Original article

Short-term creatine supplementation may alleviate the malnutrition-inflammation score and lean body mass loss in hemodialysis patients: a pilot randomized placebo-controlled trial

Running title: Creatine supplementation and lean body mass

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Clinical Relevancy Statement

Patients undergoing hemodialysis induces an imbalance between muscle protein synthesis and breakdown, leading to loss of muscle mass and function. This study found that short-term creatine supplementation attenuates the malnutrition-inflammation score and the lean body mass when compared to placebo.

Abstract

Background: Creatine supplementation has been proposed to alleviate muscle loss in various populations, but has not been investigated in hemodialysis (HD) patients. Thus, our objective was to evaluate whether creatine supplementation could attenuate the loss of lean body mass (LBM) and malnutrition-inflammation score (MIS) in HD patients. **Methods**: A randomized, placebo-controlled, double blind, parallel-design study included HD patients, of both sexes, aged 18-59 years. The patients were allocated to a Placebo Group (PG n=15; received maltodextrin, 1st week: 40g/day and 2nd-4th weeks: 10g/day) and a Creatine Group (CG n=15; received creatine plus maltodextrin, 1st week: 20g/day of creatine plus 20g/day of maltodextrin and 2nd-4th weeks: 5g/day of creatine plus 5g/day of maltodextrin).Pre and post the intervention, patients were evaluated for food intake, MIS, body composition and biochemical parameters. **Results**: CG group attenuated the MIS (Pre:5.57±0.72 *vs.* Post:3.85±0.47 score, p=0.003) compared with PG (Pre:5.71±0.97 *vs.* Post:5.36±0.95 score, p=0.317) (supplement x time p=0.017, effect size:0.964). The change of LBM was greater in CG than in PG (CG: Δ 0.95 vs PG: Δ0.13 kg). At post-intervention, 28.6% of PG patients presented LBM loss and 71.4% remain stable. In contrast, 14.4 % of CG patients had LBM loss, 42.8% remain stable and 42.8% gained. Food intake and quality of life did not change. CG increased the BMI and gait speed in post- compared to pre-moment, but no difference among the groups. **Conclusion**: In HD patients, four weeks of creatine supplementation may alleviate the MIS as well as attenuate the LBM loss compared to placebo.

Keywords: creatine, hemodialysis, lean body mass, inflammation.

Background

The malnutrition-inflammatory score (MIS) is commonly associated with morbidity and mortality in chronic kidney disease (CKD) patients undergoing hemodialysis (HD)[1] and non-dialyzed patients [2]. Additionally, a Brazilian study revealed that the MIS is a useful tool to evaluate the protein-energy wasting (PEW) in CKD patients [2]. Considering that PEW is a condition of reduced body protein and energy stores [3]and that reduced lean body mass (LBM) is negatively associated with MIS [4], a new therapeutic strategy to attenuate LBM loss and MIS values may improve the clinical outcome and the quality of life (QoL) of HD patients.

Creatine supplementation has been proposed to alleviate muscle loss in various populations [5]. Kley et al. [6]in a meta-analysis found that creatine supplementation in patients with muscular my opathies was well tolerated and may lead to an increase in muscle strength and LBM. However, the impact of creatine supplementation on LBM, MIS and QoL has not been investigated in HD patients.

Creatine supplementation may enhance muscular phosphor creatine stores and stimulate rapid recovery of adenosine triphosphate levels [7, 8]. In addition, water retention due to Cr-induced reduction in ionic strength may contribute to the gain of body weight, LBM and muscle strength [9]. Considering that creatine supplementation is safe, inexpensive and appears to positively modulate body composition in wasting and dialysis patients [8, 10, 11], we hypothesized that four weeks of creatine monohydrate supplementation would lower the MIS and the LBM loss in HD patients. Thus, our objective was to evaluate whether creatine supplementation could attenuate the loss of LBM and MIS in CKD patients undergoing HD.

Materials and Methods

Design of study

This randomized, placebo controlled and double blind clinical trial was conducted with patients of both sexes diagnosed with CKD undergoing HD, aged between 18 and 59 years. The overall study lasted six weeks, and the intervention with creatine was four weeks.

After inclusion of the patients in the study, they were randomly allocated by gender, age and LBM content. The patients signed the Informed Consent Form approved by the Research Ethics Committee of the Federal University of Goiás, number 1.470.351 and this study is part of a larger trial looking at various interventions that was previous registered in the Brazilian Registry of Clinical Trials under the code RBR-98wzgn.

Recruitment and sample selection

The sample and criteria of inclusion was composed of patients diagnosed with CKD undergoing HD treatment for more than three months at the two hemodialysis out patients' clinics in Goiânia, GO, Brazil. The Gpower® 3.1 software was used to calculate the sample size [12], in which a significance level of 5% with statistical power of 80%, effect size 0.50, two groups and two measurements (LBM and MIS) was considered, so the study population should be12 patients per group.

Exclusion criteria included patients presenting with neurological disease, severe cardiovascular diseases, physical disability (amputations, deep vein thrombosis), and patients who underwent structured physical training three months prior to the date of inclusion in the study or those already taking supplements such as creatine).

Experimental groups

The study was performed with 30 patients divided into two groups randomized by gender, age and LBM content (**Supplementary Figure 1**): 1) Placebo Group (PG): Composed of 15 patients which received maltodextrin, and 2) Creatine Group (CG): Composed of 15 patients which received creatine monohydrate. During the intervention period, one patient in each group was excluded because of non-adherence to the creatine supplementation (90% of the recommended dose was accepted as the limit of adhesion).

The intervention was separated into 3 steps after the randomization and division of the groups (**Figure 1**): 1)during the 1st week of the study, the initial evaluations were performed including food intake assessment; MIS (see below for details); blood tests; anthropometric and body composition (dual energy X-ray absorptiometry); 2) from the 2nd to the 5th week, the intervention with the creatine and the placebo (see below); and 3) during the 6th week of the study, the same parameters were reassessed within 48 hours after the last intake of the creatine and the placebo.

Protocol supplementation

The blinded intervention was performed as described in **Table 1**. The sachets containing either creatine or placebo were standardized in order to avoid any identification of the content by the patients. Creatine loading phase induces an increase rapid intramuscular creatine phosphate, which allows a small intervention period (MCKENNA et al., 2017)[U1]. [M2]Because creatine powder had no taste, whereas maltodextrin had lemon flavor, all doses of creatine contained maltodextrin. Fortunately, the addition of maltodextrin to creatine favours absorption by the gastrointestinal tract and the uptake by muscle tissue[13]. Both creatine and maltodextrin were donated by Maxtitanium®, Supley Laboratório de Alimentos e Suplementos Nutricionais, Matão, SP, Brazil.

Evaluation of food intake

Food intake assessments (24h food recall) were conducted by trained nutritionists at the beginning of the intervention (1st week), during the intervention (3rd week), and at the end of the intervention (last week).The data were calculated in the Dietpro® software (5.8 version, Agromídia Softwares, Viçosa, MG, Brazil), and the macro and micronutrients consumption of the patients were quantified.

Malnutrition-inflammation score (MIS)

MIS is an tool based on Subjective Global Assessment (SGA), which includes three other items, body mass index (BMI), serum albumin concentrations and total iron binding capacity (TIBC) [1, 14, 15]. MIS presents clinical history, physical and biochemical analysis of the patient. The clinical history consists of addressing aspects such as weight reduction in the last six months, changes in dietary intake, presence of gastrointestinal symptoms and functional capacity related to nutritional status. Physical examination includes aspects such as subcutaneous fat loss, muscle loss, the presence of edema resulting from malnutrition and ascites which have been defined as normal, mild, moderate or severe. And biochemical parameters, the albumin and TIBC exams. After completed the clinical, physical and biochemical examinations, the results can range from 1 to 30 and then the classification of the nutritional status was performed. The score $\leq$ 6 presents normality and score> 6 presents classification for malnutrition and high MIS [1, 14, 15].

Anthropometric and body composition assessment

Anthropometric data were collected in the intermediate session of the week of HD (2nd session). Weight and height were evaluated by an anthropometric digital scale (Filizola®) for later calculation of BMI. In addition, arm, calf and thigh circumferences were measured using a flexible tape measure. The data were collected in duplicate by Nutritionists trained.

The body composition was assessed by dual energy X-ray absorptiometry (DXA) (Lunar DPX NT, GE Medical Systems Lunar®, Madison, USA). In this equipment collected the total fat mass and LBM. This method was chosen because muscle mass is correlated with body size, so to quantify muscle mass, the absolute level of Skeletal Muscle Mass can be adjusted for body size in different ways. Other method, such as bioimpedance only estimates the body composition from studies that performed in DXA (CRUZ-JENTOFT et al., 2019)[M3][U4]

Quality of life

QoL was assessed by Short Form 36 (SF-36) which is a well-documented health-related instrument consisting of 36 questions and divided into eight dimensions: physical functioning, physical role functioning, pain, general health, vitality, social role functioning, emotional role functioning, mental health. The data of this from vary from 0 to 100 (worse to best status) and have been validated in a Brazilian population [16].

Biochemical analysis

The monthly biochemical analysis performed by the clinics (pre and post serum urea, phosphorus, albumin and TIBC) were collected in the patients' medical records before and after the intervention. For the exams not performed periodically, the serum was collected by nursing and stored at -80C for subsequent quantification of serum creatinine by the chemiluminescence method in the Roche® Architect 8000 equipment.

Statistical analysis

The data was deposited in Microsoft *Excel*® and transcribed into the programs Statistical Package of Social Sciences (SPSS) 18.0versionand e R Studio 3.4.3 version. Descriptive statistics (absolute and relative frequencies and standard error of the mean, SEM) were used. The continuous variables were tested for normality by the *Shapiro-Wilk* Test. Chi-square test was used to evaluate categorical variables. Differences in food intake and delta of variables among the PG and CG were tested by Wilcoxon test or Mann-Whitney and Student t test, respectively. To evaluate the interaction between supplements and intervention time, two-way ANOVA test followed post hoc of the Tukey was used. The level of statistical significance was set at 5% ($p < 0.05$).

Results

Baseline characteristics and food intake

The baseline characteristics of the patients are shown in **Table 1**.Both groups were similar for sex, age, BMI and previous comorbidities (**Table 2**), and food intake (**Table 3**).

Malnutrition-inflammation score (MIS)

The MIS showed a significant reduction in CG (Δ: -1.71) compared to PG (Δ: -0.36) ($p= 0.01$, with high effect size) (**Table 4**).

Anthropometry and body composition

Although no difference among the groups was observed ($p= 0.43$), both enhanced the body weight (PG Δ: 0.51 kg vs. CG Δ: 0.77 kg) and the BMI in post compared to pre moment. In addition, no change in arm, thigh and calf circumferences was found between the

groups (p>0.05) (**Table 4**). In contrast, the gait speed was higher in the CG (Δ: 0.05 m/sec) than PG (Δ: -0.03 m/sec), with high effect size, but no difference among the groups.

LBM was higher in CG (Δ: 0.95 kg) than in (Δ: 0.13 kg) (ANOVA supplement x time p= 0.03 and high effect size) and higher fat body mass in PG (Δ: 0.39 kg) than in CG (Δ: -0.17) (ANOVA supplement x time p= 0.02 and high effect size) (**Table 4**). Additionally, 28.6% and 71.4% of patients of PG presented in end of intervention a LBM loss and remain stable, respectively (**Figure 2A**). In contrast, in the CG 14.4% of patients LBM loss, 42.8% remain stable and 42.8% gained (**Figure 2B**). Moreover, CG presented in the end of study a reduction of delta mean fat body mass (p = 0.011, **Figure 3A**) and increase of delta mean LBM (p = 0.011, **Figure 3B**).

Biochemical analysis

Although the serum creatinine concentrations were increased in CG (Δ: 1.90 mg/dL) compared to PG (Δ: -0.82 mg/dL) (ANOVA supplement x time p= 0.001 and high effect size), serum urea pre- and post-hemodialysis concentrations and phosphorus did not alter with the treatment (p> 0.05) (**Table 4**).

Quality of life

QoL did not change in any of the eight domains assessed (**Supplementary Table 1**).

Discussion

The present study is the first to investigate the effects of 4 weeks of creatine supplementation in patients undergoing HD. We showed that supplementation was able to alleviate the MIS and LBM loss. In addition, 43% of the CG patients gained LBM where no gain was seen in patients administered the placebo. These results corroborate with the meta-

249 analysis of Candow et al. 2014 [17], who suggests that creatine supplementation may lead to
250 physiological benefits and improved body composition across various populations.

251 Regarding MIS, there was a significant reduction in CG after the intervention. Of
252 note, three patients previously classified as malnourished improved to normal values. MIS is
253 an important predictor of mortality among CKD patients on HD [15]. Likewise, a Brazilian
254 observational retrospective cohort study conducted with 171 patients revealed that the
255 instrument has 53% sensitivity and 82% specificity for mortality in patients with more than
256 24 months on HD treatment. Thus, we can observe the importance of reducing the number of
257 previously malnourished patients, and we can infer that the reduction in the score in the group
258 supplemented with creatine likely decreases the chances of death [18].

259 In the CG, there was a significant increase in body weight, BMI, gait speed and
260 LBM. These findings corroborate with Johnston et al. 2008 study, who observed that when
261 immobilizing the arm of healthy young and supplementing them with creatine, there was a
262 preservation of lean arm mass (+ 0.9%) observed by DXA whereas in the placebo group there
263 was a reduction (-3.7%) [19]. Likewise, previous studies showed that creatine
264 supplementation leads to enhanced LBM as well as body weight in young and older adults
265 [20, 21]. Similar to our study, Gotshalk et al 2008 [22] showed in older adults and elderly
266 patients that 7 days of creatine supplementation was able to increase body mass and LBM,
267 (likely, in part due to water retention) as well as to improve the time in gait test. Thus, these
268 data reinforce the initial hypothesis that short-term creatine supplementation can raise the
269 LBM and improve muscle function in older people [21] and also in adults with chronic
270 disease, as observed in the present study.

271 Regarding biochemical analyses, there was a significant increase in serum creatinine
272 concentrations in CG when compared to PG. The elevated serum creatinine levels are related
273 to the fact that approximately 2% of daily creatine is converted into the cyclic degradation

product and can leave the cells through the permeable cell membrane and enter the bloodstream without provoking toxic effects on the body[11]. Additionally, low serum creatinine concentrations (<10[6-10] md/dL), which is a good marker of nutritional status in HD patients is associated with increased mortality and reduced muscle mass [23, 24], thus we should study how poor dietary consumption impairs the loss of LBM.

According to Wallimann et al. 2017 [11], intradialytic creatine supplementation is safe and may improve the QoL of HD patients; however, in the present study, we did not observe alteration in any domains of SF-36 questionnaire. We believe the present study may encourage further research with creatine supplementation in CKD patients on HD, as we observed that creatine generated clinically relevant results, with good compliance by the patients, with no complaints of ingestion difficulties or side effects.

The present study presented positive points: 1) the use of DXA to evaluate the body composition, once it allows greater veracity in the results; 2) food intake and protein intake assessment, since we can affirm that attenuation of LBM and MIS loss were independent of food consumption, once no changes from the beginning to the end of the study were found. The main limitationof the study is: 1) we did not evaluate the hydration status which may have altered the mount of measured LBM that could be accounted for by the accumulation of intra-muscular water; 2) no physical activity test was applied.

Conclusion

In HD patients, four weeks of creatine supplementation may alleviate the MIS as well as attenuate the LBM loss compared to placebo. However, more studies are needed in the area with creatine supplementation related to muscle mass and quality of life.[M5]

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Conflict of interest statements

All authors declare no conflict of interest

Author contributions

ACBM and GDP wrote the manuscript. ACBM and RDM participated in collection of data. ACBM, ATV, JFM, BTW, CP, AL and GDP participated of analysis and interpretations of data. ACBM and GDP participated of conception and design of the. All authors read and approved the final manuscript. All authors contributed to the revision and approved the final version of manuscript.

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381 **Figures**

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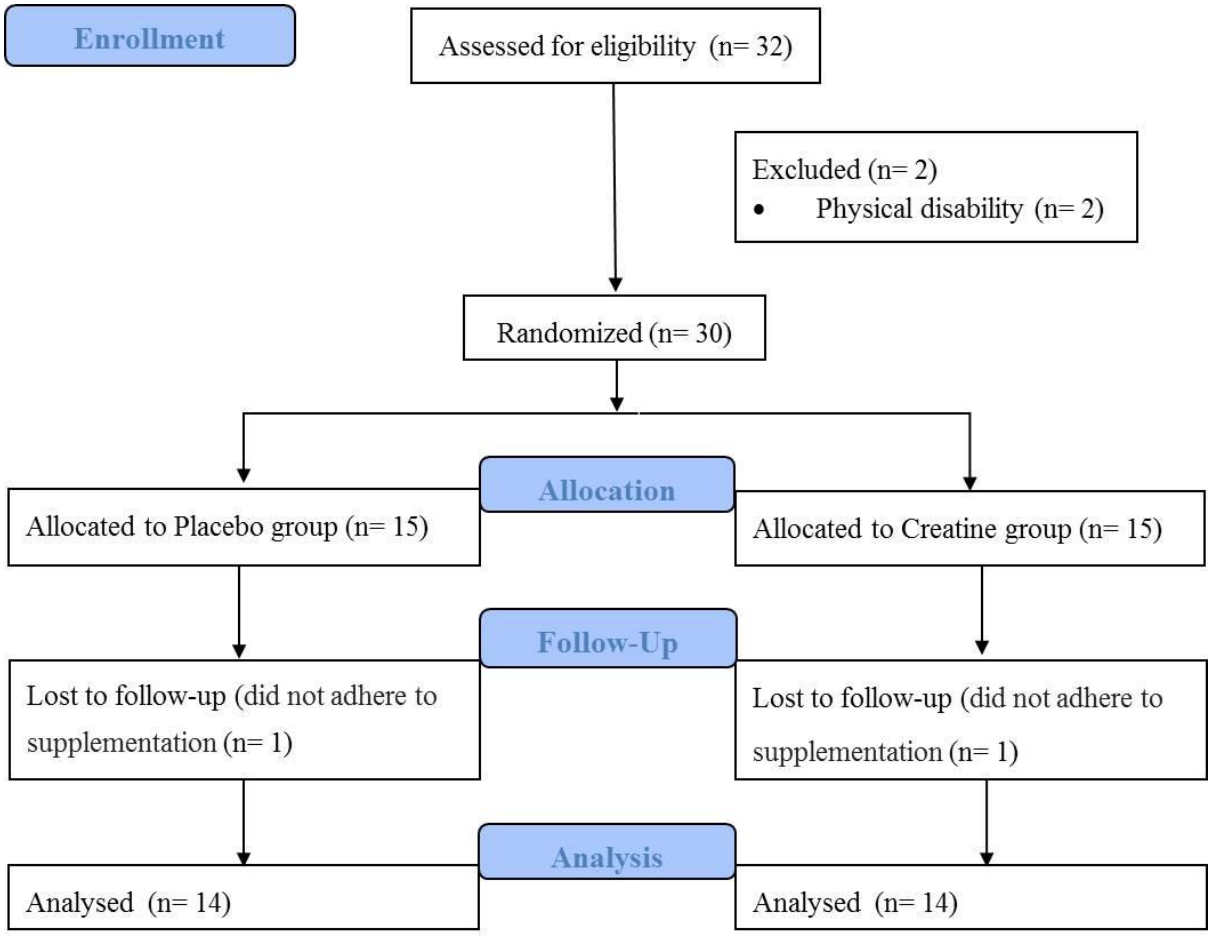

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386 **Figure 1.**Study design.

387 1ª stage: Evaluations (1ªwk); 2ª stage: Intervention (2ª to 5ª wk) and 3ª stage: Revaluations

388 (6ª wk).

389 LBM: lean body mass; MIS: malnutrition-inflammation score.

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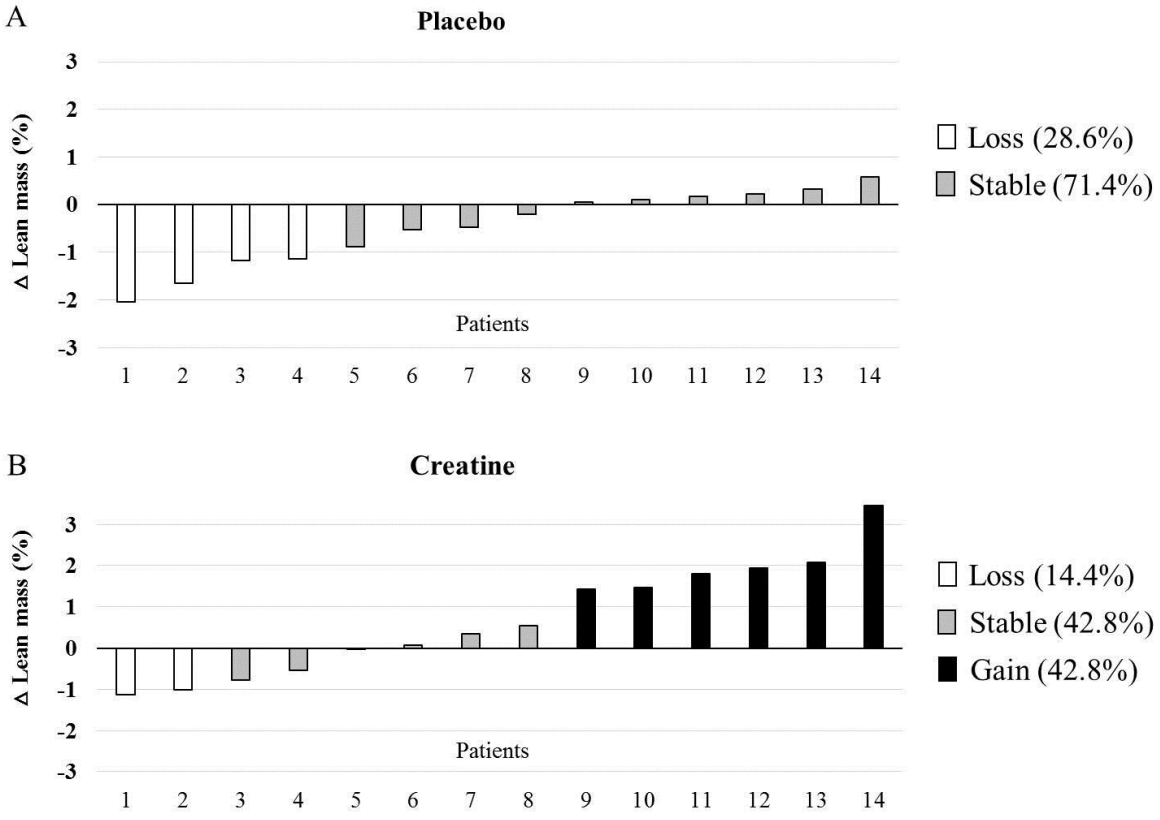

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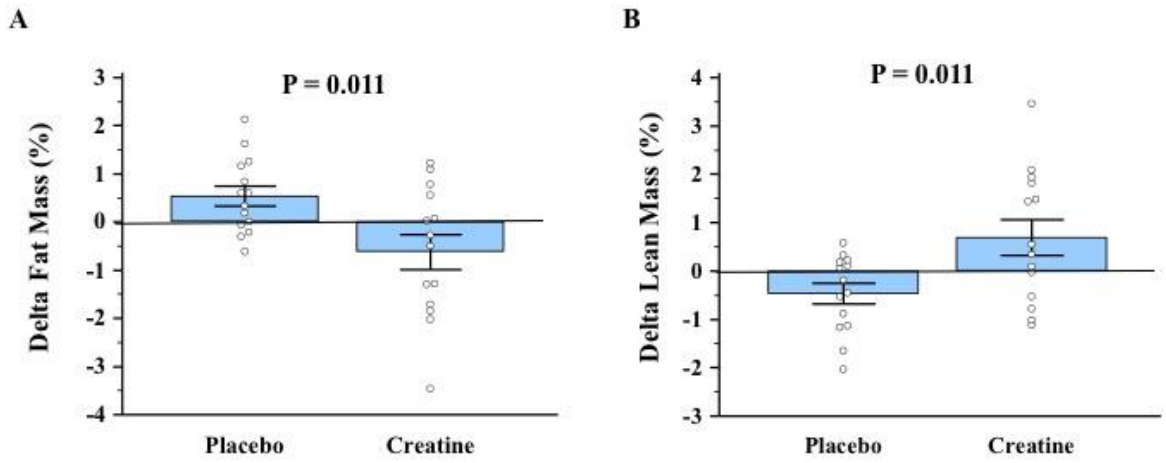
393 **Figure 2.**Delta of individual change in lean body mass (%).



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395 **Figure 3.**Delta of % change in body fat mass (A) and in lean body mass (B) measured by
396 dual X-ray absorptiometry in the treated and control groups.

Table 1. Blindedinterventionprotocol.

Groups	**1st week (loading phase)**		**2-4th week**	
	four times in day*	total in day	only one time in day#	total in day
Placebo (maltodextrin)	10g	40g	10g	10g
Creatine (maltodextrin + creatine)	5g (creatine) + 5g (malto)	20g + 20g	5g (creatine) + 5g (malto)	5g + 5g[M6]

*Breakfast, lunch, snack and dinner; #Lunch or dinner; Maltodextrin with lemon flavor.

399 **Table2.** Baseline characteristics.

Variables	Placebo (n=14) Mean ± SEM	Creatine(n=14) Mean ±SEM	p
Sex (n)[#]			
Female	5	4	0.68
Male	9	10	
Age (years)	41.79±2.72	41.86±3.32	0.98
Body mass index(kg/m²)	21.93±1.28	22.76 ± 1.41	0.60
Comorbities (n)[#]			
Hypertension	10	6	0.15
Diabetes	1	1	
Hypertension + Diabetes	0	1	
Glomerulonephritis	2	0	
Others	1	3	
Unknown	0	3	

400 #Chi-square.

401 **Table 3.**Food intake among the groups.

Variables	Placebo(n=14) Mean±SEM	Creatine(n=14) Mean±SEM	p
Energy (kcal)	1629.57±265.52	1553.46±157.42	0.80
Carbohydrate (g)	180.35±26.93	177.91±21.54	0.94
Total fat (g)	66.90±12.21	64.67±6.64	0.57
Monounsaturated fat (g)	18.64±2.35	18.30±2.30	0.80
Polyunsaturated fat (g)	15.81±2.21	15.21±1.81	1.00
Saturated fat (g)	16.16±2.25	16.17±2.26	0.98
Cholesterol (mg)	255.75±74.67	272.12±36.83	0.21
Protein (g)	76.47±14.27	65.96±8.17	0.63
Protein (g/kg b.w.)	1.31±0.23	1.14±0.16	0.54
Calcium (mg)	352.75±90.62	367.63±65.16	0.37
Iron (mg)	8.26±1.15	6.85±0.70	0.35
Phosphorus (mg)	948.06±184.36	825.70±80.32	1.00
Magnesium (mg)	177.82±22.17	168.30±20.57	0.70
Potassium (mg)	1880.31±254.44	1847.39±257.60	0.98
Sodium (mg)	3860.10±644.30	3551.40±381.10	0.66
Dietary fiber (g)	16.75±1.96	14.52±1.78	0.35

402 Mann-Whitney test; b.w.: body weight.

Table 4. Comparison of MIS, body composition and biochemical parameters among the groups.

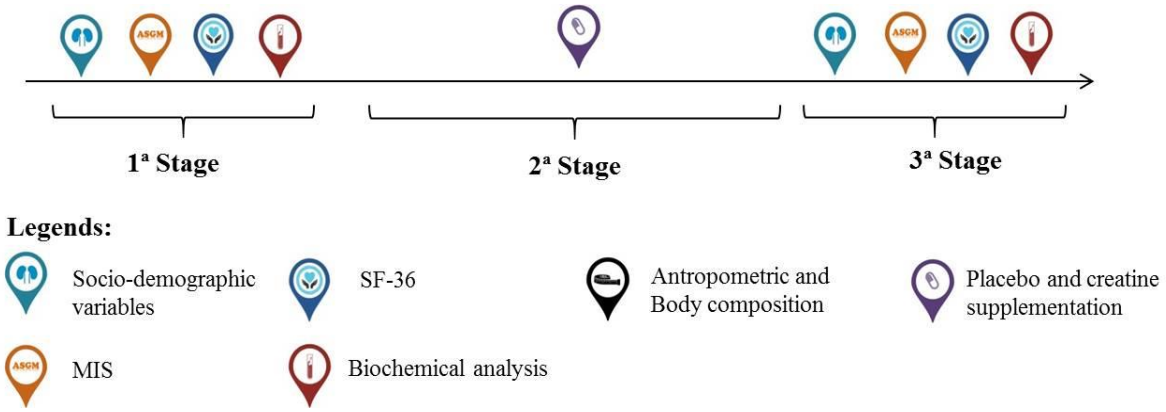
Variables	Placebo (n=14) Mean ± SEM			Creatine (n=14) Mean ± SEM					
	Pre	**Post**	**Δ**	**Pre**	**Post**	**Δ**	**Δ p**	**Effect size**	**ANOVA p**
MIS	5.71±0.97[a]	5.36±0.95 [a]	-0.36±0.39	5.57±0.72 [a]	3.85±0.47 [b]#	-1.71±0.37	**0.01***	**0.964**	**0.01***
Body composition									
Body weight (kg)	58.91±3.67	59.42±3.69#	0.51±0.21	62.07±4.83	62.84±4.81#	0.77±0.24	0.43	0.301	0.43
Body mass index(kg/m²)	21.93±1.28	22.13±1.30	0.19±0.09	22.76±1.41	23.04±1.39#	0.27±0.08	0.52	0.245	0.33
Arm circumference (cm)	27.68±1.16	27.81±1.13	0.12±0.23	28.59±1.60	28.38±1.35	-0.20±0.71	0.65	0.160	0.66
Thigh circumference(cm)	45.46±1.86	45.30±1.76	-0.15±0.58	45.61±1.94	45.96±1.93	0.35±0.14	0.41	0.312	0.41
Calf circumference(cm)	33.51±1.17	32.55±0.82	-0.96±0.74	33.77±1.42	34.04±1.40	0.27±0.16	0.11	0.608	0.11
Gait speed (m/s)	0.81±0.03	0.78±0.03	-0.03±0.04	0.72±0.03	0.78±0.03#	0.05±0.02	0.09	**0.647**	0.22
Lean body mass (kg)	41.33±2.28 [a]	41.46±2.36 [a]	0.13±0.21	42.96±2.74[b]	43.92±2.71[a]#	0.95±0.30	**0.03***	**0.832**	**0.03***
Fat body mass (kg)	15.23±2.51 [a]	15.63±2.52[b] #	0.39±0.12	16.77±2.93 [b]	16.60±2.95 [b]	-0.17±0.01	**0.02***	**0.903**	**0.02***
Biochemical parameters									
Creatinine (mg/dL)	5.86±0.60 [a]	5.03±0.45 [a]	-0.82±1.94	4.04±0.49 [b]	5.95±0.84 [a]#	1.90±0.76	**0.00***	**1.113**	**0.00***
Urea pre (mg/dL)	136.92±8.05	150.42±11.89	13.50±8.41	133.42±10.76	131.92±8.22	-1.50±7.77	0.20	0.495	0.20
Urea post (mg/dL)	36.79±6.55	30.07±6.76	-6.71±4.21	40.71±7.38	44.86±5.64	4.14±8.16	0.24	0.446	0.24
Phosphorus (mg/dL)	5.32±0.65	5.50±0.89	0.17±0.40	5.71±0.44	5.72±0.46	0.01±0.32	0.76	0.115	0.76

MIS: malnutrition inflammatory score.

* $p<0.05$ was considered as significant;#difference vs pre; a≠b difference in two-way ANOVA followed of post hoc Tukey test.

Supplementary Table 1. Quality of life among the groups.

Domains	Placebo (n=14) Mean ± SEM			Creatine (n=14) Mean ± SEM					
	Pre	Post	Δ	Pre	Post	Δ	Δp	Effect size	ANOVA p
Physical function	75.00±6.54	67.50±13.60	-7.50±16.52	71.78±10.19	75.71±10.34	3.92±2.46	0.94	0.258	0.49
Role limitation physical	42.85±9.95	44.64±19.98	1.78±22.76	42.85±13.97	51.78±14.70	8.92±9.66	0.66	0.109	0.77
Pain	55.35±7.39	57.71±10.40	2.35±12.59	62.14±8.90	65.57±8.03	3.42±7.9	0.83	0.027	0.94
General health	49.35±5.15	43.57±8.73	-5.78±11.54	38.71±7.19	40.14±6.14	1.42±4.67	0.91	0.219	0.56
Vitality	53.57±4.23	51.78±8.36	-1.78±9.64	54.28±6.54	60.35±6.51	6.07±3.32	0.73	0.291	0.44
Social function	70.53±5.94	70.53±11.83	0.00±13.55	82.14±7.14	90.17±5.10	8.03±5.17	0.83	0.209	0.58
Emotional function	59.52±12.19	47.61±19.67	-11.90±20.25	47.61±16.65	64.27±15.80	16.66±13.87	0.35	0.439	0.25
Mental health	65.71±6.04	62.28±10.48	-3.42±10.47	69.71±6.47	71.71±4.65	2.00±5.19	0.66	0.175	0.64



Supplementary Figure 1. Participant flowchart (CONSORT).