PRELIMINARY REPORT

Comparison of antihyperglycemic effects of creatine and metformin in type II diabetic patients

B Rocic PhD[1]
N Bedernjak Bajuk MD[2]
P Rocic PhD[3]
DS Weber PhD[4]
J Boras MD[1]
M Vucic Lovrencic PhD[1]

[1] Vuk Vrhovac University Clinic for Diabetes, Zagreb, Croatia
[2] University Medical Centre Ljubljana, Department for Nuclear Medicine, Ljubljana, Slovenia
Departments of [3]Biochemistry and Molecular Biology and [4]Physiology, University of South Alabama, Mobile, Alabama, USA

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Abstract

Purpose: To compare the antihyperglycemic effects of metformin and creatine in recently detected type II diabetics in a short-term clinical study.
Methods: In a 14 day simmetrically randomized crossover study, recently detected type II diabetics received either creatine (2x3 g/day) or metformin (2x500 mg/day) for five days, followed by two days of washout, followed by crossover to the opposite treatment for the next five days. Fasting and post-prandial (-15, 60, 90, 120, 180 and 240 min) blood glucose, insulin, c-peptide, creatine and lactate were measured every other day for the duration of treatment, and HbA_{1c} only at the begining and at the end of the study.
Results: Both creatine and metformin decreased glucose concentrations to similar levels at all time points vs. basal glucose values [-15, 60, 90, 120, 180, and 240 min]: 11.1±0.75 vs 9.1±0.55[a] vs 8.8±0.59[b], 14.4±0.6 vs 12.9±0.47[a] vs 13.1±0.55[a], 14.8±0.58 vs 13.0±0.46[b] vs 13.3±0.55[a], 14.1±0.6 vs 11.9±0.42[b] vs 12.5±0.51[a], 12.2±0.6 vs 9.6±0.36[c] vs 9.9±0.38[c], and 10.1±0.47 vs 7.8±0.36[c] vs 8.4±0.4[b]; ([a]P<0.05; [b]P<0.01; [c]P<0.001 vs. basal glucose values). Neither treatment altered insulin, c-peptide, or HbA_{1c}. Lactate varied during the day, but never reached the upper level of the safety reference range.
Conclusion: Short-term treatment with creatine and metformin elicits similar glucose lowering effects in recently detected type II diabetics. Further studies are necessary to determine the effect of creatine on long-term glucose and insulin regulation.

Metformin (1,1-dimethylbiguanide) is currently standard therapy for regulation of hyperglycemia in type II diabetes. Phenformin and buformin have been withdrawn from use due to high risk of lactic acidosis.[1,2] Although metformin has not been associated with lactic acidosis in otherwise healthy type II diabetics, it has been associated with acute lactic acidosis in patients with heart failure[3], and compromised pulmonary or renal function[4]. Thus, identification of additional compounds with glucoregulatory properties similar to metformin could be beneficial.

Creatine (methylguanidinoacetic acid) is a structurally closely related guanidine with a prominent role in exercising muscle metabolism.[5] Its effects have been attributed to ATP generation from phosphocreatine in exercising muscle.[6] Importantly, although long-term consequences of high doses of creatine, such as are given as an ergogenic aid, are unknown, lower doses are unlikely to pose any risks.[7] Recent reports indicate multiple physiologic roles of creatine, including a potential role in glucose homeostasis. Creatine increased muscle GLUT-4 protein expression[8], improved oral glucose tolerance[9], and increased glucose-dependent insulin secretion[10] and binding[11]. Apart from our previous study demonstrating the anti-hyperglycemic effect of creatine in type I diabetics[12], no study has investigated its effect on glucose regulation in diabetes.

In the present communication, we compare the effects of short-term creatine vs. metformin treatment on glycemic control in recently detected type II diabetics.

Methods

The study involved 30 recently detected type II diabetics (8 female, 22 male; age 45-64 yr; median 55.8±5.5 yr; BMI 32.0±1.9 kg/m^2, HbA$_{1c}$ level 9.4±2.2%) with previous diagnosis of IGT (months-years), but without anti-diabetic treatment. At initiation of study, patients were given dietary advice and asked to avoid strenuous physical activity, alcohol and smoking. *Inclusion criteria*: Signed informed consent, diagnosis of type II diabetes, fasting glucose 7.8–15.0 mmol/l, BMI 25-35 kg/m^2, absence of clinically relevant diseases. *Exclusion criteria:* Surgery in previous 3 months, alcohol abuse, recent participation in drug trials, and pregnancy. *Withdrawal criteria*: personal reasons, failure to comply, gastrointestinal side-effects, and safety concerns. In this 14 day, simmetrically randomized, open-label crossover study, 15 patients received metformin (2x500 mg, Medis, Ljubljana, Slovenia), and 15 creatine (2x3g, Fluka, Buchs, Switzerland) twice per day for five days (day 3-7), followed by a two day washout period (day 8-9), followed by transfer to the other treatment (day 10-14) (Table 1A). Blood samples were taken every other day

TABLE 1. A. Study design. B. Blood sampling protocol.

A)

	Basal (Lead-in)			Treatment Period 1					Washout		Treatment Period 2				
	N=15 →			metformin →					⊢—⊣		creatine →				
	N=15 →			creatine →					⊢—⊣		metformin →				
Day	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14

▲ randomization (after day 2)

B)

Laboratory parameters	Time (min) -30	-15	0	60	90	120	180	240
Glucose*	vein cannulation	+	therapy/ standard breakfast	+	+	+	+	+
Insulin/C-peptide*		+		+	-	+	-	+
Creatine*		+		+	-	+	-	+
HbA$_{1c}$**		+		-	-	-	-	-

(*) *Samples collected at days: 0 /basal/, 3, 5, 7, and 10, 12, 14 (Table 1A) at times indicated in Table 1B*
(**) *Samples collected at start and at the end of each treatment*

TABLE 2A. Blood glucose concentrations (mean±S.E.M., mmol/l) before (-15min) and 60,90, 120, 180 and 240 min after a standard meal in Group I (metforim day 3-7, wash-out day 8-9, creatine day 10-14, n=15), Group II (creatine day 3-7, wash-out day 8-9, metforim day 10-14, n=15), and combined results for Group I and II (n=30).

Therapy	Glucose (mean±SEM, mmol/l)					
	-15	60	90	120	180	240
Group I (n=15)						
basal	11.4±0.82	14.8±0.53	14.9±0.49	13.7±0.53	11.6±0.58	9.7±0.36
metformin	10.2±0.58	13.0±0.53	13.9±0.48	12.6±0.46	10.3±0.40	8.4±0.35
creatine	8.8±0.46	12.6±0.49	12.9±0.49	12.1±0.42	9.7±0.33	8.4±0.33
Group II (n=15)						
basal	10.8±0.68	14.0±0.66	14.7±0.66	14.5±0.68	12.8±0.62	10.5±0.57
creatine	8.8±0.55	13.6±0.60	13.8±0.60	12.9±0.58	10.1±0.44	8.4±0.46
metformin	8.0±0.45	11.9±0.42	12.1±0.40	11.1±0.36	8.8±0.31	7.2±0.38
Group I + Group II (n=30)						
basal	11.1±0.75	14.4±0.60	14.8±0.58	14.1±0.60	12.2±0.60	10.1±0.47
creatine	9.1±0.55[a]	12.9±0.47[a]	13.0±0.46[b]	11.9±0.42[b]	9.6±0.36[c]	7.8±0.36[c]
metformin	8.8±0.59[b]	13.1±0.55[a]	13.3±0.55[a]	12.5±0.51[a]	9.9±0.38[c]	8.4±0.40[b]

[a] $P<0.05$; [b] $P<0.01$; [c] $P<0.001$ vs. basal glucose

TABLE 2B. Combined (Group I and II) plasma insulin, c-peptide and creatine concentrations before (-15 min) and 60, 90, 120, 180 and 240 min after a standard meal.

Time (min)/Therapy	-15	60	120	240
	Insulin (mean ± SEM, mU/l)			
basal	21.8±2.61	62.4±5.45	64.9±5.73	32.3±2.92
metformin	20.0±2.15	52.2±4.28	60.4±4.96	26.0±2.41
creatine	19.8±2.150	65.0±5.57	68.7±5.58	27.1±2.57
	C-peptide (mean ± SEM, ng/ml)			
basal	1.85±0.10	2.58±0.18	3.98±0.23	2.66±0.28
metformin	1.86±0.11	2.68±0.22	3.93±0.30	2.83±0.21
creatine	1.82±0.10	2.88±0.20	4.18±0.30	3.09±0.21
	Creatine (mean ± SEM, μmol/l)			
basal	56.6±2.80	72.4±3.49	67.6±3.56	65.2±2.90
metformin	65.6±2.55	79.0±2.99	80.2±3.27	72.6±3.56
creatine	125.0±4.84[a]	526.0±19.7[b]	713.0±25.91[b]	405.0±20.62[b]

[a] $P<0.005$; [b] $P<0.0001$ vs. basal values

for the duration of treatment (Table 1B). The study was conducted in accordance with the Declaration of Helsinki and approved by Institutional Ethics Committees.

Blood glucose was measured with the HemoCue B-glucose Analyzer (HemoCue, Lake Forest, USA), insulin and c-peptide with chemiluminescence and radioimmunoassay, respectively (DPC, Los Angeles, USA; cross-reactivity with proinsulin (5 ng/ml) 10-20%), lactate with a commercial slide test (Eastman Kodak, Rochester, USA), and HbA_{1c} with a turbidimetric immunoassay (Roche, Basel, Switzerland, within and between-run CV were 2.8%, 1.9%, and 1.7% at HbA_{1c} levels of 4.1%, 7.2%, and 12.1%). Creatine was measured according to Cramer et al.[14]

Statistical analysis

Results for all patients (n=30) were averaged according to therapy and compared with basal values (before treatment) at all experimental time-points. Data were analyzed using one-way ANOVA followed by the Newman-Keuls test (MedCalc v.9.4.2.0, Belgium) and are expressed as mean±SEM. $P<0.05$ determined significance.

Results

Decreases in blood glucose levels were observed in response to both creatine and metformin at -15, 60 and 90 min ($P<0.05$), and a more pronounced effect at 180, and 240 minutes ($P<0.01$) post meal consumption (Table 2A). There was no difference between creatine and metformin, except at the 120 min time-point, where creatine was more effective then metformin (Table 2A). Fasting plasma insulin and c-peptide were higher than in normal healthy individuals (insulin median 8.9 mU/l; upper limit 28.4 mU/l; c-peptide median 1.5 ng/ml, upper limit 4 ng/ml) and were not affected by either creatine or metformin (Table 2B). Insulin binding to erythrocyte receptors likewise remained unchanged ($3.68\pm0.27\%_{basal}$ vs. $4.80\pm0.34\%_{endpoint}$ and $4.12\pm0.18\%_{basal}$ $4.86\pm0.41\%_{endpoint}$ for metformin and creatine, respectively). As expected over a 14 day period, HbA_{1c} values remained unchanged (not shown). Likewise, as expected, creatine elevated fasting creatine levels during application, which returned to baseline after the washout period (Table 2B). Plasma lactate varied during the day, but never reached the upper level of the safety reference range (2.5 mmol/l, not shown). No other adverse effects were observed.

Discussion

This is the first direct comparison of the antihyperglycemic effects of metformin and creatine in recently detected type II diabetics. Both creatine and metformin reduced blood glucose with no difference between the two treatments (Table 2). Results are not compromised by the crossover effect, since plasma glucose decreased equally regardless of the substance used as the primary agent. Likewise, since all patients were previously diagnosed with IGT, educated about their condition, given lifestyle and dietary advice, as well as regular medical care, possible lifestyle changes at the onset of our study are unlikely to be a confounding factor. We conclude, that at the dose applied, creatine is as effective as metformin regarding its ability to lower glucose in type II diabetics. Since only a single dose of creatine or metformin, selected based on minimal observed adverse side-effects at initiation of treatment, is used in our study, we can not determine the relative efficacy of creatine vs. metformin.

Neither metformin nor creatine increased plasma insulin. We have previously reported that creatine stimulated insulin secretion in cultured pancreatic **β**-cells.[10] The present findings, that creatine improved glycemic control but did not influence insulin levels, appear to be in opposition to these results. However, the earlier study did not account for a possible key effect of hyperinsulinemia, a hallmark of type II diabetes. Also, metformin has been shown to either restore or decrease insulin secretion[13], but most studies report that metformin does not alter insulin secretion in type II diabetes.[14,15]

The effect of creatine on, as well as the dose required for, effective long-term regulation of glucose levels and insulin secretion in type II diabetes remain to be investigated.

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Correspondence to:

Petra Rocic, Ph.D.
Department of Biochemistry and Molecular Biology
University of South Alabama, College of Medicine
307 N. University Blvd.
Mobile, AL 36688
procic@usouthal.edu