Results and *p* values	Relevant outcomes	Results and *p* values
Op't Eijnde et al. (2001)	Double-blind, placebo-controlled trial	Young and healthy subjects (men and women)	11(C)/11(Cr)	Oral administration of Cr monohydrate and/or Rehabilitation program of 10 weeks after 2 weeks of immobilization of 1 leg (a cast from groin to ankle)/12 weeks	Week 1–2: 5 g of Cr, 4 times a day Week 3–5: 5 g of Cr, 3 times a day Week 6 on: 5 g of Cr per day	Muscle GLUT4 content (immobilized leg)	During immobilization: [a]Within: S (↓ in C, $p < 0.05$) and [b]Between: S (↓ in C, $p < 0.05$) and (↑ in Cr, $p < 0.05$) During rehabilitation: Within: NS and Between: S (↑ in Cr, $p < 0.05$)	Muscle glycogen concentration (immobilized leg)	During immobilization: Within: NS and Between: NS During rehabilitation: Within: S (↑ in Cr, $p < 0.05$) and Between: S (↑ in Cr after 3 weeks, $p < 0.05$) S (↑ in Cr and C after 7 weeks, $p < 0.05$)
								Muscle PCr concentration (immobilized leg)	During immobilization: Within: (↓ in C, $p < 0.05$) and Between: S (↓ in C and ↑ in Cr, $p < 0.05$) During rehabilitation: Within: NS and Between: S (↑ in Cr, $p < 0.05$)
								Muscle free Cr concentration (immobilized leg)	During immobilization: Within: S (↑ in C and Cr, $p < 0.05$) and Between: NS During rehabilitation: Within: S (↑ in C and Cr, $p < 0.05$) and Between: NS

Table 3 continued

Study (year)	Methods	Target population	*n*	Intervention/duration of the intervention	Dose	Glucose metabolism outcomes	Results and *p* values	Relevant outcomes	Results and *p* values
								Muscle total Cr concentration (immobilized leg)	During immobilization: Within: S (↑ in Cr, $p < 0.05$) and Between: S (↑ in Cr, $p < 0.05$) During rehabilitation: Within: S (↑ in Cr, $p < 0.05$) and Between: S (↑ in Cr, $p < 0.05$)
						Plasma insulin response after OGTT	Within: NS and Between: NS		
Gualano et al. (2008)	Double-blind, randomized placebo-controlled trial	Healthy, sedentary, eutrophic, and non-vegetarian, subjects (men)	10(C)/12(Cr)	Oral administration of Cr monohydrate and/or Moderate intensity aerobic Training/12 weeks	Loading phase (the first week): 0.3 g/kg of body weight of Cr per day Maintenance phase (next 11 weeks): 0.15 g/kg of body weight of Cr per day	Plasma glucose concentration after OGTT	After 4 weeks: Within: NS and Between: NS After 8 weeks: Within: NS and Between: NS After 12 weeks: Within: NS and Between: NS	–	–
						Glucose AUC after OGTT	Within: S (↓ in Cr and C, $p = 0.005$) and Between: S (↓ in Cr, $p = 0.034$)		
						HOMA index	After 4 weeks: Within: NS and Between: NS After 8 weeks: Within: NS and Between: NS After 12 weeks: Within: NS and Between: NS		

Table 3 continued

Study (year)	Methods	Target population	*n*	Intervention/duration of the intervention	Dose	Glucose metabolism outcomes	Results and *p* values	Relevant outcomes	Results and *p* values
						Fasting insulin	After 4 weeks: Within: NS and Between: NS After 8 weeks: Within: NS and Between: NS After 12 weeks: Within: NS and Between: NS		
Gualano et al. (2011)	Double-blind, randomized placebo-controlled trial	Subjects pre-diagnosed with type 2 diabetes, physically inactive for at least 1 year, and with BMI $\geq$ 30 kg/m^2	12(C)/13(Cr)	Oral administration of Cr monohydrate and/or Moderate intensity aerobic training combined with strengthening exercises/12 weeks	5 g of Cr per day	Hb_{A1c} concentrations	Within: S (↓ in Cr, $p = 0.0001$) and Between: S (↓ in Cr, $p = 0.004$)	Muscle PCr content	Within: NM and Between: S (↑ in Cr, $p = 0.03$)
						Glycemia during MTT	Within: NS and Between: S (↓ in Cr in 0 min, $p = 0.001$), S (↓ in Cr in 30 min, $p = 0.004$), and S (↓ in Cr in 60 min, $p = 0.003$)	1-RM leg press	Within: S (↑ in Cr and C, $p = 0.007$) and Between: NS
						Insulin concentrations during MTT	Within: NS and Between: NS	1-RM bench press	Within: S (↑ in Cr and C, $p < 0.01$) and Between: NS
						C-peptide concentrations during MTT	Within: NS and Between: NS	Low back strength	Within: S (↑ in Cr and C, $p = 0.03$) and Between: NS
						Delta AUC for glucose concentration	Within: NS and Between: S (↓ in Cr, $p = 0.05$)	Handgrip strength	Within: NS and Between: NS
						Delta AUC for insulin concentration	Within: NS and Between: NS	Timed-stands test	Within: S (↑ in Cr and C, $p < 0.001$) and Between: NS
						Delta AUC for C-peptide concentration	Within: NS and Between: NS	Timed-up-and-go test	Within: NS and Between: NS
						HOMA-IR index	Within: NS and Between: NS	VO_2-VAT	Within: S (↑ in Cr and C, $p < 0.001$) and Between: NS

Table 3 continued

Study (year)	Methods	Target population	*n*	Intervention/duration of the intervention	Dose	Glucose metabolism outcomes	Results and *p* values	Relevant outcomes	Results and *p* values
						HOMA-β index	Within: NS and Between: NS	VO_2-RCP	Within: S (↑ in Cr and C, $p = 0.08$) and Between: NS
						Glucose/insulin index	Within: NS and Between: NS	VO_{2max}	Within: NS and Between: NS
						Muscle GLUT-4 content	Within: NS and Between: NS	Total training volume	Within: NM and Between: NS
						Membrane GLUT-4 content	Within: S (↑ in Cr and C, $p < 0.001$) and Between: S (↑ in Cr, $p = 0.05$)	Blood lipoproteins	Within: NS and Between: NS
						Membrane-total GLUT-4 content ratio	Within: S (↑ in Cr and C, $p < 0.001$) and Between: S (↑ in Cr, $p = 0.03$)	Blood apolipoproteins	Within: NS and Between: NS
								Body composition variables	Within: NS and Between: NS
Van Loon et al. (2004)	Double-blind, placebo-controlled trial	Young, and non-vegetarian, subjects (men)	10(C)/9(Cr)	Oral administration of Cr monohydrate/6 weeks	Loading phase (day 1–5): 5 g of Cr + 15 g of glucose + 10 g of maltodextrin, 4 times a day. Maintenance phase (day 6 on): 2 g of Cr + 15 g of glucose + 10 g of maltodextrin per day	Fasting plasma insulin concentrations	Within: NS and Between: NS	Muscle free Cr content	After loading phase: Within: S (↑ in Cr, $p < 0.05$) and Between: NS After maintenance phase: Within: S (↑ in Cr, $p < 0.05$) and Between: NS
								Muscle PCr content	After loading phase: Within: S (↑ in Cr, $p < 0.05$) and Between: S (↑ in Cr, $p < 0.05$) After maintenance phase: Within: S (↑ in Cr, $p < 0.05$) and Between: NS

Table 3 continued

Study (year)	Methods	Target population	*n*	Intervention/duration of the intervention	Dose	Glucose metabolism outcomes	Results and *p* values	Relevant outcomes	Results and *p* values
								Muscle total Cr content	After loading phase: Within: S (↑ in Cr, $p < 0.05$) and Between: S (↑ in Cr, $p < 0.05$) After maintenance phase: Within: S (↑ in Cr, $p < 0.05$) and Between: NS
						GLUT4 mRNA content	After loading phase: Within: NS and Between: NS After maintenance phase: Within: NS and Between: NS	Muscle ATP content	After loading phase: Within: NS and Between: NS After maintenance phase: Within: NS and Between: NS
								Muscle glycogen content	After loading phase: Within: NS and Between: S (↑ in Cr, $p < 0.05$) After maintenance phase: Within: S (↑ in Cr, $p < 0.05$) and Between: NS
								Muscle glycogen content (relative change)	After loading phase: Within: S (↑ in Cr, $p < 0.05$) and Between: S (↑ in Cr, $p < 0.05$) After maintenance phase: Within: NS and Between: NS
						Muscle GLUT4 protein content	After loading phase: Within: NS and Between: NS After maintenance phase: Within: NS and Between: NS	Glycogen synthase mRNA content	After loading phase: Within: NS and Between: NS After maintenance phase: Within: NS and Between: NS

Table 3 continued

Study (year)	Methods	Target population	*n*	Intervention/duration of the intervention	Dose	Glucose metabolism outcomes	Results and *p* values	Relevant outcomes	Results and *p* values
								Glycogen mRNA content	After loading phase: Within: NS and Between: NS After maintenance phase: Within: NS and Between: NS
Newman et al. (2003)	Single-blind, placebo-controlled trial	Healthy active, but untrained Subjects (men)	9(C)/10(Cr)	Oral administration of Cr monohydrate/ 38 days	Loading phase (day 1–5): 5 g of Cr + 3.75 g of glucose + 4 times a day. Maintenance phase (day 6 on): 3 g of Cr + 3 g of glucose per day	Plasma glucose concentrations during OGTT	After loading phase: Within: NM and Between: NS After maintenance phase: Within: NM and Between: NS	Muscle total Cr content	After loading phase: Within: NM and Between: S (↑ in Cr, $p < 0.05$) After maintenance phase: Within: NM and Between: S (↑ in Cr, $p < 0.05$)
						Plasma insulin concentrations during OGTT	After loading phase: Within: NM and Between: NS After maintenance phase: Within: NM and Between: NS	Muscle ATP content	After loading phase: Within: NM and Between: NS After maintenance phase: Within: NM and Between: NS
						Fasting plasma insulin	After loading phase: Within: NM and Between: NS After maintenance phase: Within: NM and Between: NS		
						Glucose-insulin index	After loading phase: Within: NM and Between: NS After maintenance phase: Within: NM and Between: NS	Muscle glycogen content	After loading phase: Within: NM and Between: NS After maintenance phase: Within: NM and Between: NS

Table 3 continued

Study (year)	Methods	Target population	*n*	Intervention/duration of the intervention	Dose	Glucose metabolism outcomes	Results and *p* values	Relevant outcomes	Results and *p* values
						Index of insulin sensitivity during OGTT	After loading phase: Within: NM and Between: NS After maintenance phase: Within: NM and Between: NS		
Derave et al. (2003)	Double-blind, randomized, placebo-controlled trial	Healthy subjects (men and women)	11(C)/11 (Cr)/11(Cr + protein)	Oral administration of Cr monohydrate and/or Rehabilitation program of 6 weeks after 2 weeks of immobilization of 1 leg (a cast from groin to ankle)/8 weeks	Week 1–2: 5 g of Cr, 4 times a day Week 3 on: 2.5 g of Cr per day, 40 g of protein per day, and 6.7 g of amino acids per day	Protein expression of GLUT4 (immobilized leg)	During immobilization: Within: S (↓ in C and Cr, $p < 0.05$) and Between: NS During rehabilitation: Within: S (↑ in Cr and Cr + protein, $p < 0.05$) and Between: S (↑ in Cr and Cr + protein, $p < 0.05$)	Muscle glycogen content (immobilized leg)	During immobilization: Within: NS and Between: NS During rehabilitation: Within: S (↑ in Cr and Cr + protein, $p < 0.05$) and Between: S (↑ in Cr and Cr + protein, $p < 0.05$)
								Muscle free Cr concentration (immobilized leg)	During immobilization: Within: S (↑ in Cr + protein, $p < 0.05$) and Between: NS During rehabilitation: Within: S (↑ in Cr and Cr + protein, $p < 0.05$) and Between: NS
						Glucose AUC in a 2-h OGTT	During immobilization: Within: NS and Between: NS During rehabilitation: Within: S (↑ in Cr + protein, $p < 0.05$) and Between: S (↑ in Cr + protein, $p < 0.05$)	Muscle PCr concentration (immobilized leg)	During immobilization: Within: NS and Between: NS During rehabilitation: Within: NS and Between: S (↑ in Cr + protein, $p < 0.05$)

Table 3 continued

Study (year)	Methods	Target population	*n*	Intervention/duration of the intervention	Dose	Glucose metabolism outcomes	Results and *p* values	Relevant outcomes	Results and *p* values
								Muscle total Cr concentration (immobilized leg)	During immobilization: Within: NS and Between: NS During rehabilitation: Within: S (↑ in Cr and Cr + protein, $p < 0.05$) and Between: NS
								Muscle fiber-type composition	During immobilization: Within: NS and Between: NS During rehabilitation: Within: NS and Between: NS
						Plasma insulin levels	During immobilization: Within: NS and Between: NS During rehabilitation: Within: NS and Between: NS	Maximal isometric knee extension torque (immobilized leg)	During immobilization: Within: S (↓ in C, Cr and Cr + protein, $p < 0.05$) and Between: NS During rehabilitation: Within: S (↑ in C and Cr + protein, $p < 0.05$) and Between: NS
								Recovery indexes extensor muscles (immobilized leg)	During immobilization: Within: NS and Between: NS During rehabilitation: Within: S (↑ in Cr and Cr + protein, $p < 0.05$) and Between: NS

Table 3 continued

Study (year)	Methods	Target population	*n*	Intervention/duration of the intervention	Dose	Glucose metabolism outcomes	Results and *p* values	Relevant outcomes	Results and *p* values
								Body weight	During immobilization: Within: S (↑ in Cr and Cr + protein, $p < 0.05$) and Between: NS During rehabilitation: Within: S (↑ in C, Cr and Cr + protein, $p < 0.05$) and Between: NS
Alves et al. (2012)	Double-blind, randomized placebo-controlled trial	Subjects pre-diagnosed with type 2 diabetes, physically inactive for at least 1 year, and with BMI ≥ 30 kg/m^2	12(C)/13(Cr)	Oral administration of Cr monohydrate and/or moderate intensity aerobic training combined with strengthening exercises/12 weeks	5 g of Cr per day	IR-β expression	Within: NS and Between: NS	–	–
						AKT-1 expression	Within: NS and Between: NS		
						MAPK p42/44 expression	Within: NS and Between: NS		
						AMPK-α expression	Within: NS and Between: NS		
						Correlation between changes in AMPK-α levels and changes in GLUT-4 translocation	$r = 0.71$ $p < 0.001$		
						Correlation between changes in AMPK-α expression and changes in Hb_{1Ac} levels	$r = -0.68$ $p < 0.001$		
						Correlation between changes in Hb_{1Ac} levels and GLUT-4 translocation	$r = -0.89$ $p < 0.001$		

Table 3 continued

Study (year)	Methods	Target population	*n*	Intervention/duration of the intervention	Dose	Glucose metabolism outcomes	Results and *p* values	Relevant outcomes	Results and *p* values
Safdar et al. (2008)	Double-blind, crossover, randomized placebo-controlled trial	Healthy, young, non-obese men	12	Oral administration of Cr monohydrate/6 weeks	Loading phase (3 days): 20 g/day Maintenance phase (10 days): 5 g/day	PKB/AKT-1 expression and protein	Between: ↑ 2.1-fold and 4.2-fold in Cr, respectively, $p < 0.05$	FFM	Between: ↑ 1.0 kg in Cr, $p = 0.02$
						MAPK expression	Between: ↑ 1.8-fold in Cr, $p < 0.05$	Muscle total Cr content	Between: ↑ in Cr, $p < 0.001$

AKT-1 akt protein kinase B, *AMPK* activated protein kinase, *ATP* adenosine triphosphate, *AUC* area under the curve, *BMI* body mass index, *C* control group, *Cr* creatine, *G* group, *GLUT* glucose transporter, Hb_{A1C} glycosylated hemoglobin *HOMA* homeostatic model assessment, *HOMA-IR* insulin resistance index, *IR* insulin receptor, *MAPK p42/p44* p42/p44 mitogen-activated kinase, *mRNA* messenger RNA, *MTT* meal tolerance test, *NM* not mentioned, *NS* not significant, *OGTT* oral glucose tolerance test, *PCr* phosphocreatine, *RM* repetition maximum, *RNA* ribonucleic acid, *S* significant, VO_2 maximal oxygen consumption, VO_2-*RCP* oxygen consumption correspondent to respiratory compensation point, VO_2-*VAT* oxygen consumption correspondent to ventilator anaerobic threshold

[a] "Within", refers to within groups comparisons

[b] "Between" refers to between groups comparisons

tissues. Although they used different rodent models, both are type 2 diabetics, intervention period (8 weeks), and a similar dose of creatine (2 %). In contrast, Nicastro et al. (2012) induced severe muscle wasting and insulin resistance in rats by giving them dexamethasone, and after only 7 days of intervention, they found that creatine supplementation aggravated the dexamethasone-induced insulin resistance. The authors attributed the discrepancy regarding the effects of creatine on glucose metabolism to species-specific responses to creatine supplementation. In fact, Tarnopolsky and colleagues (Tarnopolsky et al. 2003) showed that creatine could induce hepatitis in mice, but not in rats, suggesting that creatine may promote different responses even in species closely related. These findings suggest that caution should be exercised in any extrapolation from animal data to humans in creatine investigations. Thus, although not all of the studies had positive results, this may have been due to their methodological approaches; creatine supplementation, in general, was able to improve glucose metabolism in animals experiencing insulin resistance.

Two (Souza et al. 2006; Araújo et al. 2013) out of four animal studies (Souza et al. 2006; Freire et al. 2008; Vaisy et al. 2011; Araújo et al. 2013) that examined the effects of creatine supplementation combined with exercise training on glucose metabolism demonstrated beneficial outcomes. Freire et al. (2008) and Vaisy et al. (2011) used different supplementation protocols than the other studies (diets supplemented with 2 and 2.5 % creatine, respectively). No influence of creatine supplementation on glucose metabolism was seen in these studies (Freire et al. 2008; Vaisy et al. 2011). Both studies had comparable intervention periods, the animals performed similar exercise training (swimming), and the supplementation protocol was similar, suggesting that one of the previous factors mentioned explains the lack of glucose metabolism improvement. Previous studies (Brannon et al. 1997; McMillen et al. 2001) that have supplemented animals with a diet containing 2 % creatine have showed a significant increase in creatine and phosphocreatine muscle content; however, Freire et al. (2008) did not measure these parameters and Vaisy et al. (2011) did not find a significant difference in these contents. Therefore, it is possible that the supplementation protocol used in these studies was not able to cause changes in the muscles and thus on glucose metabolism, despite the fact that other studies have demonstrated that creatine supplementation generates physiological adaptations (Eijnde et al. 2001; Van Loon et al. 2004). Freire et al. (2008) also submitted the animals to lower intensity exercise training compared with other studies that demonstrated the alterations in muscle glycogen content and, consequently, higher rate of muscle glucose uptake (Ren et al. 1994; Nakatani et al. 1997; Garcia-Roves et al. 2003). Another confounding factor is the cafeteria diet used by Vaisy et al. (2011)

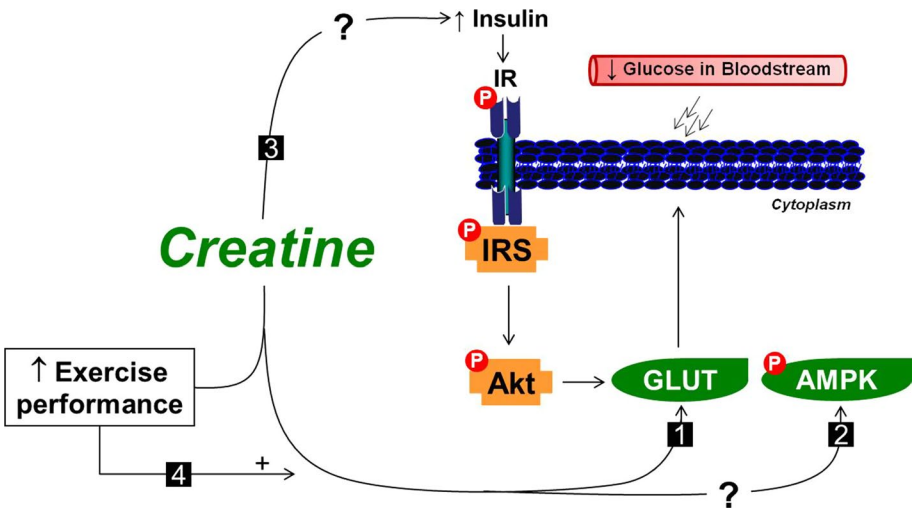

Fig. 2 Main action mechanisms of creatine on glucose homeostasis. Three mechanisms are described: creatine supplementation leads to *1* GLUT translocation to the membrane to use glucose as an energy source, thus reducing the blood glycemia; *2* AMPK stimulation, an energy sensor that induces the modulation of glucose and fatty acids oxidation; and *3* a probable effect on insulin's secreting capacity that increases the blood insulin concentrations that can bind to insulin receptor (IR), which stimulates the insulin receptor substrate (IRS) and activates Akt, leading to GLUT translocation to the plasmatic membrane and attenuation of blood glycemia; *4* maximize exercise performance (ergogenic effect) on GLUT and AMPK, improving insulin sensitivity

which induced a state of glucose intolerance in addition to muscular insulin resistance (Petry et al. 1997; Holemans et al. 2004). Thus, the different stimuli may have generated these disparate results. The other two animal studies, Souza et al. (2006) and Araújo et al. (2013), administered a loading phase followed by a maintenance phase of creatine supplementation over 8 weeks and submitted the animals to high-intensity swimming or treadmill exercise, respectively. Previous studies had already demonstrated the efficacy of this supplementation protocol in different exercise types (Brannon et al. 1997; Tarnopolsky et al. 2003; Op't Eijnde et al. 2001). These interventions were able to improve glucose metabolism. Thus, depending on the supplementation protocol and exercise training used, creatine supplementation was able to improve glucose metabolism in healthy and active animals with a potentially synergistic effect when both interventions were used.

The last four rodent studies enrolled in this systematic review assessed healthy animals, and the intervention consisted of creatine supplementation alone (Eijnde et al. 2001; Young and Young 2002; Rooney et al. 2002; Ju et al. 2005). Eijnde et al. (2001) and Young and Young (2002) did not find a difference in glucose metabolism between the control and supplemented groups either after 5 days of 5 g of creatine/kg of body weight per day or after 300 mg/kg of body weight per day over 5 weeks. Although the authors had different supplement amounts and intervention periods, Eijnde et al. (2001) showed increased creatine content in slow-twitch soleus muscle and Young and Young (2002) in fast-twitch muscle. Despite reaching different types of muscle fibers, glucose uptake was not improved, suggesting that the increase in creatine content in the muscle was not the main factor in producing effects on glucose metabolism. Although Rooney et al. (2002) found an increase in muscle creatine content, they did not find an association between this parameter and the improvement in glucose metabolism after 4 and 8 weeks of treatment. Previous studies (Alsever et al. 1970; Bolea et al. 1997; Van Loon et al. 2000) have demonstrated that the guanidinium group in creatine produces a structure similar to arginine, a potent insulin secretion stimulator, which explains the altered pancreatic insulin secretion. However, even with this impaired insulin secretion, plasma glucose response was not changed, reinforcing the need for studies to explain the mechanisms, by which glucose metabolism is affected. Ju et al. (2005) recognizing the importance of understanding how glucose metabolism is influenced by creatine supplementation at the molecular level observed that 3 weeks of intervention led to an increase in creatine supplementation-induced GLUT4 expression in the skeletal muscle of rats. Nevertheless, biochemical parameters, such as plasma glucose and insulin levels, were not measured.

Human studies

Stacey 1933 tested the effect of creatine ingestion on glucose concentrations in humans. Since then, only a few well-designed studies have evaluated the effects of creatine on glucose metabolism in humans (Op't Eijnde et al. 2001;

Newman et al. 2003; Derave et al. 2003; Van Loon et al. 2004; Safdar et al. 2008; Gualano et al. 2008, 2011; Alves et al. 2012), as shown in Table 3. All of the trials were placebo-controlled, 1 was single-blind (Newman et al. 2003), 7 were double-blind (Op't Eijnde et al. 2001; Derave et al. 2003; Van Loon et al. 2004; Safdar et al. 2008; Gualano et al. 2008, 2011; Alves et al. 2012), and 7 were randomized (Op't Eijnde et al. 2001; Newman et al. 2003; Van Loon et al. 2004; Safdar et al. 2008; Gualano et al. 2008, 2011; Alves et al. 2012). One trial that enrolled vegetarian individuals was excluded, because this specific population has lower total muscle creatine content and an increased capacity to load creatine into muscle after supplementation, which would lead to a limitation of this review (Watt et al. 2004). Six trials investigated the effects of creatine supplementation in healthy participants (Op't Eijnde et al. 2001; Newman et al. 2003; Derave et al. 2003; Van Loon et al. 2004; Safdar et al. 2008; Gualano et al. 2008) and two in T2DM patients (Gualano et al. 2011; Alves et al. 2012). Six studies (Op't Eijnde et al. 2001; Newman et al. 2003; Derave et al. 2003; Van Loon et al. 2004; Safdar et al. 2008; Gualano et al. 2008) used a creatine supplementation loading phase followed by a maintenance phase, and two studies maintained the same low dosage for the entire experiment (Gualano et al. 2011; Alves et al. 2012). Five trials tested only creatine (Op't Eijnde et al. 2001; Safdar et al. 2008; Gualano et al. 2008, 2011; Alves et al. 2012), 2 trials tested creatine plus glucose (Newman et al. 2003; Van Loon et al. 2004), and 1 creatine and/or protein and amino acids (Derave et al. 2003). Some trials included moderate intensity aerobic training combined with strengthening exercises (Gualano et al. 2008, 2011; Alves et al. 2012) or a rehabilitation program after immobilization (Op't Eijnde et al. 2001; Derave et al. 2003).

The studies that did not submit the participants to exercise failed to improve glucose tolerance and insulin sensitivity based on the oral glucose tolerance test (OGTT) (Newman et al. 2003) and fasting glucose and insulin concentrations (Van Loon et al. 2004), despite an increased muscle creatine content. Although creatine supplementation alone increased muscle glycogen storage by 18 %, the muscle *GLUT4* mRNA and/or GLUT4 protein content, *glycogen synthase-1,* and *glycogenin-1* mRNA expression were not affected (Van Loon et al. 2004). The authors hypothesized that this effect may have been related to a modest insulinotropic creatine capacity, as noted in the experimental study conducted by Rooney et al. (2002). Newman et al. (2003) verified that fasting plasma insulin levels after short-term creatine supplementation tended to increase by approximately 30 %, which was not statistically significant. The different rates of insulin secretion in the trials may be explained by differences in the dosage and duration of the interventions.

Studies on creatine supplementation and exercise training in healthy individuals found additional effects on glucose metabolism outcomes when compared with creatine supplementation alone. In fact, the absence of exercise may explain the null effects of creatine in the studies mentioned above (Newman et al. 2003; Van Loon et al. 2004). When creatine supplementation was combined with exercise training and carbohydrate intake, muscle creatine storage increased and urinary creatine loss decreased (Devries and Phillips 2014). Creatine supplementation attenuated the reduction of GLUT4 protein during muscle disuse (Op't Eijnde et al. 2001) and increased muscle GLUT4 content to higher than baseline levels during subsequent rehabilitation (Op't Eijnde et al. 2001; Derave et al. 2003). Moreover, the area under the glucose curve from the oral glucose tolerance test (OGTT) decreased at the end of the re-training (Derave et al. 2003) and training periods (Gualano et al. 2008) in groups supplemented with creatine plus protein or creatine only. This could be related to either improved pancreatic insulin secretion or to increased peripheral insulin sensitivity. Researchers have suggested that this effect is more likely due to improved peripheral insulin sensitivity rather than to facilitated insulin secretion (Derave et al. 2003; Gualano et al. 2008). One reason is that it is unlikely that the improved glucose tolerance in the creatine plus protein group was caused by the elevation of GLUT4 expression in the experimental leg, because the trained knee extensor muscle group represents only a small part of the total muscle mass and GLUT4 expression was not augmented in the contralateral control leg. There is substantial evidence to indicate that changes in insulin sensitivity can occur independently of changes in skeletal muscle GLUT4 expression (Pedersen et al. 1990). Muscle GLUT4 seems to be associated with total muscle creatine content. After immobilization, Op't Eijnde et al. (2001) showed an increase of 13 % ($p < 0.05$) in total muscle creatine, which was accompanied by a trend in increasing muscle GLUT4 protein (9 %, not statistically significant). In contrast, Derave et al. (2003) did not observe changes in total muscle creatine content and muscle GLUT4 protein content after immobilization. Differences in the total muscle creatine may be associated with the amount of creatine supplemented, which was higher in the studies conducted by Op't Eijnde et al. (2001) and Gualano et al. (2008).

Some studies have suggested that a creatine-mediated increase in muscle GLUT4 protein was associated with increased 5′ adenosine monophosphate-activated protein kinase (AMPK) activity and a decreased phosphocreatine to creatine ratio (Ponticos et al. 1998; Ceddia and Sweeney 2004). However, in both trials (Op't Eijnde et al. 2001; Derave et al. 2003) and in creatine and placebo groups, the phosphocreatine to creatine ratio decreased proportionately during immobilization and remained below the

baseline value during the subsequent rehabilitation period. Thus, evidence of a possible creatine-induced enhancement of AMPK activity was not found in these human studies. Op't Eijnde et al. (2001) speculated that cellular hydration promoted by creatine supplementation acted as an anabolic proliferative signal, activating the mitogen-activated protein kinase (MAPK) signaling cascade. This cascade plays a pivotal role in muscle protein synthesis regulation, which may be involved in GLUT4 synthesis regulation and degradation in muscle cells. Therefore, the increased levels of muscle GLUT4 protein may lead to elevated muscle glycogen content (Op't Eijnde et al. 2001; Derave et al. 2003) and an improvement in postprandial glucose profile (Derave et al. 2003; Gualano et al. 2008). These results corroborated with Safdar et al. (2008) which observed an increase protein kinase B (PKBa/Akt1) and p38MAPK pathway.

Two double-blind, randomized placebo-controlled trials examined the effects of creatine in patients diagnosed with T2DM (Gualano et al. 2011; Alves et al. 2012). In both studies, creatine and placebo groups underwent a moderate intensity aerobic training combined with strengthening exercises. Creatine supplementation decreased HbA1c, the area under the glucose curve, and glycemia at 0, 30, and 60 min, respectively, of a meal tolerance test, and increased GLUT4 translocation (but not total GLUT4 content) when compared to placebo (Gualano et al. 2011). Therefore, creatine supplementation increased muscle GLUT4 content in healthy individuals (Derave et al. 2003; Op't Eijnde et al. 2001) as well as GLUT4 translocation in T2DM patients (Gualano et al. 2011), which is important in the control of insulin resistance. Exercise training was able to resolve impaired GLUT4 translocation in the diabetic patients. Interestingly, this response was further enhanced by creatine supplementation, suggesting that this supplement acts directly on T2DM pathogenesis (Gualano et al. 2011). Similarly, the creatine only group showed improved glycemic control, suggesting that the addition of the supplement might have maximized the effects of exercise on insulin sensitivity. According to Alves and colleagues (Alves et al. 2012), the decreased HbA1c levels and increased GLUT-4 translocation were significantly associated with the increased AMPK-α protein expression. AMPK signaling is activated following a rise in the adenosine monophosphate (AMP) to adenosine triphosphate (ATP) ratio within the cell and responds by adjusting the rates of ATP-consuming and ATP-generating pathways. The signaling cascades initiated by AMPK activation exert effects on glucose and lipid metabolism, gene expression, and protein synthesis. AMPK signaling has been considered as an important mediator of muscle contraction-induced GLUT4 translocation and a target for pharmacological interventions to treat altered glucose homeostasis (Towler and Hardie 2007). As previously mentioned, creatine supplementation may potentially affect AMPK signaling by inducing a decrease in the phosphocreatine to creatine ratio, which would represent a change in the energy state of the muscle cell (Ponticos et al. 1998; Ceddia and Sweeney 2004). In human trials, creatine supplementation in conjunction with exercise training enhanced the favorable effects on glycemic control in healthy and individuals with T2DM. In Fig. 2, we summarize the main physiological and molecular mechanisms, by which creatine supplementation positively effects glucose homeostasis in both rodents and humans.

Conclusion

Based on clinical studies, creatine supplementation, particularly when combined with training, may potentially affect glucose uptake. In addition, creatine can maximize exercise capacity on GLUT and AMPK, improving insulin sensitivity. However, there are a very limited number of clinical interventions testing the effects of creatine supplementation in glucose metabolism precluding the prescription of this dietary supplement as part of the treatment of conditions characterized by insulin resistance. Regarding animal studies, the results were largely divergent confirming that species-specific responses do exist in relation to creatine studies. Given the potential of this intervention as an antiglycemic agent, evidenced by (scant) experimental and clinical data, further studies are needed to better understand the effects and underlying mechanism of creatine supplementation in modulating glycemia.

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Compliance with ethical standards

Conflict of interest We declare that we have no conflicts of interest.

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