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The Effects of Creatine Supplementation on Biochemical, Body Composition, and Performance Outcomes in Humans: A Meta-analysis

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Creatine supplementation has been widely used for athletes and in some studies it has been proved effective; however, there remain some moderator variables that still require meta-analysis. Therefore, the purpose of this study was to conduct such an analysis on the effects of creatine supplementation on biochemical, body composition, and physical performance variables. From a total of 120 experimental studies found in databases, only 55 studies (46 %) were considered appropriate and/or contained the necessary information to obtain effect sizes. Creatine supplementation produced biochemical changes, including increases in excretion parameters. Anthropometric variables, body fat percentage, and lean mass were favorably changed by creatine supplementation. Improved peak power, total work, force power, and a maximal repetition (1RM) were also found following creatine supplementation. There was an evident placebo effect in the variables meta-analyzed; however, there was a clear increase in total work beyond the placebo effect. In summary, creatine supplementation consistently showed positive biochemical, body composition, and power changes in humans.

key words: *Meta-analysis, Creatine, Power, Body Composition, Placebo, Placebo Effect, Nutritional Supplements*

Introduction

During the late 80's and the beginning of the 90's it was common practice within professional and amateur athletes to consume several types of ergogenic substances. Creatine (Cr) was one of those substances aimed at inducing changes in strength, power, and body composition, and overall, to increase performance.

In a study with 229 physically-active participants (Sheppard, Raichada, Kouri,

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Stenson-Bar-Maor, & Branch, 2000), it was found that 69% consumed a mean dose of 12.25 g Cr/day as a nutritional supplement. In another study (Schilling et al., 2001), it was reported that professional athletes of different sports consumed Cr for a period of time of 0.8 to 4 years. During that time, the athletes consumed a similar dose of 13.7 g Cr/day in the overload phase.

It has been demonstrated that Cr consumers are predominantly involved in strength and power activities (Sheppard et al., 2000). This can be explained by two reasons. First, the general perception of people of different ages at an anecdotal level is that Cr consumption allows increases in body mass and muscular force when combined with a strength training program (Gotshalk, Volek, Staron, Denegar, Hagerman, & Kramer, 2002; Juhn, 1999; Lamb, 1999; Poortmans & Francaux, 2000; Terjung et al., 2000). Secondly, the scientific literature that have found positive effects of Cr supplementation on physical performance variables have relied upon anaerobic intermittent and repetitive exercise performed at near or maximal capacity (e.g., 90-100% maximal oxygen consumption [VO_{2max}]) for a short duration (e.g., < 1 min) (Dawson, Cutler, Moody, Lawrence, Goodman, & Randall, 1995; Gotshalk et al., 2002; Greenhaff, Bodin, Soderlund, & Hultman, 1994; Kamber, Koster, Kreis, Walker, Boesch, & Hoppeler, 1999; Kreider, Ferreira, Wilson, Grindstaff, Plisk, Reinardy, Cantler, & Almada, 1998; Preen, Dawson, Goodman, Lawrence, Beilby, & Ching, 2001; Prevost, Nelson, & Morris, 1997; Rossiter, Cannell, & Jakeman, 1996; Terjung et al., 2000; Volek, Kraemer, Bush, Boetes, Incledon, Clark, & Lynch, 1997).

Although some benefits of Cr supplementation have been reported on body composition and anaerobic endurance, these findings appear to be equivocal. For example, in several studies (Balsom, Söderlund, Sjödin, & Ekblom, 1995; Becque, Lochmann, & Melrose, 2000; Burke, Chilibeck, Davison, Candow, Farthing, & Smith-Palmer, 2001; Dawson et al., 1995; Green, Hultman, Macdonald, Sewell, & Greenhaff, 1996; Greenhaff et al., 1994; Kamber et al., 1999; Kreider et al., 1998; Maganaris & Maughan, 1998; Mihic, MacDonald, McKenzie, & Tarnopolsky, 2000; Murphy, Watsford, Coutts, & Richards, 2005; Preen et al., 2001; Rebello-Mendes, Pires, Oliveira, & Tirapegui, 2004; Snow, McKenna, Kemp, Stathis, & Zhao, 1998; Volek, Duncan, Mazzetti, Staron, Putukian, Gómez, Pearson, Fink, & Kraemer, 1999; Volek, Duncan, Mazzetti, Putukian, Gómez, & Kraemer, 2000) changes in body composition were reported, specifically increases in lean and total body mass. According to Poortmans and Francaux (2000), other researchers, although in a

smaller percentage, tend to differ with the previous results. For these, the main argument is that they have found that body composition remains stable in spite of supplementation with Cr (Bermon, Venembre, Sachet, Valour, & Dolisi, 1998; Green, McLester, Smith, & Mansfield, 2001; Grindstaff, Kreider, Bishop, Wilson, Wood, Alexander, & Almada, 1997; Hamilton, Meyers, Skelly, & Marley, 2000; Larson-Meyer, Hunter, Trowbridge, Turk, Ernest, Torman, & Harbin, 2000; Rockwell, Walberg-Rankin, & Toderico, 2001; Vandenberghe, Goris, Van Hecke, Van Leemputte, Vangerven, & Hespel, 1997).

On the other hand, there are no consistent results in short term (e.g. < 10 d) and long term (e.g., > 10 d) Cr supplementation. Poortmans and Francaux (2000) suggested two hypotheses that explain the differences that are reported in the studies on body composition. One of them refers to the participation of subjects with different levels of physical training (e.g., trained, sedentary and physically active), the reason, it could be speculated, is that the subjects do not respond equally to the protocols of supplementation with Cr. Under this same line of possible confounding variables, Greenhaff et al. (1994) showed that the gain in total muscle Cr values after supplementation varied between each person. Also it has been suggested that the net gain subsequent to the treatment depends on the initial Cr levels (Greenhaff, 1995; Lamb, 1999).

The second hypothesis attributes differences in body composition relative to gender. Several studies in which the participants are female have reported no significant changes in body mass (Grindstaff, Kreider, Bishop, Wilson, Wood, Alexander, & Almada, 1997; Hamilton et al., 2000; Larson-Meyer et al., 2000; Prevost, Nelson, & Morris, 1997). In some studies the menstrual cycle stage was not controlled for, although changes in anaerobic power and body mass throughout three stages of the cycle were not found (Giacomoni, Bernard, Gavarry, Altare, & Falgairette, 2000).

Other hypotheses could be formulated to explain the differences in the results found in these studies. For example, the dose and the time of supplementation vary from one study to another (Greenhaff, 1995; Juhn, 1999; Poortmans & Francaux, 2000; Terjung et al., 2000), which reasonably alters considerably to the total consumption of Cr. The previous statement assumes that it should be a specific dose and timing for Cr supplementation to achieve an ergogenic effect.

Another methodological inconsistency detected in Cr supplementation intervention studies was related to the instrumentation used to measure physical

performance, body composition and some biochemical parameters. In order to measure body composition, sophisticated and highly precise instruments like magnetic resonance imaging (MRI) or the hydrostatic weighing technique have been used (Larson-Meyer et al., 2000; Op 'T Einje & Hespel, 2001; Rockwell, Walberg-Rankin, & Toderico, 2001; Volek et al., 1997); however, other apparatus and less accurate techniques have included skinfold calipers, bioelectrical impedance and body fat prediction equations, such as body mass index (BMI) (Bermon et al., 1998; Haff, Kirksey, Stone, Warren, Johnson, Stone, O'Bryant, & Proulx, 2000; Volek et al., 2000).

At this moment, three theories exist that basically explain how Cr can improve performance during anaerobic exercise. First, it is mentioned that following Cr supplementation the total Cr and phosphocreatine (PCr) levels would be higher and consequently more potential energy would be available; that is to say, greater ATP concentration during anaerobic exercise of very short duration (e.g., < 30 s) (Williams & Branch, 1998). Consistent evidence exists that demonstrates Cr supplementation in a dose between 2 - 30 g/day is able to increase the levels of total creatine (TCr) (TCr = Cr + PCr) from 10 - 60 % of its baseline values (Balsom et al., 1995; Casey, Constantin-Teodosiu, Howell, Hultman, & Greenhaff, 1996; Green et al., 1996; Greenhaff et al., 1994; Kreis, Kamber, Koster, Felblinger, Slotboom, Hoppeler, & Boesch, 1999; McConell, Shinewell, Stephens, Stathis, Canny, & Snow, 2005; Preen et al., 2001; Rockwell, Walberg-Rankin, & Toderico, 2001; Snow et al., 1998; Volek et al., 2000). Nevertheless, ATP levels had remained stable when compared to placebo (PL) or control (CT) conditions.

Secondly, the most accepted theory at this moment indicates that the improvement in physical performance in intermittent anaerobic exercise is due to the increase in the rate of PCr resynthesis during resting periods between intensive bouts of exercise. By means of muscular biopsy analyses, Greenhaff et al. (1994) demonstrated that Cr supplementation accelerates the resynthesis of PCr a minute later to have made intense isometric exercise. Similarly, others (Smith, Montain, Matott, Zientara, Jolesz, & Fielding, 1998) using magnetic resonance imaging (MRI), confirmed an increase in the rate of PCr resynthesis and, in addition, they demonstrated that this was not affected by the age of the participants. In spite of these findings, others (Vandenberghe, Van Hecke, Van Leemputte, Vanstapel, & Hespel, 1999) did not find any effect of supplementation with Cr on the PCr resynthesis.

The last theory indicates that Cr use could have the potential to diminish lactate accumulation, since the organism would have to rely less on the anaerobic metabolism. Most studies do not support this theory since lactate concentrations are similar in the groups or conditions of Cr supplementation, PL, or CT during and after anaerobic maximum exercise (Burke, Pyne, & Telford, 1996; Dawson et al., 1995; Pluim, Ferrauti, Broekhof, Deutekom, Gotzmann, Kuipers, & Weber, 2006; Preen et al., 2001; Snow et al., 1998).

In this context, it is possible to state that in general, the results on the effects of Cr supplementation on physical performance are still conflicting. Although in the studies previously described there have been positive effects of supplementation with Cr in physical performance or biochemical parameters; in several studies positive effects of supplementation with Cr were not reported for power, work, force and speed in different groups of athletes (Burke, Pyne, & Telford, 1996; Green et al., 2001; Perret, Mueller, & Knecht, 2006; Pluim et al., 2006; Rebello-Mendes et al., 2004; Redondo, Dowling, Graham, Almada, & Williams, 1996; Snow et al., 1998; Terrillion, Kolkhorst, Dolgener, & Joslyn, 1997). What does seem to be consistent is that the studies that demonstrate an ergogenic effect of Cr supplementation focus on repetitive and maximum exercise (90 - 100% VO_{2max}), mainly when performed on cycle ergometers, or when performance was measured by means of muscular contractions against a resistance (Greenhaff, 1995; Kamber et al., 1999; Kreider et al., 1998; Preen et al., 2001).

Thus, the hypotheses that also explain the methodological variability and inconsistencies in the findings on body composition could also be applied to the physical performance findings. Nevertheless, other moderator variables might have importance; for example, Lamb (1999), has considered that the effect of Cr on performance and body composition is small when comparing mean differences between Cr, CT and PL conditions. Other relevant moderator variables include the number of repetitions and the total volume of repetitive exercise to produce muscular fatigue. For example, there are reports where subjects induced maximum fatigue (i.e, > number of repetitions) and found performance improvements especially during the final stages of physical effort (Aaserud, Gramvik, Olsen, & Jensen, 1998; Balsom et al., 1995; Engelhardt, Neumann, Berbalk, & Reuter, 1998; Kamber et al., 1999; Preen et al., 2001). On the contrary, others have used a lower number of repetitions and did not find changes in physical performance (Green et al., 2001; Redondo et al., 1996; Snow et al., 1998; Terrillion et al., 1997). In spite

of the latter, a study exists that contradicts this theory, finding effects in performance in the initial stages of prolonged interval exercise (Kreider et al., 1998). A possible explanation could be found when considering that Cr is not necessarily bound to an increased rate of PCr resynthesis; but rather to maintain a relatively stable speed of resynthesis as the intermittent exercise extends.

In summary, the experimental evidence as well as narrative reviews about Cr supplementation, including a meta-analytic qualitative review (Ransone & Park, 2002) as it relates to anthropometric, biochemical, and physical performance variables are still conflicting. Others (Juhn, 1999; Poortmans & Francaux, 2000; Terjung et al., 2000; Williams & Branch, 1998) have also reached the same conclusion. Nevertheless, these narrative reviews depend more on the technique and the skill of author(s) to integrate, to group and to interpret the results of many studies, rather than a systematic statistical analysis.

Therefore, a consensus is lacking about whether or not Cr supplementation should be used as a reliable ergogenic nutritional strategy. For that reason, the purpose of this study was to use the statistical technique of meta-analysis initially proposed by Glass (1977), to be able to quantify the true magnitude that Cr supplementation has on the different biochemical, body composition and physical performance variables.

Method

Salazar, Petruzzello, Landers, Etnier, and Kubitz (1993), recommend to follow 6 standard steps to develop a meta-analysis: a) identification of the problem; b) search of scientific literature; c) coding scheme of the moderator variables and their levels (independent variable); d) effect size (ES) calculation; e) correction of the E.S.; and, f) statistical analysis.

Identification of the problem. Based on the literature review and on conclusions from several narrative reviews (Dorado, Sanchis, Chavarren, & Lopez, 1997; Juhn, 1999; Lamb, 1999; Poortmans & Francaux, 2000; Terjung et al., 2000), it was necessary to determine and to quantify the effect of Cr supplementation on the main dependent variables of body composition and physical performance, in order to look for a possible explanation about the inconsistency in the findings reported in experimental studies.

Search of scientific literature

In order to locate articles and reviews related to the subject, the following keywords in English and Spanish (in parenthesis) were used: creatine (creatina), ergogenic supplements (suplementos ergogénicos), phosphocreatine (fosfocreatina o creatina fosfato), sport performance (rendimiento deportivo) and anaerobic intermittent exercise (ejercicio anaeróbico intermitente). These keywords were introduced in the data bases SportDiscuss®, ADONIS® and Medline. Abstracts were excluded from the study.

Coding scheme of the moderator variables

The moderator variables independently examine a possible effect on the dependent variables (e.g., physical performance, body composition) due to Cr supplementation. The variables were selected and codified in two forms: a) a priori judgment; and b) according to theories that propose that strange variables could explain the differences in the results.

Moderator or independent variables were grouped in interest areas with their respective levels based on: a) relation to the characteristics of the subjects; b) training characteristics; c) measurement of physical performance; d) body composition assessment; e) measurement of biochemical parameters; f) form of supplementation with Cr and PL; g) research design; and, h) post - test characteristics (Table 1).

In order to take maximal advantage of the meta-analytical technique (Salazar et al., 1993), the table of moderator variables includes the aspects that might cause variability across the different studies. In addition, the research design was also included as a moderator variable, which has been neglected in most meta-analysis. The variables included in the area of research design in detail analyze the internal and external validity of the studies (subject selection and allocation, experimental design, randomization of the treatments, and form of comparison in crossover designs). It was also quantified separately for the magnitude of the effect that had the experimental groups or conditions (i.e., Cr, PL, and CT) compare their impact on the dependent variables: a) peak power; b) total work; c) peak force; d) 1RM; e) total body mass; f) body fat percentage; g) lean mass; and h) biochemical variables (Table 2).

Table 1. *Moderator variables*

Interest area	Specific coding scheme
· Subject characteristics	· Demographics and general information: sample size, age, body mass, gender, VO_{2max}, fitness status, other.
· Training characteristics	· Duration: days, weeks. · Frequency: days/week. · Intensity: %VO_{2max}, %HR_{max}, % RM. · Modality of training: aerobic, anaerobic, mixed, not reported.
· Measurement of physical performance	· Training instrument: free weights, hydraulic machines, pulley machines, isokinetic machines, cycle ergometers, treadmill, other. · Test modality: aerobic, anaerobic, mixed. · Physical quality measured: strength, speed, power, aerobic endurance, anaerobic. · Measurement type: interval, continuous, mixed. · Instrument used to measure performance: treadmill, cycle ergometer, free weights, isokinetic machine, force platform, other.
· Body composition assessment	· Instruments used to measure body mass, body fat, and lean body mass: electronic scale, bioimpedance, skinfold calipers, hydrostatic weighing, magnetic resonance imaging, DEXA, other.
· Measurement of biochemical parameters	· Measurement technique: muscle biopsy, magnetic resonance imaging, spectrophotometry, chromatography, portable analyzer, mixed.
· Creatine supplementation	· Duration: days. · Frequency: times x week. · Creatine dose: daily dose (gr), fragmented dose (gr x dose), total volume (gr). · Placebo dose: daily dose (gr), fragmented dose (gr x dose), total volume (gr). · Type of substance: pure creatine, placebo [CHO, other], mixed [Cr + CHO]), caloric intake (Kcal).
Research design	· Subject assignment: random, non-random, paired. · Treatment assignment: double blind, blind [simple]. · Experimental design: between groups, within subjects, mixed. · Washout period: days. · Comparison in within subjects design: Pre Post Control, Pre Post Placebo, Pre Post Experimental. · Comparison in between subjects design: Experimental vs. Control, Experimental vs. Placebo, Placebo vs. Control.
Post-test characteristics	· Rest between repetitions, total number of repetitions, mean repetition time (min) · Cumulativetime (min), · Mean distance (m), total cumulative distance (m) · Sample frequency (Hz) · Time at where measurement was taken (min) · Time to complete test (min), number of test,time to re-test (days).

Effect size (ES) calculation

The ES is considered the central unit of study in the meta-analysis (Salazar et al., 1993). This consists of a standardized value that allows an establishment of the magnitude of differences between the experimental groups or conditions (Thomas, Salazar, & Landers, 1991). For the calculation of the ES, the formula used was proposed by Glass (1977), that explores means (M) and the standard deviation (SD) of a comparison group [($M_{Experimental}$ - $M_{Control}$)/ $SD_{Control}$]. The ES of the experimental designs is obtained as follows:

1. For repeated measures designs:

($M_{Pre\ Treatment}$ - $M_{Post\ Treatment}$)/ $SD_{Pre\ Treatment}$

2. For research designs where there are comparisons between experimental subjects or groups, the formulas used were:

a. ($M_{Post\ Experimental}$ - $M_{Post\ Placebo}$) / $SD_{Post\ Placebo}$

b. ($M_{Post\ Experimental}$ - $M_{Post\ Control}$) / $SD_{Post\ Control}$

c. ($M_{Post\ Placebo}$ - $M_{Post\ Control}$) / $SD_{Post\ Control}$

Correction of the ES

Rosenthal (1984) and Salazar et al. (1993), showed the necessity to correct the original value of each ES in a meta-analysis. These authors consider that in the studies with small samples they could underestimate the true effect of a treatment, in comparison with other studies that contain larger number of subjects. Thus, the final result of each mean ES would not necessarily reveal the true tendency and magnitude of the treatments, those that later are generalized to the population. Therefore, each ES was multiplied by the following correction formula (Etnier, Salazar, Landers, Petruzzello, Han, & Nowell, 1997; Hedges & Olkin, 1985):

1 - [3 / (4 m ? 9)], where m = ($N_{Experimental}$ + $N_{Comparison\ group}$) - 2

Statistical Analyses

The statistical analyses were computed by using a statistical software package (Statistical Package for Social Sciences®, 1998). One-way analysis of variance (ANOVA) was used in order to determine the influence on the ES of each independent variable. The meta-analytical Z score was used to determine if the ES

was different from zero (0), for which the Stouffer method described by Rosenthal (1984) was used. Based on the classification by Cohen (Thomas, Salazar, & Landers, 1991), the magnitude of the ES was determined as follows: a) ES $\leq$ 0.40, small; b) ES = 0.41 to 0.69, moderate; and c) ES $\geq$ 0.70, large.

Two basic criteria were used to choose the more important dependent variables in each area of study. First, the variables that showed the higher number of ES (i.e., ESn) were chosen. Secondly, there had to be coherence between the effects found and the logic of the final conclusions when interpreting together the three types of global ES (i.e., ES of the Experimental Condition; ES of the Placebo Condition; and ES of the Experimental Condition versus Placebo).

Therefore, an ES that in the *experimental condition* showed a positive magnitude (the + sign is omitted), and in addition is found to be statistically significant ($p < .05$) will be interpreted as meaning that Cr supplementation affected the dependent variable in a positive way. On the other hand, negative ES (i.e., negative sign (-) means that Cr supplementation impaired the outcome in the dependent variable.

In a similar way, in the *placebo condition*, the direction of the signs and the differences from zero in the magnitude of the ES ($p < .05$) will be interpreted equally to the experimental condition analysis. Nevertheless, it is necessary to take into account that a dependent variable that changes due to a placebo would indicate a psychological or mental response of the subject (i.e., placebo effect).

In the final interpretation about the effects of Cr supplementation, it is necessary to compare the ES of the *experimental condition* with the ES obtained in the *experimental condition - placebo condition*; in order to compare the magnitudes and to determine similar characteristics as far as the direction of the results; in other words, the sign of the ES (i.e. + or -), the magnitude of the ES (i.e., large, moderate, or small [Thomas, Salazar, & Landers, 1991]), and the statistical significance (i.e., $p < .05$).

The previous comparison permits us to determine which analysis is more sensible in detecting changes in the dependent variables. Consequently, the magnitudes of the global ES, as well as those obtained in the independent or moderator variables cannot be examined separately.

Results

In this study, a total of 43 dependent variables (N = 43) were examined by means of a meta-analytic technique. Global ES were computed based on the information provided by the experimental studies (N = 55).

It is important to restate the significance of the preceding sign in the ES estimation to remember that in the calculations for repeated measurement designs or within subject designs (experimental condition and placebo condition), a positive sign (+) indicates that the treatment improved a dependent variable, while on the other hand, a negative sign (-) impaired the dependent variable. In the case of the analyses of the experimental versus placebo conditions (i.e., between subjects), the direction of the sign indicates which treatment had a higher impact on the dependent variable. Thus, if the sign is positive (+) it indicates that Cr supplementation improved the outcome in the dependent variable measured; however, if the resulting sign is negative (-), then a placebo effect occurred.

Finally, a significant ES (i.e., $p < 0.05$) following the omnibus ANOVA is considered relevant since it shows that the ES is significantly different from 0. Thus, the most relevant and consistent information of all the global analyses appear summarized in four tables grouped by areas of study: a) biochemical parameters (Table 2); b) body composition (Table 3); and c) physical performance (Tables 4 and 5).

Biochemical Parameters

The results presented in Table 2 reflect that there is no placebo effect on the biochemical parameters, since none of the ES were statistically significant ($p > .05$). These results opposed the ones found for the physical performance variables (Tables 4 and 5), which show independent effects of Cr and placebo alone; as well as a combined effect of both substances (i.e., Cr + PL).

The ES in the experimental condition also clearly show that the protocols of supplementation with Cr increase the levels of free Cr (ES = 3.58) and TCr (ES = 4.49) in the human body. This is clear evidence that there are statistically significant physiological changes ($p < .05$) from pre-test to post-test.

It is important to emphasize that in the experimental condition there was also a significant ($p < .05$) increase in plasma creatine (ES = 6.15) and plasma creatine

kinase levels (ES = 1.47), both parameters clearly associated with the net TCr and Cr gains following Cr supplementation. Nevertheless, these results must be interpreted cautiously due to the small number of ES analyzed (TCr, ES_n = 2; Cr, ES_n = 5).

The analysis for the variables PCr, ATP and lactate showed that Cr supplementation did not affect the concentrations in any of these biochemical parameters ($p > .05$). It is worth mentioning the high variability in lactate ES, the biochemical parameter most studied (general ES_n = 64).

On the other hand, the results in the experimental condition also demonstrate that supplementation with Cr causes a significant increase ($p < .05$) in the parameters related to the excretion or removal of byproducts from the organism, for instance, urea (ES = 1.07), creatinine (ES = 2.64), and creatine (ES = 72.06). It is necessary to take into account that ES on the creatine excretion is not different from zero ($p > .05$), probably explained by its high variability (i.e., SD).

With respect to urea excretion, in the experimental condition a significant change from pre-test to post-test was observed (ES = 1.07, $p < .05$), which agrees with the reduction in plasma urea (ES = - .22). However, the N to obtain ES was below minimum in the case of plasma urea, experimental condition (ES_n = 2), and experimental versus placebo (ESn = 1), although the magnitude of the change was significant ($p < .05$).

ES originating of the post-test measurements (i.e., experimental condition versus placebo), do not allow us to emphasize several results due to the limited number of ES (Table 2). In this condition, ATP had an important sample (ES_n = 10), but it did not show a significant magnitude ($p > .05$), which implies that Cr supplementation does not improve ATP levels in the body. This result contradicts results reported by others (Green et al., 1996).

Body composition. The results do not indicate a placebo effect in the dependent variables related to body composition (Table 3) since none (ES) were significant in the placebo condition ($p > .05$).

On the other hand, the most important results with respect to Cr supplementation indicated a significant change ($p < .05$) in body composition, specifically, increased lean mass (ES = .61; $p < .05$) and reduced body fat % (ES = -.34; $p < .05$). In spite of this, in the experimental condition, total body mass (ES = .42) did not reach statistical significance ($p > .05$); nevertheless, according to Thomas et al. (1991) the ES magnitude could be considered moderate.

Table 2. *Global ES for biochemical parameters*

Dependent Variables	Experimental Condition			Placebo Condition			Experimental vs. Placebo		
	ES	SD	ES_n	ES	SD	ES_n	ES	SD	ES_n
TCr	3.58*	2.60	18	3.69	9.30	6	-.83*	.20	2
Cr	4.49*	3.52	18	-.28	.31	3	1.51	-	1
PCr	-.56	6.81	21	-.08	.87	6	-.08	-	1
Lactate	4.21	16.96	36	2.17	5.76	26	-.07	.36	2
ATP	-.98	2.26	18	.25	.83	3	.59	1.44	10
Plasma creatine	6.15*	4.21	2	.36	.26	2	-.97*	.36	2
Plasma CK	1.47*	1.43	5	.04	1.76	2	1.49*	.96	4
Plasma urea	-.22*	.08	2	.41	.39	2	.13	-	1
Urine volume	.74	-	1	.03	-	1	.18	-	1
Creatine excretion	72.06	204.9	4	29.27	59.01	4	.68*	.37	3
Creatine excretion	2.64*	1.79	5	-.25	.52	5	6.52	-	1
Urea excretion	1.07*	.49	3	.01	.39	3	.56*	.07	2

Note. ES: Mean effect size; ES_n: Number of effect sizes computed; SD: Standard deviation; *: $p < .05$; TCr: Total creatine; Cr: Free creatine; PCr: Creatine phosphate; ATP: Adenosine triphosphate.

Table 3. *Global ES related to body composition*

Dependent Variables	Experimental Condition			Placebo Condition			Experimental vs. Placebo		
	ES	SD	ES_n	ES	SD	ES_n	ES	SD	ES_n
Total body mass	.42	1.55	35	.11	.20	28	-.02	1.21	33
Fat mass (%)	-.34*	.47	12	-.18	.34	12	.07	.65	12
Fat mass	.04	.25	6	.03	.32	6	.37	1.02	6
Lean mass	.61*	.81	13	.20	1.41	13	.58*	.91	14

Note. ES: Mean effect size; ES_n: Number of effect sizes computed; SD: Standard deviation; *: $p < .05$.

Physical Performance

The main results shown in Table 4 indicate that there is a placebo and Cr effect in the variables that examined physical performance. The results demonstrated that there is a significant increase in peak power, peak force, and 1 RM ($p < .05$), both, during Cr and PL administration.

The experimental condition shows significant ES ($p < .05$) in the four variables of physical performance; however, the ES magnitudes in the placebo condition were significant ($p < .05$), excluding the total work.

On the other hand, the ES in the experimental versus placebo condition were significant ($p < .05$), demonstrating that the real effect of improvement attributed to

Cr supplementation is even greater than that produced with placebo administration. In other words, the Cr effect is real and above (over) a placebo effect.

The real magnitude of the experimental condition can be computed as follows: ES experimental condition - ES placebo condition. This formula follows a logical reasoning since the data in both conditions belong to the same subjects who crossover the experimental treatments. Therefore, the real magnitude for peak power (ES = .50) is considered high according to Thomas, Salazar, and Landers (1991). Total work did not show a placebo effect (ES = .70).

The real magnitude in the other variables is considered high by using the terminology of Thomas, Salazar, and Landers (1991). For example, the real ES for peak force and 1 RM is equivalent to 1.61 and 1.63, respectively (Table 5).

It is necessary to mention that the ES calculated for the experimental versus placebo conditions clearly demonstrates that the treatment with Cr surpasses the placebo in the post-test measurements ($p < .05$). This finding confirms the final conclusion that there is a Cr effect, real and significant, even in the presence of an observed placebo effect.

Table 4. *Global ES for physical performance*

Dependent Variables	Experimental Condition			Placebo Condition			Experimental vs. Placebo		
	ES	SD	ES_n	ES	SD	ES_n	ES	SD	ES_n
Peak power	.89*	1.03	35	.39*	.73	35	.80*	1.41	63
Total work	.70*	.71	31	-.01	.29	29	.71*	.72	29
Peak force	4.70*	3.27	19	3.09*	2.00	19	1.75*	1.57	19
1 RM	2.47*	2.61	10	.84*	1.12	10	.27*	.41	23

Note. ES: Mean effect size; ES_n: Number of effect sizes computed; SD: Standard deviation; *: $p < .05$.

Table 5. *Real magnitude of ES for performance variables*

Dependent variables	Experimental Condition	Placebo Condition	Experimental vs. Placebo	Real Magnitude (ES_{Exp} $ES_{Placebo}$)
	MES	MES	MES	MES
Peak power	.89	.39	.80	.50
Total work	.70	-.01	.71	.71
Peak force	4.70	3.09	1.75	1.61
1 RM	2.47	.84	.27	1.63

Note. MES: Mean effect size.

Moderator Variables

One-way ANOVA was computed in order to examine mean ES by independent variables or moderator variables. These tests were only computed when sufficient ES were available. All moderator variables were examined in the effects on the dependent variables peak power, total work, peak force, and 1 RM (Table 6). However, only the moderator variables gender, duration of supplementation, total volume of Cr, and type of substance were chosen since they consistently show the same result pattern when examined across the dependent variables. Furthermore, due to the placebo effect found, the analysis took into account only the calculations from the experimental versus the placebo conditions.

Gender

Studies in which only males participated elicited higher ES than mixed groups ($p < .05$) (Table 6). For instance, ES for peak power in mixed groups (i.e, males and females) had smaller ES (ES = -.08) than only male categories (ES = 1.18). In addition, the magnitude of ES is different from zero ($p < .05$).

The one-way ANOVA tests for the ES of the experimental condition versus placebo shown in table 6 indicate that gender categories in peak power and total work were statistically different ($p < .05$).

The ES for males in total work was different from zero (ES = 84). However, in the variables peak force and 1 RM there were no significant gender differences ($p > .05$); although the ES magnitude for males was different from zero in 1 RM ($p < .05$).

Duration of the Supplementation

In general, prolonged Cr supplementation schemes increased the magnitude of the effect. This is clearly observed in ES of the variables peak force, 1 RM, and inconsistently in peak power (Table 6). This finding contradicts the results of the ES found on peak power (i.e., 4-9 days) and total work (i.e., 4-6 days). With the exception of 1 RM, none of the categories across the dependent variables reached statistical significance. This might have been due to sample dilution when performing the categorization of variables.

Total Creatine Volume

ANOVA tests revealed significant mean ES differences only in the categories for 1 RM ($p < .05$) for total Cr volume. Significant ES were observed for total volumes $\geq$ 350 gr up to 600 gr.

Type of Substance

The analyses did not show significant differences between the categories of types of substances in any of the four examined variables (i.e., peak power, total work, peak force, and 1 RM). However, there were ES statistically different from zero, for instance, peak power and total work showed significant ES for the category of mixed substance (e.g., creatine + carbohydrate), but this finding was inconsistent in the other dependent variables.

Table 6. *Effects of moderator variables in physical performance measures (experimental vs. placebo conditions)*

Moderator variable	Peak Power		Total work		Peak force		1 RM	
	Categories	ES	Categories	ES	Categories	ES	Categories	ES
Gender								
	Males	1.18*	Males	.84*	Males	1.90*	Males	.26*
	Mixed	-.08	Mixed	-.14	Mixed	1.52	Females	.46
Supplementation duration (days)								
	4-9	.82*	4-6	.80*	42-47	1.52	5-36	.09
	40-45	3.57	7-9	-.03	72-77	1.90*	37-38	.39*
	80-85	.31*					69-100	.58*
Total Cr volume (gr)								
	100-200	.82*	80-100	.80*	300-500	1.90*	150-200	.04
	500-600	.31*	180-200	-.03	700-900	1.52	350-400	.75*
	= 900	3.57					450-500	.78*
							550-600	.45*
Type of substance								
	Pure	.31			Creatine	1.92*	Creatine	.25*
	creatine	1.04*	Mixed	.70*	Mixed	1.41	Mixed	.39*
	Mixed							

Note. ES: Mean effect size; *: ES $\neq$ 0, $p < .05$

Discussion

The current meta-analysis examined the effects of Cr supplementation on biochemical parameters, body composition, and physical performance in humans. This quantitative technique systematically generated several types of ES that helped to explain some of the conflicting findings observed in the scientific literature. On the other hand, interesting and new effects that have not been studied with sufficient rigor in scientific literature were found, for instance, a considerable placebo effect.

It is important to emphasize the efforts of others in trying to summarize the literature on Cr supplementation in order to clarify the subject; however, no clear consensus has been reached. Up to now, the findings might be discouraging and confusing for regular Cr consumers, coaches and researchers. Most of the qualitative revisions have concluded that the area of Cr supplementation have produced conflicting findings which require further investigation (Juhn, 1999; Lamb, 1999; Lemon, 2002; Poortmans & Francaux, 2000; Terjung et al., 2000).

In order to better understand the discussion of the results, they are presented in the following order: a) biochemical parameters; b) body composition; and c) physical performance.

Biochemical parameters. According to the results of the present meta-analysis it is possible to affirm that Cr supplementation significantly changed the biochemical parameters, by increasing the levels of TCr and free Cr of the body. This finding confirms the different experimental studies in which treatments with Cr were applied and increased TCr levels were found (Balsom et al., 1995; Casey et al., 1996; Green et al., 1996; Greenhaff et al., 1994; Kreis et al., 1999; McConell et al., 2005; Preen et al., 2001; Rockwell, Walberg-Rankin, & Toderico, 2001; Snow et al., 1998; Volek et al., 1999). The evidence of the present meta-analysis is solid and it can be concluded that the experimental procedures used to change the levels of Cr in the body are valid and that they significantly increase the reserves of free Cr and TCr, which agrees with other studies that measured these parameters (Balsom et al., 1995; Harris, Soderlund, & Hultman, 1992).

It is also important to emphasize the consistency that exists between free Cr and TCr with the increase in the levels of urea excretion, creatinine and creatine, which implies that supplementation with Cr is assimilated and processed by the organism. Changes specifically in the levels of creatinine excretion have been reported in other studies (Bermon et al., 1998; Harris, Soderlund, & Hultman, 1992; Peyrebrune,

Nevill, Donaldson, & Cosford, 1998; Rebello-Mendes et al., 2004; Rossiter, Cannell, & Jakeman, 1996; Vandenberghe et al., 1997). Therefore, it is recommended that research be conducted to determine if there are any long term health consequences related to an increase in these excretion parameters. Although Cr supplementation has been used successfully in clinical settings (Guerrero-Oliveros & Wallimann, 1998; Stout, Eckerson, May, Coulter, & Bradley-Popovich, 2001), this recommendation is also based on previous findings of long term creatine supplementation on potential gyrate atrophy (Vannas-Sulonen, Sipilä, Vannas, Simell, & Rapola, 1985).

Poortmans and Francaux (2000) suggested studying the modification in the balance of the excretion parameters, which now appears to be an excellent recommendation, since in this meta-analysis it was demonstrated that there was an important alteration in the homeostasis of the organism. According to Terjung et al. (2000), there is evidence that relates creatinine excretion to renal dysfunction; nevertheless, the American College of Sports Medicine (Terjung et al., 2000) does not have a definitive position since they detected some limitations in the design of the studies reviewed.

With respect to the ATP levels, it was not demonstrated that Cr supplementation could improve or increase these reserves; therefore, the explanation that attributes the improvement in physical performance as result of increased ATP levels is discarded. The lactate levels did not show significant changes attributable to Cr supplementation. This was an unexpected finding since it has been speculated (Kreider, 2000) that if there is a higher energy availability from increased TCr stores, then the PCr metabolism would supply more energy to the working muscles. This would imply a reduction in the dependency of lactic acid metabolism, and consequently, a smaller lactate production would result during intermittent (e.g., > 3 repetitions), and maximum (e.g., 90 - 100 % VO_{2max}) exercise. However, it is necessary to emphasize the high variability in the lactate values, which suggests that other confounding variables influence the results. Finally, it is important to mention that the biochemical parameters did not show a placebo effect in any of the dependent variables studied.

Newman, Hargreaves, Graham, and Snow (2003) revealed that TCr stores in the body due to Cr supplementation significantly changed when applying the phase known as overload, a short time period when supplementation is often given in elevated doses (e.g., 20 gr Cr · d-1). Nevertheless, in the same study when the

researchers extended the period of supplementation by giving smaller doses of Cr more days (known as the maintenance phase), the researchers did not find differences with respect to the overload phase. This fact demonstrated that there might be a “roof” in the body’s ability to store Cr (i.e., TCr). It is also possible that prolonged supplementation periods do not have the intended effect since the storage limit is likely to be reached.

Body Composition

In this study it was found that Cr supplementation changed the body composition profile. Concretely, increases in lean mass were consistently found following Cr supplementation. The ES for lean mass found in this study was higher than the ES reported by Nissen and Sharp (2003), 0.61 ($p < 0.05$) and 0.26 ($p < 0.001$), respectively; although those authors only meta-analyzed 18 studies. We also found that body fat percentage decreased. These results were expected and support previous findings of those studies in which there were reported increases in muscle mass and total body mass (Balsom et al., 1995; Becque, Lochmann, & Melrose, 2000; Bermon et al., 1998; Burke et al., 2001; Dawson et al., 1995; Green et al., 1996; Greenhaff et al., 1994; Harris, Soderlund, & Hultman, 1992; Kamber et al., 1999; Kreider et al., 1998; Maganaris & Maughan, 1998; Mihic et al., 2000; Murphy et al., 2005; Peyrebrune et al., 1998; Preen et al., 2001; Rossiter, Cannell, & Jakeman, 1996; Snow et al., 1998; Vandenberghe et al., 1997; Volek et al., 1999; Volek et al., 2000). In a study in the elderly (Gotshalk et al., 2002), it was demonstrated that Cr supplementation increased total and lean mass significantly.

In spite of the previous findings, in the present meta-analysis it was found that the fat mass did not change following Cr supplementation (Table 3). The reduction in the fat percentage is explained by the overall change in the percent distribution of the total mass, because when lean mass is increased following Cr supplementation there is a concomitant change in fat percentage, however, in terms of fat mass. The consistency in the results of body composition allows affirming categorically that, in general, Cr supplementation combined with exercise training increases muscle mass. However, Branch (2003) reported no changes in body composition based on a meta-analysis of 96 studies when training state of the subject (i.e., trained vs. untrained) and gender were taken into consideration.

In the body composition variables studied, no placebo effect was found.

Furthermore, it is also important to mention that the total mass did not change significantly following Cr supplementation; however, the magnitude of the change can be considered moderate and positive, meaning a trend towards an increase in total mass. A high variability in the ES for total mass was found, therefore, other confounding variables are likely to influence the results. A possible explanation about the physiological mechanism responsible for the increases in lean mass might be the high rate of protein synthesis, possibly by a positive nitrogen balance in the body. There is also an increase in the intracellular liquid retention, which in turn stimulates muscle hypertrophy (Poortmans & Francaux, 2000).

Physical Performance

One of the most important findings of this meta-analysis is the combined effect of Cr supplementation and placebo on physical performance. This means that physical performance can be enhanced not only due the Cr supplementation itself, but also due to a psychological deceit (i.e., placebo), which allows subjects to perform better due to intrinsic expectations and possibly due to what we call “a psychological reserve”.

The ES found in this study for the physical performance variables range from .70 to 4.70 ($p < .05$), which agrees with the findings of the 18 studies meta-analyzed by Nissen and Sharp (2003), who reported a mean ES = 0.36 for net strength gain ($p < .001$). Similar results were reported by Dempsey, Mazzone and Meurer (2002), who meta-analyzed 16 studies and concluded that Cr supplementation combined with resistance training increased strength. In conclusion, it is demonstrated that Cr supplementation improved physical performance (i.e., peak power, total work, peak force and 1 RM); however, the ES magnitude of the experimental condition demonstrated a combined effect of Cr and the placebo.

In summary, Cr supplementation is widely used in athletic populations (Stanton & Abt, 2000). Based on the findings of this meta-analysis, Cr supplementation elicited significant biochemical changes widely reported in previous reviews (Mujika & Padilla, 1997), including consistent increases in excretion parameters (Burke et al., 2001). These changes apparently contributed to performance enhancements in peak power, total work, force power, and 1 RM as reported in several studies (Barnett, Hinds, & Jenkins, 1996; Bosco et al., 1997; Burke, Silver, Holt, Smith Palmer, Culligan, & Chilibeck, 2000; Cooke, Grandjean, & Barnes, 1995; Gilliam, Hohzorn, Martin, & Trimble, 2000; Harris, Viru, Greenhaff, & Hultman, 1993;

Mujika, Padilla, Ibáñez, Izquierdo, & Gorostiaga, 2000; Pearson, Hamby, Russel, & Harris, 1999; Schneider, McDonough, Fadel, & Berwick, 1997; Tarnopolsky & MacLennan, 2000; Vandebuerie, Vanden Eynde, Vandenberghe, & Hespel, 1998). It is likely that such changes could have been mediated by yet unclear physiological mechanisms (Rawson, Gunn, & Clarkson, 2001; Rico-Sanz & Mendez, 2000; Steenge, Lambourne, Casey, Macdonald, & Greenhaff, 1998; Van Leemputte, Vandenberghe, & Hespel, 1999). For total work there was a significant placebo effect; however, the Cr effect was even more powerful. The Anthropometric variables of body fat percentage and lean mass were also positively changed by Cr supplementation. In summary, Cr supplementation consistently shows biochemical, body composition and power changes in humans.

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