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Long-term creatine supplementation is safe in aged patients with Parkinson disease

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Abstract

The food supplement creatine (Cr) is widely used by athletes as a natural ergogenic compound. It has also been increasingly tested in neurodegenerative diseases as a potential neuroprotective agent. Weight gain is the most common side effect of Cr, but sporadic reports about the impairment of renal function cause the most concerns with regard to its long-term use. Data from randomized controlled trials on renal function in Cr-supplemented patients are scarce and apply mainly to healthy young athletes. We systematically evaluated potential side effects of Cr with a special focus on renal function in aged patients with Parkinson disease as well as its current use in clinical medical research. Sixty patients with Parkinson disease received either oral Cr (n = 40) or placebo (n = 20) with a dose of 4g/d for a period of 2 years. Possible side effects as indicated by a broad range of laboratory blood and urine tests were evaluated during 6 follow-up study visits. Overall, Cr was well tolerated. Main side effects were gastrointestinal complaints. Although serum creatinine levels increased in Cr patients because of the degradation of Cr, all other markers of tubular or glomerular renal function, especially cystatin C, remained normal, indicating unaltered kidney function. The data in this trial provide a thorough analysis and give a detailed overview about the safety profile of Cr in older age patients.

Keywords: Creatine; Renal function; Cystatin C; Neurodegeneration; Parkinson disease; Human
Abbreviations: α(1)M, α(1)-microglobulin; AlbU, albumin in urine; ALS, amyotrophic lateral sclerosis; β(2)M, β(2)-microglobulin; CK, creatine kinase; Cr, creatine; Crn, creatinine; CysC, cystatin C; GFR, glomerular filtration rate; HD, Huntington disease; MANOVA, multivariate analysis of variance; OTC, over-the-counter; PCr, phosphorylcreatine; PD, Parkinson disease; RCT, randomized controlled trial; UPDRS, Unified Parkinson Disease Rating Scale.

1. Introduction

The food supplement creatine (Cr) is a natural guanidine compound that plays a pivotal role in the regulation of cellular energy metabolism. The creatine kinase (CK) reaction promotes the transfer of the γ-phosphate group of adenosine triphosphate to the guanidino group of Cr to yield adenosine diphosphate and high-energy phosphorylcreatine (PCr). The CK/Cr/PCr system serves as an energy buffer by connecting the mitochondrial sites of energy production with cytosolic sites of energy consumption in tissues with high energy demand such as brain and muscle (for review see [1,2]).

Currently, Cr is widely used as an ergogenic nutritional supplement by athletes, and it is well tolerated in this population. It has been estimated that more than one third of college athletes regularly use Cr to improve muscular performance [3].

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In vitro and in vivo studies indicate neuroprotective effects of Cr in several animal models of neurodegenerative or acute neurologic diseases such as Huntington disease (HD), Parkinson disease (PD), amyotrophic lateral sclerosis (ALS), or ischemic stroke (for review [4]). In addition, we have recently shown in aged mice that long-term Cr supplementation results in prolonged lifespan, better performance on memory tasks, and a decreased accumulation of the age-related pigment lipofuscin in the hippocampus [5].

Based on these encouraging results in rodents, Cr is now being tested increasingly in human neurodegenerative disease such as HD, PD, and ALS [6-10]. These studies implicate the possible benefits of long-term administration of Cr to aged individuals with significant comorbidity rather than to healthy young athletes. The widespread use of Cr therefore warrants the acquisition of adequate knowledge about associated side effects and health risks.

The only consistently reported side effect of Cr is weight gain [11,12]. Yet there have been some safety concerns regarding an adverse effect of Cr on renal function. These concerns were based on 2 case reports implicating Cr as the cause of renal dysfunction in 2 males, aged 20 and 25 years [13,14]. One of these patients had a preexisting nephrotic syndrome before taking Cr. Recently, there was an additional report about a young healthy athlete who developed a reversible intersititial nephritis after consuming Cr in combination with other bodybuilding-related substances [15].

Randomized controlled trials (RCT) systematically investigating the side effects and health hazards associated with long-term Cr intake are scarce and focus only on healthy young athletes. From these studies, it was concluded that Cr has no negative impact on renal or hepatic function [16-21].

Creatine is an emerging nutritional supplement not only in young athletes but also in aged patients with neurodegenerative disease and comorbidity. Thus far, Cr safety data are lacking for the latter patient group. We conducted an RCT in aged individuals with PD to test the hypothesis that long-term Cr supplementation does not lead to severe side effects and renal dysfunction in a study population not consisting of healthy young athletes. The data provided by this trial will help research and patient care in evaluating risks associated with long-term Cr intake in aged individuals.

2. Methods and materials

2.1. Patients

The study protocol was approved by the local ethics committee of the University of Munich (Munich, Germany). After giving informed consent, 60 patients with early PD were enrolled at a university hospital clinic for movement disorders between October 2000 and May 2003. Patient flow is outlined in Fig. 1, and demographic data are given in Table 1. Exclusion criteria were younger than 45 years, known renal disease, prestudy use of Cr, and PD severity more than 2.5 on the Unified Parkinson Disease Rating Scale (UPDRS).

2.2. Intervention and study protocol

Patients received either oral Cr (n = 40; Creapure, SKW Trostberg, Trostberg, Germany) or a placebo (n = 20) in a blinded fashion at a loading dose of 20 g daily for 6 days, followed by 2 g daily for 6 months, and 4 g daily for the remainder of the study. Comparable dosage regimens lead to an increase in total brain Cr concentration of 8% to 10% [22]. Patients were advised to dissolve the Cr powder in cold water or preferably juice and to avoid simultaneous consumption of caffeine. Study visits were performed in the mornings (9-11 AM) at baseline and after 1, 3, 6, 12, 18, and 24 months. At each visit, patients completed questionnaires on possible adverse effects of Cr. A physical examination was performed, patients were weighed, and blood and urine samples were collected and analyzed in the hospital central laboratory on the same day. Blood tests in serum (reference range in square brackets) comprised sodium [135-145 mmol/L], potassium [3.5-5.0 mmol/L], creatinine (Crn) [71-115 μmol/L in male, 53-106 μmol/L in female], urea [2.9-17.8 mmol/L], bilirubin [<17.1 μmol/L], alkaline phosphatase [<135 U/L], γ-glutamyltransferase [<55 U/L in male; < 38 U/L], alanine aminotransferase [<45 U/L in male; <35 U/L in female], aspartate aminotransferase [<40 U/L in male; <33 U/L in female], cholinesterase [5.0-13.3 kU/L], CK [<180 U/L in male; <155 U/L in female], albumin [530-758 μmol/L], white blood count [4-11 $\times$ 10^6/L], red blood cell count [4.5-6.3 $\times$ 10^{12}/L in male; 4.2-5.1 10^{12}/L in female], hemoglobin [8.48-10.91 mmol/L in male; 7.27-9.7 mmol/L in female], hematocrit [0.38-0.52 in male; 0.36-0.46 in female], platelets [150-440 $\times$ 10^9/L], cystatin C (CysC) [0.57-0.96 mg/L in male; 0.5-0.96 mg/L in female], and β(2)-microglobulin (β(2)M) [0.8-2.6 mg/L]. Urinary tests consisted of a test strip analysis, an analysis of urinary sediment, as well as the quantification of creatinine [g/L], total protein content [g/L], albumin (AlbU) [<0.03 g/L], and α(1)-microglobulin (α(1)M) [<0.012 g/L].

For statistical analysis of renal function tests, we defined 5 different categories based on pathologic laboratory findings occurring after the start of the trial: (I) *New tubular damage* is defined as elevated α(1)M levels; (II) *New impairment of glomerular filtration rate* (GFR) is defined as elevated CysC; (III) *New microalbuminuria* is defined as AlbU levels between 0.03 and 0.2 g/L; (IV) *New hematuria* is defined as a positive finding of erythrocytes in the urine; (V) *New renal damage* is defined as the presence of either one of categories I to IV or elevated serum levels of β(2)M.

2.3. Literature search

A Pubmed literature search with the syntax “Creatine [in title] AND (clinical trial OR RCT)” and limiting publication

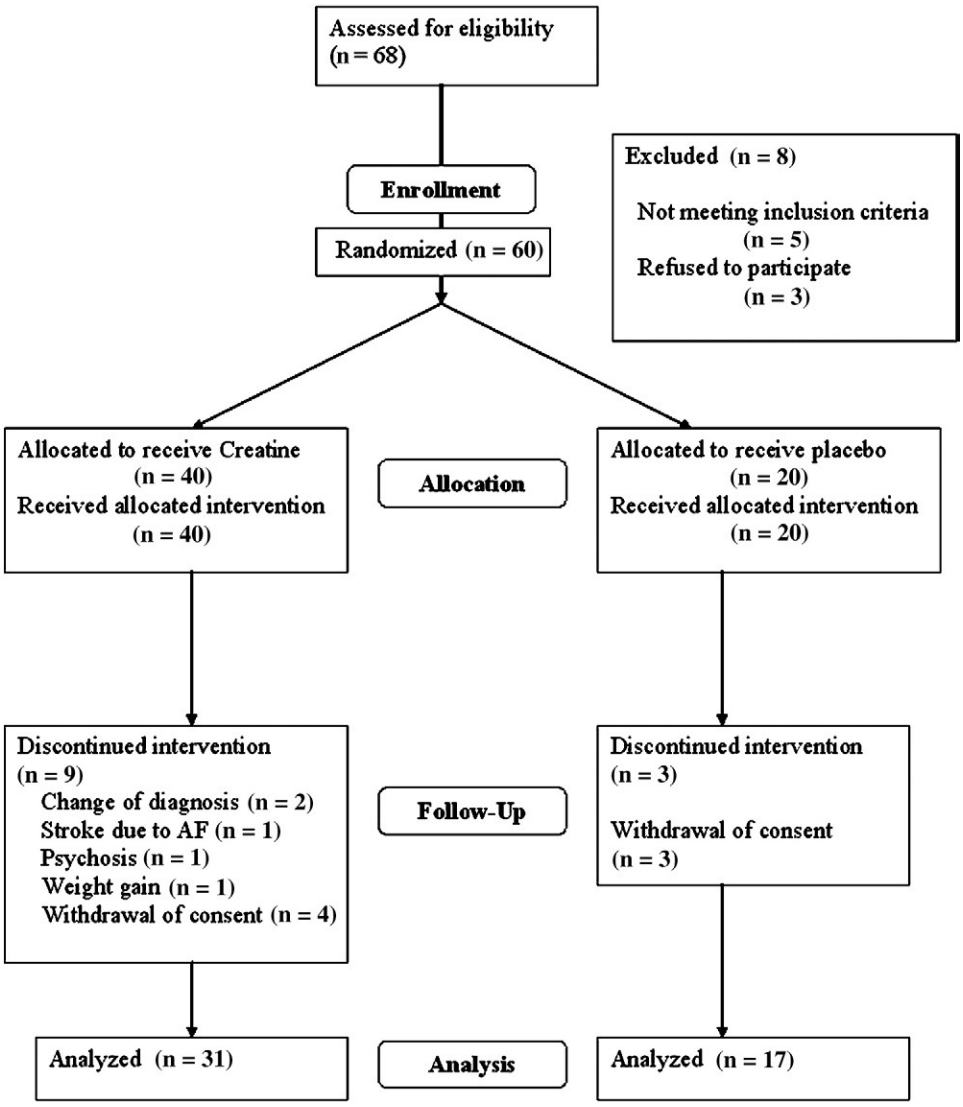

Fig. 1. Patient flow chart.

date to 2000 to 2005 was performed to identify RCTs on the use of Cr. To be eligible for analysis, trials had to fulfill the following criteria: state the number of patients and controls, state the duration of Cr supplementation, state the dosage of Cr, state the indication for the trial, and state the results. Trials were divided into 3 categories: therapeutical, ergogenic, and basic research trials. The latter refers to trials where Cr was given to test its pharmacodynamics or its influence on immunologic parameters.

2.4. Statistical analysis

All statistical analyses were performed with the SPSS 12.0 software package (SPSS Inc, Chicago, Ill). For each visit, frequencies of adverse events were compared by Fisher exact test. A multivariate analysis of variance (MANOVA) repeated measure design was applied to test for significant group and time effects on quantitative scale variables, followed by univariate F tests if applicable. As the group sizes were unequal, the MANOVA was corrected for unequal sample sizes in SPSS. The level of significance was defined as $P < .05$.

3. Results

Results of the literature review on the use of Cr in medical research are given in Table 2. A total of 2064 patients were treated in 136 RCTs between 2000 and 2005 alone. Positive

Table 1
Demographics and baseline characteristics

	Cr	Placebo
Age (y)	60.0 (9.4)	58.7 (11.3)
Female patients	12	5
Male patients	28	15
Disease duration (y)	2.5 (1.4)	2.1 (2.0)

Values given as means ± SD for patients treated with Cr (n = 40) or placebo (n = 20).

Table 2
Summary of RCTs with Cr between 2000 and 2005

	Therapeutic trial	Ergogenic trial	Basic research trial	Total
No. of trials	32	71	33	136
No. of patients	811	796	457	2064
Age ± SD (y)	41.3 (24.0)	32.6 (15.8)	26.9 (8.9)	32.8 (16.8)
Mean (±SD) Cr dose (g)	8.2 (5.0)	14.5 (7.9)	11.3 (7.7)	12.3 (7.7)
Mean (±SD) duration of RCT (wk)	18.5 (21.7)	2.9 (3.8)	5.6 (7.8)	6.9 (12.7)
Positive effect (%)	40.6	74.6	n/a	n/a

effects were reported in 40.6% of therapeutic trials and in 74.6% of studies with the aim of improving physical performance (ergogenic trials).

After 1 year of therapy, serum Crn levels were significantly higher in the Cr group as compared to the placebo group, but this difference was not sustained between 12 and 24 months (Table 3; Fig. 2). None of the other markers of renal function were significantly increased in the Cr group, and findings suggestive of new renal damage were comparable between groups (Table 4). The CysC levels as a marker for the GFR remained similar between groups (Table 3). Patient age was inversely correlated with CysC levels (Pearson correlation coefficient, $r = -.34$ with $P = .01$).

There was a significant increase in gastrointestinal complaints after 2 years of therapy in the Cr group, whereas symptoms suggestive of new renal dysfunction did not differ between groups (Table 5). There was no significant weight gain in the Cr group (from 77.4 ± 14.7 kg at baseline to 80.6 ± 15 kg after 24 months; $P = .38$).

Dropout rates were statistically not different between groups with 23% in the Cr group and 15% in the placebo group ($P = .73$; for reasons, see Fig. 1).

4. Discussion

Creatine is a widely used ergogenic compound by athletes, and most trials in this population indicate ergogenic effectiveness of Cr. In addition, Cr has been increasingly considered in medical conditions such as neurodegenerative disease, muscle disease, and rehabilitation medicine. Whereas Cr is considered safe in healthy young athletes, little is known about its long-term effects in aged individuals. Yet, this is exactly the group of patients (eg, PD patients as in this study) that will receive Cr as an over-the-counter (OTC) attempt of self-medication, by following advice of their physicians, or in the course of clinical trials. Moreover, it is evident that Cr supplementation has to be given for a long period to be effectively neuroprotective. It is not surprising, therefore, that the only available long-term safety data so far stem from neurodegeneration trials. In an RCT on the effect of 6 months of 5 g Cr in 104 patients with ALS, the investigators reported that neither serious nor nonserious adverse events could be attributed to the study medication. Serum Crn and urea levels remained normal throughout the trial [10]. Another RCT on 175 patients with ALS who took Cr in a dose of

Table 3
Results of blood and urine tests

	Baseline		12 mo		24 mo		P*
	Placebo	Cr	Placebo	Cr	Placebo	Cr	
Sodium	141 (2.3)	140 (2.1)	142 (2.0)	142 (1.6)	141 (2.7)	142 (2.3)	.85
Potassium	4.4 (0.4)	4.3 (0.3)	4.3 (0.2)	4.4 (0.3)	4.4 (0.2)	4.2 (0.3)	.16
Crn	88 (9)	88 (9)	88 (18)**	106 (18)**	97 (18)	97 (18)	.002***
Urea	11 (2.9)	12 (2.9)	10.7 (2.5)	12 (2.9)	11.1 (1.8)	12.1 (2.5)	.95
Bilirubin	12 (9)	10 (7)	10 (5)	12 (9)	12 (7)	12 (10)	.12
AP	81 (26)	75 (16)	75 (24)	72 (14)	79 (34)	79 (22)	.69
gGT	28 (17)	41 (32)	27 (15)	42 (38)	31 (20)	39 (31)	.35
ALT	26 (11)	25 (9)	24 (9)	26 (15)	26 (16)	28 (14)	.61
AST	44 (12)	44 (7)	47 (12)	51 (9)	31 (16)	29 (10)	.45
ChE	9.4 (2.1)	9.2 (2.0)	8.9 (2.1)	8.8 (1.8)	8.3 (2.0)	8.4 (1.8)	.70
CK	80 (54)	97 (53)	102 (80)	129 (60)	95 (59)	156 (135)	.21
WBC	6.5 (1.7)	6.2 (1.4)	6.6 (1.8)	6.4 (1.1)	6.2 (1.6)	6.8 (1.3)	.02***
Hb	9 (0.6)	9 (0.7)	8.7 (0.6)	8.9 (1.3)	8.6 (0.7)	9 (0.6)	.09
Platelets	245 (72)	244 (74)	246 (56)	224 (76)	247 (76)	252 (53)	.42
β(2)M	1.1 (0.6)	1.1 (0.5)	1.2 (0.3)	1.2 (0.3)	1.5 (0.5)	1.3 (0.3)	.26
CysC	0.8 (0.1)	0.8 (0.1)	0.9 (0.2)	0.8 (0.1)	0.9 (0.2)	0.8 (0.1)	.84
CrnU	1.2 (0.6)	1.0 (0.6)	0.9 (0.4)	1.0 (0.6)	1.3 (0.9)	1.1 (0.5)	.17

Values given as means (±SD) in patients treated with Cr (n = 31) or placebo (n = 17); reference range see Patients in the Methods and materials section. AP indicates alkaline phosphatase; gGT, γ-glutamyltransferase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ChE, cholinesterase; WBC, white blood cell count; Hb, hemoglobin; CrnU, creatinine in urine.

* Level of significance as measured by MANOVA repeated measure test.

** $P < .05$ in the post hoc analysis.

*** $P < .05$.

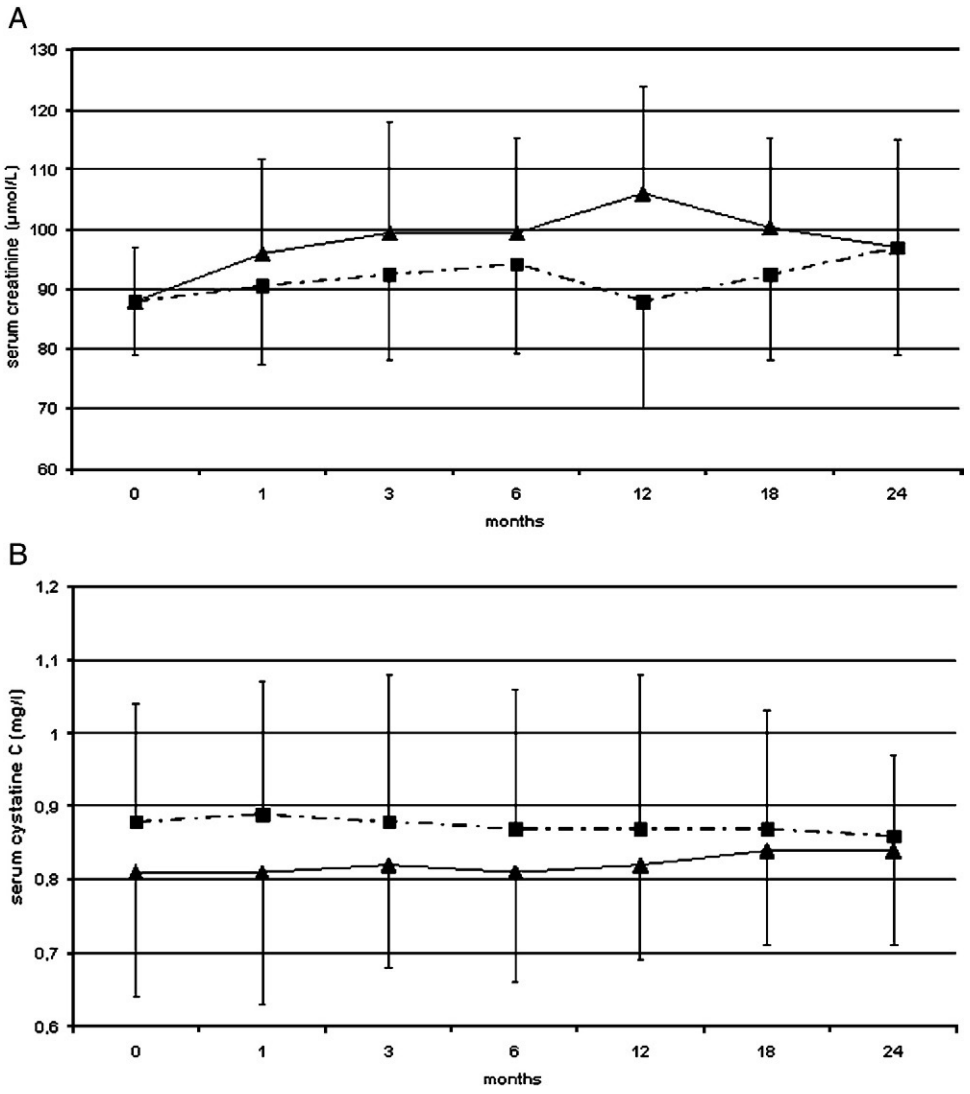

Fig. 2. Change of mean serum Crn (A) and CysC (B) levels during 24 months of treatment with Cr (triangles) or placebo (squares) (error bars indicate either + [going up] or − [going down] SD [only to one side for better clarity]). The rise in Crn after 1 year is not paralleled by significant changes in CysC levels, thus indicating preserved renal function.

10 g/d for 16 months yielded comparable safety results—adverse effects were comparable between groups and measures of renal function (Crn, urea) and hepatic function remained normal. Three subjects of the Cr group discontinued study medication for gastrointestinal side effects (diarrhea, nausea) [23]. The latter were also the only adverse events in our trial, which occurred significantly more often in the Cr-treated patients (Table 5).

As renal dysfunction is considered to be the most serious health threat that may be caused by Cr supplementation, we thoroughly investigated the potential impairment of kidney function for a 2-year period by means of serum and urinary markers. Creatinine in serum increased in the Cr group in contrast to the placebo group. This is in accordance with the results of a 1-year trial in 41 patients with HD [8]. Also, additional markers for tubular or glomerular damage were not elevated in the Cr group. Cystatin C is a low molecular weight basic protein with a stable production rate, which is freely filtered by the glomeruli. It has been suggested as a reliable screening test for early renal damage and as superior to Crn in detecting temporal changes of renal function

Table 4
Summary of tests of renal function

	Placebo (%)	Cr (%)	*P**
New tubular damage	11	15	.52
New impairment of GFR	7	11	.59
New microalbuminuria	8	11	.61
New hematuria	17	21	.52
New renal damage	33	43	.36

Incidence of newly diagnosed renal damage within the 24-month study period in patients treated with Cr (n = 31) or placebo (n = 17). For definitions of categories see Patients in the Methods and materials section.

* Level of significance in Fisher exact test.

Table 5
Adverse events

	Baseline		12 mo		24 mo	
	Placebo	Cr	Placebo	Cr	Placebo	Cr
Obstipation	0	21*	5	8	6	6
Diarrhea	5	8	0	0	0	3
Meteorism	20	13	0	0	0	13
Nausea	5	8	10	5	0	3
Total gastrointestinal symptoms	40	51	20	21	6	29*
Dizziness	5	8	20	13	18	10
Insomnia	0	5	0	0	0	0
Skin irritation	5	3	0	3	0	0
Fatigue	40	33	25	34	41	32
Headache	5	8	10	3	0	0
Sexual dysfunction	5	0	0	3	0	0
Polyuria/pollakisuria	0	3	0	3	0	0
Edema	5	0	0	0	0	3
Nervousness	5	3	5	0	0	0
Palpitation	5	3	0	3	0	6
Impaired concentration	25	18	30	26	47	32
Cramps	5	3	0	0	0	0

Values given as % of patients in the respective group (patients treated with Cr [n = 31]; patients treated with placebo [n = 17]).

* Significant group differences with $P < .05$ in Fisher exact test.

[24,25]. In our patients, CysC remained normal even in Cr patients who experienced an increase in serum Crn. These data show that increases in serum Crn upon Cr supplementation does not necessarily reflect impairment of renal function. Instead, these increases are most likely because of an increased total Cr concentration in the whole body with a concomitant higher rate of degradation of Cr to Crn and as such are a marker for compliance. However, we would recommend routine testing of renal function after the first months of Cr treatment. In the case of elevated serum Crn, we would encourage further testing of Cr-independent markers of renal function, such as serum CysC, instead of immediate substance withdrawal.

Although there were no group differences in the occurrence of laboratory tests implicating renal dysfunction, it is a noteworthy finding by itself that the incidence of test results outside the reference range was very high for controls (33%) and Cr patients (43%). This points to the chosen criteria that were very sensitive for measures of kidney dysfunction. Our statistical analysis shows that CysC levels correlated inversely with patient age and were independent of treatment group status.

To our knowledge, the provided laboratory data are the most extensive workup for renal function published so far in aged Cr users with or without underlying chronic illness.

Another safety concern regarding Cr supplementation has been the purity of the product. Creatine is freely distributed as OTC substance in a growing market of food supplements that has led to the introduction of a large variety of different Cr producers and distributors with likely varying quality standards of Cr production. Depending on the synthesis procedure, variable amounts of contaminants such as dicyandiamide, dihydrotriazines, and Crn can be found in the end product [26,27]. Also, there have been reports of Cr products with traces of anabolic steroids. In fact, a recent systematic analysis of 42 OTC Cr products in the United States and in Europe has found significant amounts of norandrostenedione in one of the Cr products with presence of the 2 main metabolites of nandrolone in urine [28]. It is therefore necessary to stress the importance of the highest Cr purity and quality control, especially in the case of long-term supplementation. This is particularly relevant for consumers when ordering unknown or undocumented brands off the Internet.

Regarding the neuroprotective potential of Cr in the previously published data from this study population, we did not find differences with objective imaging variables for loss of dopaminergic neurons. But patients in the Cr group had less need for additional symptomatic therapy during the course of the trial and performed better in a subscale of the UPDRS testing for depression [7]. In sharp contrast to the ergogenic indications for Cr, results of its use in neuroprotection trials were so far not very convincing. Still, in an attempt to identify substances worth future consideration for neuroprotection trials, Cr was not found to be futile [29]. Therefore, it is likely that use of Cr in aged patients with significant comorbidity will increase in the clinic. In this context, our data on the safety profile of Cr are valuable because we studied patients with a common neurodegenerative disease and regular intake of medication (eg, levodopa, cabergoline, ropinirole, pramipexole).

It has to be stressed that our data stem from a long-term neurodegeneration trial with PD patients. Therefore, one limitation of our study is that the findings cannot automatically be generalized to healthy aged individuals. Yet, we do not see evidence for a special impact of PD on kidney function and certainly patients with PD cannot be considered to be at special renal risk. Also, to our knowledge, there are no reports about protective effects of PD or its symptomatic treatment on renal function. It is clear that when assessing a patient's individual risk for Cr-related side effects, one has to take into consideration concomitant diseases and regular medication. Although Cr is safe in patients with PD, it might have a negative impact on patients with underlying renal disease as for example in advanced stage diabetic patients or on patients who take nephrotoxic drugs.

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References

[1] Wallimann T, Wyss M, Brdiczka D, Nicolay K, Eppenberger HM. Intracellular compartmentation, structure and function of creatine kinase isoenzymes in tissues with high and fluctuating energy demands: the "phosphocreatine circuit" for cellular energy homeostasis. Biochem J 1992;281:21-40.

[2] Wyss M, Kaddurah-Daouk R. Creatine and creatinine metabolism. Physiol Rev 2000;80:1107-213.

[3] Froiland K, Koszewski W, Hingst J, Kopecky L. Nutritional supplement use among college athletes and their sources of information. Int J Sport Nutr Exerc Metab 2004;14:104-20.

[4] Baker SK, Tarnopolsky MA. Targeting cellular energy production in neurological disorders. Expert Opin Investig Drugs 2003;12:1655-79.

[5] Bender A, Beckers J, Schneider I, Holter SM, Haack T, Ruthsatz T, et al. Creatine improves health and survival of mice. Neurobiol Aging 2007 Apr 6 [Electronic publication ahead of print].

[6] Bender A, Auer DP, Merl T, Reilmann R, Saemann P, Yassouridis A, et al. Creatine supplementation lowers brain glutamate levels in Huntington's disease. J Neurol 2005;252:36-41.

[7] Bender A, Koch W, Elstner M, Schombacher Y, Bender J, Moeschl M, et al. Creatine supplementation in Parkinson disease: a placebo-controlled randomized pilot trial. Neurology 2006;67:1262-4.

[8] Verbessem P, Lemiere J, Eijnde BO, Swinnen S, Vanhees L, Van Leemputte M, et al. Creatine supplementation in Huntington's disease: a placebo-controlled pilot trial. Neurology 2003;61:925-30.

[9] Tabrizi SJ, Blamire AM, Manners DN, Rajagopalan B, Styles P, Schapira AH, et al. High-dose creatine therapy for Huntington disease: a 2-year clinical and MRS study. Neurology 2005;64:1655-6.

[10] Shefner JM, Cudkowicz ME, Schoenfeld D, Conrad T, Taft J, Chilton M, et al. NEALS Consortium. A clinical trial of creatine in ALS. Neurology 2004;63:1656-61.

[11] Terjung RL, Clarkson P, Eichner ER, Greenhaff PL, Hespel PJ, Israel RG, et al. American College of Sports Medicine roundtable. The physiological and health effects of oral creatine supplementation. Med Sci Sports Exerc 2000;32:706-17.

[12] Kraemer WJ, Volek JS. Creatine supplementation. Its role in human performance. Clin Sports Med 1999;18:651-66.

[13] Pritchard NR, Kalra PA. Renal dysfunction accompanying oral creatine supplements. Lancet 1998;351:1252-3.

[14] Koshy KM, Griswold E, Schneeberger EE. Interstitial nephritis in a patient taking creatine. N Engl J Med 1999;340:814-5.

[15] Thorsteinsdottir B, Grande JP, Garovic VD. Acute renal failure in a young weight lifter taking multiple food supplements, including creatine monohydrate. J Ren Nutr 2006;16:341-5.

[16] Pline KA, Smith CL. The effect of creatine intake on renal function. Ann Pharmacother 2005;39:1093-6.

[17] Kreider RB, Melton C, Rasmussen CJ, Greenwood M, Lancaster S, Cantler EC, et al. Long-term creatine supplementation does not significantly affect clinical markers of health in athletes. Mol Cell Biochem 2003;244:95-104.

[18] Mihic S, MacDonald JR, McKenzie S, Tarnopolsky MA. Acute creatine loading increases fat-free mass, but does not affect blood pressure, plasma creatinine, or CK activity in men and women. Med Sci Sports Exerc 2000;32:291-6.

[19] Robinson TM, Sewell DA, Casey A, Steenge G, Greenhaff PL. Dietary creatine supplementation does not affect some haematological indices, or indices of muscle damage and hepatic and renal function. Br J Sports Med 2000;34:284-8.

[20] Schroder H, Terrados N, Tramullas A. Risk assessment of the potential side effects of long-term creatine supplementation in team sport athletes. Eur J Nutr 2005;44:255-61.

[21] Poortmans JR, Francaux M. Long-term oral creatine supplementation does not impair renal function in healthy athletes. Med Sci Sports Exerc 1999;31:1108-10.

[22] Lyoo IK, Kong SW, Sung SM, Hirashima F, Parow A, Hennen J, et al. Multinuclear magnetic resonance spectroscopy of high-energy phosphate metabolites in human brain following oral supplementation of creatine-monohydrate. Psychiatry Res 2003;123:87-100.

[23] Groeneveld GJ, Veldink JH, van der Tweel I, Kalmijn S, Beijer C, de Visser M, et al. A randomized sequential trial of creatine in amyotrophic lateral sclerosis. Ann Neurol 2003;53:437-45.

[24] Uzun H, Ozmen Keles M, Ataman R, Aydin S, Kalender B, Uslu E, et al. Serum cystatin C level as a potentially good marker for impaired kidney function. Clin Biochem 2005;38:792-8.

[25] Levin A. Cystatin C, serum creatinine, and estimates of kidney function: searching for better measures of kidney function and cardiovascular risk. Ann Intern Med 2005;142:586-8.

[26] Benzi G, Ceci A. Creatine as nutritional supplementation and medicinal product. J Sports Med Phys Fitness 2001;41:1-10.

[27] Brudnak MA. Creatine: are the benefits worth the risk. Toxicol Lett 2004;150:123-30.

[28] Baume N, Mahler N, Kamber M, Mangin P, Saugy M. Research of stimulants and anabolic steroids in dietary supplements. Scand J Med Sci Sports 2006;16:41-8.

[29] NINDS NET-PD Investigators. A randomized, double-blind, futility clinical trial of creatine and minocycline in early Parkinson disease. Neurology 2006;66:664-71.