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Does creatine supplementation affect renal function in patients with peripheral artery disease? A randomized, double blind, placebo-controlled, clinical trial

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1 *Original article*

2 **Does creatine supplementation affect renal function in patients with peripheral**
3 **artery disease? A randomized, double blind, placebo-controlled, clinical trial.**

4

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22 **ABSTRACT**

23 **Background:** Case studies and reviews have shown that creatine supplementation can
24 affect kidney function.

25 **Objective:** The objective of this study was to verify the effects of eight weeks of
26 creatine supplementation on renal function (creatinine clearance – primary outcome)
27 in patients with symptomatic peripheral arterial disease.

28 **Methods:** Twenty-nine patients, of both genders, were randomized (1:1) in a double-
29 blind manner for administration of Placebo (PLA, n=15) or creatine monohydrate (Cr,
30 n = 14). The supplementation protocol consisted of 20g/day for one week divided into
31 four equal doses (loading phase), followed by single daily doses of 5g in the
32 subsequent seven weeks (maintenance phase). Before and after the supplementation
33 period, markers of renal function, serum creatinine, creatinine excretion rate, and
34 creatinine clearance were evaluated. The Generalized Estimation Equation Model was
35 used for comparison between groups. The level of significance was $P < 0.05$.

36 **Results:** No significant differences were found between groups before and after the
37 intervention for serum creatinine (Cr - pre 1.00 ± 0.15 ml/dl vs. post 1.07 ± 0.16
38 ml/dl; PLA pre 1.30 ± 0.53 ml/dl vs. post 1.36 ± 0.47 ml/dl, $p = 0.590$), creatinine
39 excretion rate (Cr - pre 81.73 ± 43.80 mg/dl vs. post 102.92 ± 59.57 mg/dl; PLA pre
40 74.37 ± 38.90 mg/dl vs. post 86.22 ± 39.94 mg/dl, $p = 0.560$), or creatinine clearance
41 (Cr pre 108 ± 59 ml.min⁻¹.1.73 m⁻² vs. post 117 ± 52 ml.min⁻¹.1.73 m⁻²; PLA pre $88 \pm$
42 49 ml.min⁻¹.1.73 m⁻² vs. post 82 ± 47 ml.min⁻¹.1.73 m⁻², $p = 0.366$).

43 **Conclusions:** Eight weeks of creatine supplementation is safe and does not
44 compromise the renal function of patients with peripheral arterial disease

45

46 Key words: Peripheral arterial disease; dietary supplements; safety; renal
47 insufficiency.

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48 **INTRODUCTION**

49 Peripheral arterial disease (PAD) affects more than 200 million individuals
50 worldwide¹. In Brazil, PAD affects 10.5% of individuals over 18 years of age and is
51 higher in the age group above 50 years². Patients with symptomatic PAD present a
52 high prevalence of chronic kidney disease³, which has been associated with increased
53 hospitalization and a high mortality risk⁴. The main recommendation for reducing
54 these impacts is to carry out walking⁵. These patients present reduced capacity⁶ and
55 barriers to the practice of physical activity⁷. Therefore, one of the primary therapeutic
56 targets in these patients is improvement in walking capacity^{8,9}.

57 Creatine (Cr) and phosphocreatine are naturally bioenergetic compounds,
58 essential for adenosine triphosphate homeostasis. Previous studies have shown that Cr
59 supplementation improved neuromuscular performance in patients with chronic
60 diseases, including McArdle's disease¹⁰, amyotrophic lateral sclerosis¹¹, and heart
61 failure¹².

62 Despite these positive effects, concerns have been raised regarding the
63 potential adverse effects of Cr supplementation on renal function¹³, given that some
64 case reports describe impairments in renal function after Cr supplementation^{14,15}. For
65 example, Kuehl et al¹⁴ reported impairment in renal function after regular Cr
66 supplementation for 3 months, which was reverted one month after discontinuation of
67 the supplementation. Pritchard and Kalra¹⁵ reported deterioration in renal function
68 after two months of Cr supplementation in a 25-year-old man with a previous history
69 of renal dysfunction.

70 Studies have reported the potential effects of creatine supplementation on
71 functional capacity¹⁶, mainly in improving walking capacity, and increasing the
72 supply of muscle oxygen¹⁷ and microcirculation¹⁸. However, patients with PAD

73 present impaired renal function¹⁹. Therefore, although a potential therapeutic effect
74 might occur in PAD patients, as suggested by a review study²⁰, it is necessary to
75 understand the effects on the renal function of these patients, who usually present
76 comorbidities. In fact, investigating the safety of this supplement will contribute to
77 future studies related to improvement in functional capacity in PAD patients. Our
78 hypothesis was that creatine supplementation would not affect renal function. Thus, in
79 the present study we report the effects of eight weeks of oral Cr supplementation on
80 renal function (creatinine clearance) in symptomatic PAD patients.

81

82 **METHOD**

83 *Experimental design*

84 An 8-week double-blind, placebo-controlled study was conducted from
85 December 2016 to October 2017 in São Paulo, Brazil (registered at clinicaltrials.gov
86 as NCT02993874). This manuscript is reported according to the CONSORT
87 guidelines²¹. The present study is part of a clinical trial aimed primarily at exploring
88 the effects of creatine supplementation on functional capacity (in particular walking
89 capacity) in patients with arterial disease and symptoms of intermittent claudication.

90 Patients were randomly assigned to the experiment, in a 1:1 ratio, in blocks of
91 4-6 considering sex and total walking distance, to receive either Placebo (PLA; n= 15)
92 or Creatine monohydrate (Cr; n= 14) supplementation according to a computer-
93 generated treatment sequence in a double-blind design. The primary outcome was
94 creatinine clearance. Secondary outcomes were serum creatinine and creatinine
95 excretion rate. The control variable was plasma creatine. Participants were assessed at
96 baseline (pre) and after eight weeks (post).

97

98 *Participant recruitment and screening*

99 Patients were recruited from a specialized vascular center. The sample
100 consisted of 29 patients of both sexes (aged 43-84 years) diagnosed with PAD and
101 symptoms of intermittent claudication. The inclusion criteria were: presence of
102 intermittent claudication symptoms during the six-minute walking test, ankle brachial
103 index <0.90 in one or both lower limbs, and absence of chronic renal insufficiency
104 (creatinine clearance <30ml/min). Exclusion criteria were: musculoskeletal disorders
105 that could prevent participation and adverse effects caused by supplementation (i.e.,
106 gastric discomfort or diarrhea). This study was approved by the Ethics Committee of
107 the Hospital Israelita Albert Einstein, Brazil (process 62601416.7.0000.0071). All
108 patients gave informed consent prior to participation.

109 *Creatine supplementation protocol and blinding procedure*

110
111 Patients received plain packages containing placebo (PLA) (dextrose)
112 (Probiotica, Sao Paulo, Brazil) or creatine monohydrate (Cr) supplementation
113 (Creapure, AlzChem Trostberg GmbH, Germany), 20g/day for one week divided into
114 four equal doses (loading phase), followed by single daily doses of 5g for the next
115 seven weeks (maintenance phase). During the loading phase, supplements were
116 presented in four packages and patients were instructed to ingest the supplement
117 packages at breakfast, lunch, dinner, and before bed time. During the maintenance
118 phase, patients consumed the supplement as a single dose with their lunch. The
119 supplement packages were coded so that neither the investigators nor the participants
120 were aware of the contents until completion of the analyses. Quality control and the
121 purity of creatine were guaranteed by the manufacturer. The supplements were

122 provided by a staff member of our research team who did not participate in the data
123 acquisition, analyses, or interpretation (figure 1).

124 ***INSERT FIGURE 1 HERE***

125 *Preliminary assessment*

126

127 Clinical characteristics were obtained during a vascular consultation. Body
128 mass (kg) and stature (m) were measured (Welmy, São Paulo, Brazil) and the body
129 mass index was calculated. The ankle brachial index was calculated by the quotient
130 between ankle systolic and brachial systolic blood pressure. Arm blood pressure was
131 measured using the auscultation technique, while ankle blood pressure (in the dorsalis
132 pedis artery or posterior tibial artery) was measured with a Doppler ultrasound
133 (Martec DV600, Ribeirão Preto, Brazil). An aneroid sphygmomanometer was
134 employed in both measurements, as previously described⁵. A trained experienced
135 assessor performed all measurements.

136

137 *Renal function*

138

139 The markers of renal function, serum creatinine, creatinine excretion rate,
140 and creatinine clearance were analyzed through blood samples collected from the
141 antecubital vein and stored in 10 ml tubes (BD Vacutainer®) containing separator clot
142 (Z Serum separator clot). Urine was collected during a 24-hour period, neglecting the
143 first collection. For measurement of urinary volume, beakers of 500 to 1000 ml were
144 used. Blood and urinary creatinine levels were determined by the Jaffé method
145 without deproteinization²². A blind assessor in a specialized laboratory performed all
146 evaluations. All patients were in a fasted state.

147

148 *Plasma creatine*

149 Adherence to the supplementation was determined in a sub-sample of nine
150 patients through plasma creatine levels, using High Performance Liquid
151 Chromatography (HPLC) (FL SPD-20A Shimadzu®, Kyoto, Japan), as previously
152 described²³.

153

154 *Dietary intake*

155

156 Food intake was assessed by means of a 24-hour food recall performed before
157 and after the intervention period. Protein intake was analyzed by the software
158 (Nutripad 2.0, Brazil). Participants were instructed to maintain their eating habits
159 throughout the study. The water intake was *ad libitum*.

160

161 *Statistical analysis*

162

163 Based on a previous study²⁴, with an effect size of 0.50, $\alpha = 0.05$, and power
164 of 80%, the sample size for detecting a significant interaction was 26 patients (13 per
165 group)(GPower software 3.19). Normality of the data was analyzed by the Shapiro-
166 Wilk test. The comparison between the general characteristics of the sample was
167 performed using the t-test for independent samples or Mann-Whitney U test,
168 depending on data distribution. The categorical data were compared by the Chi-square
169 test. Comparisons between groups at baseline were tested by the Mann-Whitney U
170 test. The Generalized Estimation Equation Model was used to compare adherence,
171 dietary intake, and markers of renal function between groups. All analyzes were

172 performed using SPSS (Statistical Package for Social Sciences), version 21. Statistical
173 significance was defined as $P < 0.05$.

174

175 **RESULTS**

176

177 Initially, 160 patients were interviewed for eligibility in this study; of these
178 118 did not meet the inclusion criteria, 5 refused to participate, and 5 were not
179 included for other reasons such as: difficulty in communication (two subjects),
180 difficulty in traveling because they lived far away (one patient), being involved in
181 another study (two patients). Thirty-two patients started the study, with 17 being
182 allocated in the PLA group and 15 in the Cr group. During the intervention period,
183 three patients were excluded for the following reasons: withdrawal after preliminary
184 examinations due to personal problems ($n = 1$), gastric discomfort ($n = 1$), and pleural
185 effusion ($n = 1$). Twenty-nine patients completed the study (PLA $n = 15$ and Cr
186 $n = 14$)(figure 2).

187 ***INSERT FIGURE 2 HERE***

188 No significant statistical differences were identified in the general
189 characteristics of study participants (Table I).

190 ***INSERT TABLE I HERE***

191 Patients taking Cr presented higher plasma creatine levels than the placebo
192 group (PLA - pre $30.4 (12.2 - 48.6) \mu\text{mol/l}$ vs. post $48.9 (18.5 - 79.2) \mu\text{mol/l}$; Cr - pre
193 $39.3 (11.0 - 67.7) \mu\text{mol/l}$ vs. post $136.0 (93.6 - 178.4) \mu\text{mol/l}$; $P = 0.042$) (figure 3). In
194 addition, both groups demonstrated similar amounts of protein intake before and after
195 the intervention period (PLA - pre $49.7 (32.6 - 66.9) \text{ g}$ vs. post $61.1 (43.4 - 78.9) \text{ g}$;
196 Cr - pre $59.2 (39.2 - 79.3) \text{ g}$ vs. post $52.6 (38.9 - 66.2) \text{ g}$; $P = 0.133$)

197 ***INSERT FIGURE 3 HERE***

198 Figure 4 presents the results of Cr on the general markers of renal function.
199 No significant differences were found between groups for serum creatinine (PLA –
200 pre (1.25 (0.98 – 1.52) mg/dl vs. post 1.29 (1.04 – 1.54) mg/dl; Cr – pre 1.02 (0.89 –
201 1.16) mg/dl vs. post 1.10 (1.01 – 1.19) mg/dl, $P = 0.499$), creatinine excretion rate
202 (PLA – pre 71.7 (52.1 – 91.3) mg/dl vs. post 83.4 (62.2 – 104.5) mg/dl; Cr - pre 74.2
203 (50.2 – 98.4) mg/dl vs. post 100.5 (70.2 – 130.8)mg/dl, $P = 0.387$), or creatinine
204 clearance (PLA – pre 87.2 (62.1 – 112.2) ml.min⁻¹.1.73 m⁻² vs. post82.8 (59.2 –
205 106.4) ml.min⁻¹.1.73 m⁻²; Cr - pre 98.8 (66.8 – 130.9) ml.min⁻¹.1.73 m⁻² vs. post113.4
206 (86.5 – 140.2) ml.min⁻¹.1.73 m⁻², $P = 0.310$). Regarding individual responses to
207 creatine supplementation, changes in general markers of renal function were within
208 the normal range for all patients.

209

210 ***INSERT FIGURE 4 HERE***

211

212 Discussion

213

214 The results of the present study showed that 8 weeks of Cr supplementation,
215 composed of 1 week of loading and 7 weeks of maintenance, did not alter markers of
216 renal function in patients with symptomatic PAD.

217 The results of plasma creatine demonstrated that patients adhered to the Cr
218 supplementation, as the plasma creatine levels increased from 40.5 ml/dl to almost
219 160 ml/dl. These results were similar to Harris²⁵ who also reported increases in
220 muscle creatine to values close to 160 mmol/kg of dry muscle, after a period of Cr

221 supplementation. In addition, both groups presented similar intakes of protein, which
222 was not an intervening factor in our findings.

223 In the present study, creatinine clearance, the gold standard marker of renal
224 function was not altered after Cr supplementation. Similar results were observed in
225 healthy young individuals^{26, 27}, and patients with diabetes^{24, 28}, chronic heart failure^{12,}
226 ²⁹, and kidney disease³⁰. Gualano et al²⁴ performed Cr supplementation in patients
227 with diabetes at doses of 5g for 12 weeks. Additionally, the same group of researchers
228 performed a Cr supplementation protocol in a single kidney patient for 35 days
229 (20g/day for 5 days, followed by 5g/day for the next 30 days)³⁰. These findings
230 demonstrate that regardless of protocol, time, and sample, creatine supplementation
231 does not affect renal function. In addition, the results expand the current knowledge,
232 showing that Cr supplementation is considered safe even in patients at high risk of
233 renal and cardiovascular disease.

234 A key point of the present study is the method of assessing renal function.
235 Other studies with creatine supplementation have used glomerular filtration rate
236 (GFR)^{24, 27} as a marker of renal function. However, GFR has some limitations. One of
237 these is that the equations used to estimate glomerular filtration cannot be generalized
238 to all populations due to variations in muscle mass, age, sex, and ethnicity³¹. Thus,
239 our findings strengthen the knowledge on the safety of creatine supplementation for
240 renal function in PAD patients, as creatinine clearance is considered the gold standard
241 in the evaluation of renal function³².

242 Individual analyzes of renal function markers demonstrated that there was
243 large intra-individual heterogeneity in both groups. It is well established that
244 variability in markers of renal function is a risk factor in the progression of chronic

245 kidney disease and death^{33,34}. A recent study showed that diabetic patients have a 7%
246 higher risk of dialysis/death due to variability in renal function markers³³. It is
247 noteworthy that half of the participants in the present study (Cr 50% and PLA 60%)
248 were diabetic, which is one of the possible factors responsible for the intra-individual
249 heterogeneity. Based on this, our findings suggest that creatine supplementation, in
250 addition to being safe for renal function, may be an important strategy in PAD
251 patients with diabetes, since it promotes potential effects on glucose uptake, reducing
252 the risk of mortality²⁴.

253 From a practical point of view, the results of this study indicate the safety of
254 creatine supplementation for patients with peripheral artery disease. Therefore,
255 interventions based on Cr supplementation can be used in order to improve muscular
256 performance in PAD patients, as occurs in other clinical populations¹⁶ known to
257 present muscle atrophy³⁵, reduced strength³⁶, and walking impairment^{6,37}.

258 The present study has some limitations. Our results are restricted to patients
259 with PAD without chronic renal failure, and whether these results are replicable in
260 patients with PAD with renal impairment, needs to be investigated. Creatine
261 supplementation was performed for 8 weeks, and it is not known if longer periods of
262 Cr supplementation affect markers of renal function. It is worth noting that our
263 findings are restricted to the proposed Cr supplementation protocol (loading and
264 maintenance phase) and cannot be applied for other doses in patients with
265 symptomatic peripheral arterial disease.

266 The patients in the present study were using antihypertensive drugs, which
267 may affect renal responses. However, since the majority of PAD patients are under
268 hypertension drug therapy, our findings increase the practical applicability of the
269 results.

270

271 **Conclusion**

272 Eight weeks of creatine supplementation does not alter markers of renal
273 function in patients with symptomatic PAD.

274

275 **Conflict Interest**

276 The authors declare no conflict of interest with CREAPURE.

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283

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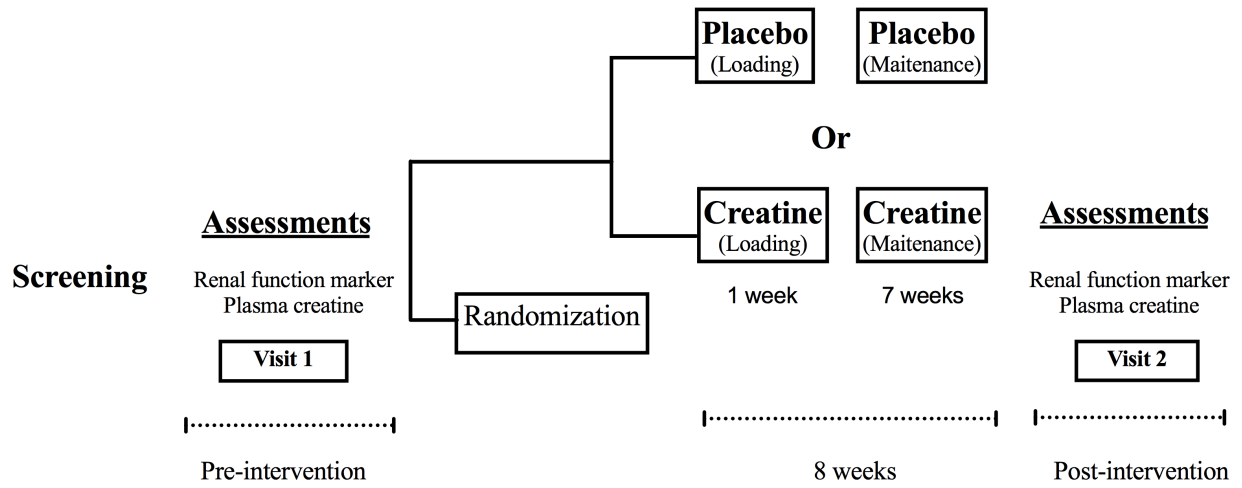
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434 **FIGURE LEGEND**435 **Figure 1.** Study design436 **Figure 2.** Flow diagram437 **Figure 3.** Creatine plasma before and after the supplementation period in a sub-
438 sample (n = 9 – PLA = 5, Cr = 4).439 **Figure 4.** General markers of renal function PLA (n=15); Cr (n=14) and individual
440 PLA (n=12); Cr (n=11) of renal function data: (A) serum creatinine, (B) creatinine
441 excretion rate, and (C) creatinine clearance. Reference value Brazilian Society
442 Cardiology and Nephrology³⁸: dashed line.

443

	PLA (N=15)	Cr (N= 14)	p-value
Women (%) ^a	54	46	0.56
Age (years) ^a	64 ± 8	64 ± 10	0.54
Weight (kg) ^a	77 ± 10	68 ± 17	0.18
Height (m) ^a	1.64 ± 0.09	1,60 ± 0.06	0.21
Body mass index (kg/m ²) ^a	28.7 ± 3.1	26.7 ± 6.5	0.43
Ankle-brachial index (mmHg) ^a	0.50 ± 0.13	0.51 ± 0.16	1.00
Claudication onset distance (m) ^a	143 ± 84	143 ± 65	0.88
Total waking distance (m) ^a	371 ± 81	344 ± 82	0.65
Serum creatinine (mg/dl) ^b	1.25 ± 0.5	1.02 ± 0.2	0.23
Creatinine excretion rate (mg/dl) ^b	71.7 ± 35.4	74.2 ± 41.7	0.78
Creatinine clearance (ml.min ⁻¹ 1.73m ⁻²) ^b	87.2 ± 45.2	98.8 ± 55.5	0.50
<i>Related comorbidities (%)</i>			
Hypertension ^c	86.7	78.6	0.67
Diabetes ^c	60.0	50.0	0.43
Dyslipidemia ^c	6.7	7.1	0.74
Current smoking ^c	78.6	78.6	0.68
Coronary artery disease ^c	46.7	28.6	0.26

Data are presented as mean and standard deviation for numerical variables and frequency for categorical variables. ^aT-test for independent samples. ^bMann-Whitney U test. ^cChi-square test. PLA – placebo group. Cr – creatine group.



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