

**JEPonline**  
**Journal of Exercise Physiologyonline**

**Official Journal of The American  
Society of Exercise Physiologists (ASEP)**

**ISSN 1097-9751**

An International Electronic Journal  
Volume 4 Number 4 November 2001

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Exercise Nutrition

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**D-PINITOL AUGMENTS WHOLE BODY CREATINE RETENTION IN MAN**

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**ABSTRACT**

M. GREENWOOD, R.B. KREIDER, C. RASMUSSEN, A.L. ALMADA, AND C.P. EARNEST. **D-Pinitol Augments Whole Body Creatine Retention In Man. JEPonline.** 2001;4(4):41-47. Previous research has indicated that creatine retention is influenced by the intramuscular creatine concentration, and extracellular concentrations of glucose and insulin. The purpose of this study was to examine whether co-ingestion of D-pinitol (plant extract with insulin sensitizing characteristics) with creatine affects whole body creatine retention. Twenty male subjects with no history of creatine supplementation participated in this study. Subjects donated 24-hr urine samples for 4 days. After an initial control day designed to determine normal daily creatine excretion rates, subjects were matched according to body mass and randomly assigned to ingest in a single blind manner either a placebo (P=4 x 5 g of dextrose), creatine monohydrate (CM=4 x 5 g), CM with low dose D-pinitol (LP=4 x 5 g creatine + 2 x 0.5 g D-pinitol), or CM with high dose D-pinitol (HP=4 x 5 g creatine + 4 x 0.5 g D-pinitol) for 3 days. Additionally, another group ingested 2 x 0.5 g D-pinitol for 5-d followed by ingesting 4 x 5 g CM + 2 x 0.5 g D-pinitol for 3-d (Pre-P). Creatine retention was estimated by subtracting total urinary creatine excretion from total supplemental creatine intake over the 3-d period. Data were analyzed by ANOVA. Results revealed that whole body creatine retention over the 3 day loading period was significantly greater in the LP and Pre-P groups (P=0±0; CM=36.6±9; LP=49.7±3; HP=36.7±13; Pre P=46.7±6 g, p=0.001). This extrapolated to a significantly greater percentage of creatine retention in the LP and Pre-P groups (P=0±0; CM=61±15; LP=83±5; HP=61±22; Pre P=78±9 %, p=0.001). Results suggest that ingesting creatine with low doses of D-Pinitol may augment whole body creatine retention in a similar manner as has been reported with co-ingestion of high levels of carbohydrate or carbohydrate and protein. Additional research is warranted to investigate the possible influence that D-pinitol may have on insulin sensitivity and whole body creatine retention.

**Key Words:** Exercise, Insulin, Sport Nutrition, Dietary Supplementation, Ergogenic Aid

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## INTRODUCTION

Creatine loading has been reported to increase muscle creatine and phosphocreatine content by 5 to 30%. The typical method of creatine loading has been to ingest 5 g of creatine monohydrate, 4 times per day, for 3 to 7 days. However, some intra-subject variability has been reported in the literature regarding the magnitude that creatine stores are increased in response to creatine loading and how elevations in muscle creatine content affect performance (1). Researchers who have investigated the variability in creatine retention have found that creatine uptake into muscle is influenced by intramuscular creatine concentration and extracellular concentrations of glucose and insulin (2,3). In this regard, studies have suggested that individuals who start creatine supplementation with low muscle creatine and phosphocreatine content are more responsive to creatine supplementation. Moreover, that co-ingestion of creatine with large amounts of glucose (i.e., 35-95 g) and/or combinations of glucose and protein (~50 g each) enhance creatine storage (2-5) apparently in response to increases in insulin (6). Theoretically, co-ingestion of creatine with nutrients that affect insulin levels and/or sensitivity may enhance creatine retention.

D-pinitol (3-O-methyl-chiroinositol) is a plant extract that has been reported to possess insulin-like properties (7,8). In this regard, D-pinitol has been reported to stimulate glucose uptake into L6 cells and glycogen synthesis (9,10). L6 cells, originally derived from rat skeletal muscle, propagate as mononucleated myoblasts but differentiate by spontaneous cellular fusion into multinucleated primary myotubes. Insulin stimulation of glucose transport in L6 muscle cells results predominantly from the translocation to the cell surface of the glucose transporter, GLUT4, thus serving as a viable means to assess glucose uptake *in vitro*. Since D-pinitol has been reported to stimulate glucose uptake in L6 cells and promote glycogen synthesis, it is plausible that D-pinitol supplementation with creatine may promote creatine retention. Furthermore, the ingestion of D-pinitol prior to creatine loading may enhance insulin sensitivity and thereby promote greater creatine retention. The purpose of this study was to perform a pilot/proof of concept trial to examine whether D-pinitol supplementation during creatine loading would affect whole body creatine retention in man. In addition, we wanted to determine whether supplementing the diet with D-pinitol prior to creatine loading would promote greater effects.

## METHODS

### Subjects

Twenty apparently healthy males with no history of creatine use participated in this pilot study. All subjects in this investigation participated in a familiarization session. During the familiarization session, subjects were informed as to the experimental procedures, completed a personal/medical history form, exercise history form, creatine supplementation history form, and signed informed consent statements in adherence with the human subject's guidelines of Arkansas State University and the American College of Sports Medicine. Subjects were descriptively (mean±SEM) 23.4±1.7 yrs, 82.4±8 kg, and 181±7 cm. No subject in this trial was a vegetarian and all subjects reportedly consumed daily diets inclusive of meat.

### Supplementation Protocol

Subjects donated a 24 hr urine sample on the day preceding the initiation of supplementation in order to establish the subject's normal daily excretion of creatine in response to their normal diet. After this control day, subjects were matched according to total body mass and randomly assigned to ingest in a single-blind manner one of the following supplements four times daily for 3 days.

- **Placebo (P):** 5 g of dextrose with one 0.5 g capsule of corn starch.
- **Creatine Monohydrate (CM):** 5 g of CM with one 0.5 g capsule of corn starch.
- **Creatine Monohydrate with Low Dose D-Pinitol (LP):** 5 g of CM with alternating servings of one 0.5 g capsule of corn starch or D-pinitol.

- **Creatine Monohydrate Powder with High Dose Pinitol (HP):** 5 g of CM with one 0.5 g capsule of D-pinitol.
- **D-Pinitol Pre-Load (Pre-P):** 1 capsule of D-pinitol (0.5 g each serving) consumed twice/day for 5 days followed by the ingestion 5 g of CM with alternating servings of one 0.5 g capsule of corn starch or D-pinitol.

Subjects were instructed to mix the powdered supplements with water and to ingest the supplements at 8:00 a.m., 12:00 p.m., 4.00 p.m., and 8.00 p.m. each day in order to standardize supplement intake. Dextrose and creatine powders were comprised of similar mesh size, texture, taste, and appearance and were placed in generic single serving packets for single-blind administration. A pharmacist encapsulated the placebo and D-pinitol supplements in generic capsules. The CM used in the study was from SKW (Trotsberg, Germany) and the D-pinitol was obtained from Humanetics Corp. (Minneapolis, MN) as Inzitol™. Subject compliance in taking the supplements was verified daily by research assistants and all subjects were instructed to maintain their regular eating habits during the investigation period. Subjects' dietary intake was monitored with daily nutritional logs that were turned in each morning and it was noted that all subjects were meat eaters.

### Procedures

During the familiar session, subjects were instructed by the primary investigator on how to record nutritional intake on the provided nutritional log sheets. In addition, the primary investigator disseminated in a single blind manner the respective creatine products along with a verbal and written description of the supplementation protocol. Subjects were provided eight 3 L urine collection containers in order to collect 24 hr urine samples over the course of the study and were also requested to record the number of times they urinated each day. The 24 hr baseline urine sample time parameter was initiated at 8 am the day before supplementation protocols began. Subjects were asked to refrigerate their urine samples during the 24 hr time period.

Subjects reported daily to the Human Performance Laboratory between 7 & 8 am in order to drop off urine samples. Subjects also turned in daily nutritional intake logs, which included type and amount of fluid ingested over the 24 hr time period. Urine volume and fluid intake for the 24 hr period recorded. Urine samples were vortexed and a standard qualitative urinalysis was performed to assess urine specific gravity (Chem Strip 10SG, Roche Diagnostics, Indianapolis, IN). In addition, approximately 10 mL of urine was transferred into labeled urine storage tubes and stored at -80 °C. Urine samples were shipped on dry ice to researchers in the Department of Biomedical Sciences, Queen's Medical Center, at the University of Nottingham, England for blinded analysis of creatine and creatinine levels using standard high performance liquid chromatography (HPLC) (2,3,5).

Daily creatine and creatinine excretion (g) were determined by multiplying daily excretion (g/L) by urine volume expressed in L. Daily creatine retention was calculated by subtracting daily creatine excretion (g) from daily supplemental creatine (20 g). Cumulative creatine retention was determined by subtracting the total amount of creatine excreted over the 3 day supplementation period from the total amount of creatine supplemented to the diet during the 3 day loading period (i.e., 60 g). Percent creatine retention was determined by dividing the cumulative amount of creatine retained over the supplementation period by the total amount of creatine supplemented to the diet.

### Statistic Analysis

Data were analyzed by repeated measure ANOVA with LSD post-hoc procedures for all daily measurements. A factorial ANOVA with LSD post-hoc procedure was used to assess all cumulative (i.e., 3 days) data measures. Data were analyzed using the SPSS for Windows version 10.05 statistical package (SPSS Inc., Chicago, IL). Statistical significance was determined as  $p=0.05$ . Data are presented as means $\pm$ SEM.

## RESULTS

No significant interactions ( $p>0.05$ ) were observed among groups in fluid intake, urine specific gravity, or urinary creatinine excretion. Table 1 presents mean daily urine volume, creatine excretion, and creatine retention observed for the placebo (P), creatine monohydrate (CM), low-dose D-pinitol (LP), high-dose D-Pinitol (HP), and pre-pinitol loading (Pre-P) groups. No significant interactions were observed among groups in urine volume. Daily creatine excretion expressed in g/L increased in all groups ingesting creatine during the supplementation period in comparison to their control day and the placebo group. Significant differences were also observed among the creatine supplementation treatments. Post-hoc analysis generally revealed that creatine excretion was greater in the CM and HP groups in comparison to the LP and Pre-P groups. Significant group effects ( $p=0.001$ ) were also observed among daily estimated creatine retentions during the 3-d creatine loading period. Average daily creatine retention was  $0\pm 0$ ,  $12.2\pm 1.3$ ,  $16.6\pm 1.3$ ,  $12.2\pm 1.3$ , and  $15.6\pm 1.3$  g/day for the P, CM, LP, HP, and Pre-P groups respectively. Post-hoc analysis revealed that average daily creatine retention was significantly greater in the LP and Pre-P groups in comparison to the P, CM, and HP groups ( $p<0.05$ ).

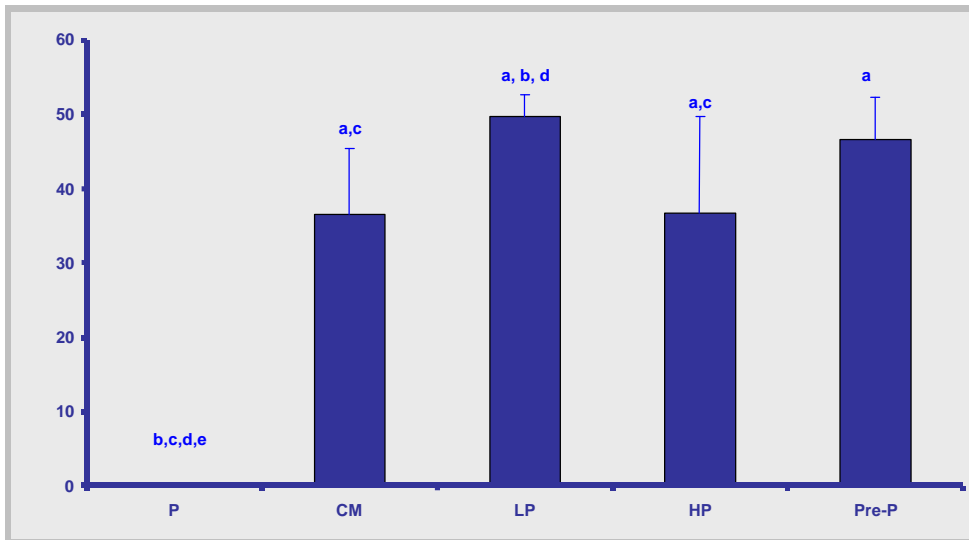
**Table 1. Daily urine volume, urinary creatine excretion, and estimated creatine retention observed for the placebo (P), creatine monohydrate (CM), low-dose D-pinitol (LP), high-dose D-Pinitol (HP), and pre-pinitol loading (Pre-P) groups.**

	<i>Control</i>	<i>Day 1</i>	<i>Day 2</i>	<i>Day 3</i>
<b>Urine Volume (L)</b>				
<i>P</i>	1.50±0.54	2.12±0.47	1.74±0.50	1.63±0.45
<i>CM</i>	2.16±0.70	3.10±1.10	2.66±1.32	3.31±1.13
<i>LP</i>	1.98±0.78	3.51±1.78	4.11±2.03	2.85±1.32
<i>HP</i>	1.73±0.70	2.44±0.87	2.48±1.24	2.22±0.60
<i>Pre-P</i>	3.04±1.80	2.53±1.27	2.65±1.42	1.51±1.30
<b>Urine Creatine (g/L)</b>				
<i>P</i>	0.14±0.08	0.16±0.05 <sup>cdef</sup>	0.12± <sup>cdef</sup>	0.12±0.06 <sup>cdef</sup>
<i>CM</i>	0.54±0.64 <sup>cdef</sup>	5.54±2.55 <sup>abd</sup>	8.58±3.78 <sup>abdef</sup>	9.28±6.3 <sup>abdf</sup>
<i>LP</i>	0.24±0.19 <sup>cdef</sup>	2.87±0.80 <sup>abc</sup>	3.89±0.89 <sup>abce</sup>	3.56±1.80 <sup>abcef</sup>
<i>HP</i>	0.18±0.05 <sup>cdef</sup>	4.05±2.10 <sup>ab</sup>	11.50±13.45 <sup>abcdf</sup>	7.74±4.6 <sup>abd</sup>
<i>Pre-P</i>	0.46±0.30 <sup>cdef</sup>	4.33±1.74 <sup>ab</sup>	2.98±2.22 <sup>abce</sup>	6.00±2.29 <sup>abcd</sup>
<b>Creatine Retention (g/d)</b>				
<i>P</i>		0±0 <sup>cdef</sup>	0±0 <sup>cdef</sup>	0±0 <sup>cdef</sup>
<i>CM</i>		14.46± 2.55 <sup>bd</sup>	11.41±3.76 <sup>bd</sup>	10.72±6.30 <sup>bdf</sup>
<i>LP</i>		17.13±0.80 <sup>bc</sup>	16.11±0.89 <sup>bce</sup>	16.44±1.80 <sup>bce</sup>
<i>HP</i>		15.95±2.09 <sup>b</sup>	8.50±13.45 <sup>bdf</sup>	12.26±4.6 <sup>bd</sup>
<i>Pre-P</i>		15.67±1.74 <sup>b</sup>	17.02±2.22 <sup>bce</sup>	13.99±2.30 <sup>bc</sup>

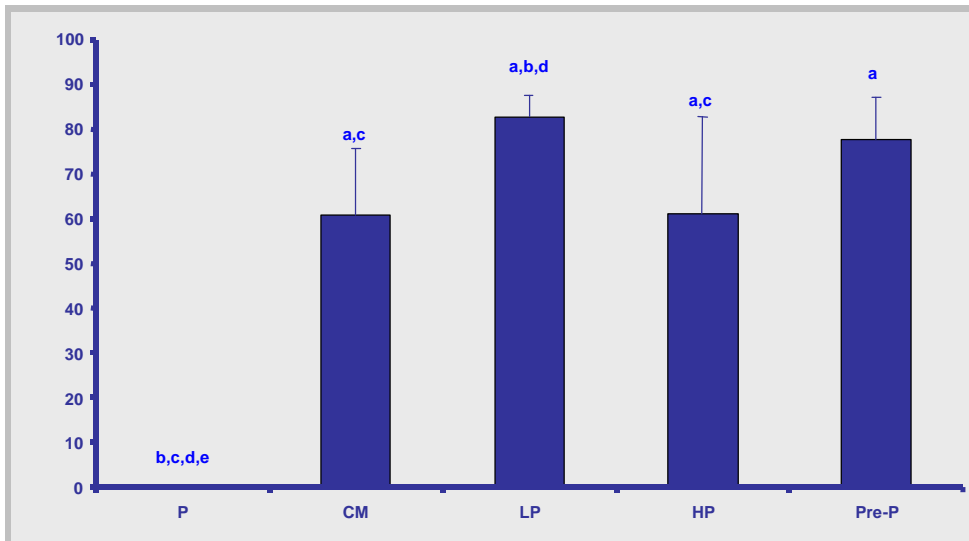
a =  $p<0.05$  difference from control day ; b =  $p<0.05$  from the P group ; c =  $p<0.05$  from the CM group ; d =  $p<0.05$  from the LP group ; e =  $p<0.05$  from the HP group ; f =  $p<0.05$  from the Pre-P group.

Figure 1 presents the estimated cumulative creatine retention expressed in grams observed during the 3 day loading period. ANOVA revealed significant differences among groups ( $p=0.001$ ) in total creatine retention ( $P = 0\pm 0$ ;  $CM=36.6\pm 9$ ;  $LP=49.7\pm 3$ ;  $HP=36.7\pm 13$ ;  $Pre-P=46.7\pm 6$  g). Post-hoc analysis indicated that creatine supplementation increased whole body creatine retention in all groups in comparison to P group ( $p<0.05$ ). Moreover, that creatine retention was significantly greater ( $p<0.03$ ) in the LP in comparison to the CM and HP groups and tended to be greater ( $p=0.08$ ) in the Pre-P group in comparison to the CM and HP groups. Figure 2 presents the estimated cumulative percentage of supplemental creatine retained during the 3 day loading period.

The percentage of supplemental creatine retained was  $0 \pm 0$ ,  $61 \pm 15$ ,  $83 \pm 5$ ,  $61 \pm 22$ , and  $78 \pm 9$  % for the P, CM, LP, HP, and Pre-P groups, respectively. Significant differences ( $p=0.001$ ) were similarly observed among groups when creatine retention was expressed as a percentage of total creatine supplemented in the diet.



**Figure 1.** Three-day cumulative creatine retention for the placebo (P), creatine monohydrate (CM), low-dose D-pinitol (LP), high-dose D-Pinitol (HP), and pre-D-Pinitol loading (Pre-P) groups. Data are means $\pm$ SD, a =  $p < 0.05$  from placebo. b= $p < 0.05$  from CM. c= $p < 0.05$  from LP. d= $p < 0.05$  from HP. e= $p < 0.05$  from Pre-P.



**Figure 2.** Percentage of creatine retained during the 3 day loading period for the placebo (P), creatine monohydrate (CM), low-dose D-pinitol (LP), high-dose D-Pinitol (HP), and pre-D-Pinitol loading (Pre-P) groups. Data are means $\pm$ SD. a =  $p < 0.05$  from placebo ; b= $p < 0.05$  from CM ; c= $p < 0.05$  from LP ; d= $p < 0.05$  from HP ; e= $p < 0.05$  from Pre-P.

## DISCUSSION

The major finding from this study is that low dose of D-pinitol supplementation during creatine loading appears to augment whole body creatine retention. Results also indicate that ingesting a higher dose of D-pinitol did not augment creatine retention in comparison to a standard creatine supplementation protocol. Interestingly, pre-dosing with D-pinitol had the same affect as the co-administration of low dose D-pinitol. Given that the pre-dosing group ingested the same schema of creatine and low pinitol as the low pinitol group, it appears that no further benefit seems to be gained by “pre-sensitizing” ones system with D-pinitol prior to creatine supplementation.

These findings are important for several reasons. First, until now the only known method for enhancing creatine uptake has been by co-ingestion of creatine with large amounts of glucose (e.g., 35-95 g) and/or glucose and protein (~50 g each) (2-5). Results of this pilot trial suggest that pinitol may have a direct effect on insulin sensitization, which may thereby facilitate creatine uptake. Second, the apparent influence that low-dose D-pinitol supplementation has on whole body creatine retention is similar to that exhibited indirectly via carbohydrate as carbohydrate triggers the release of insulin and insulin facilitates creatine uptake (6). It is possible that since D-pinitol may have insulin like effects, the need to ingest large amounts of carbohydrate or carbohydrate and protein during creatine loading may either reduced or eliminated.

Harris and coworkers (1) were among the first to show that the oral creatine monohydrate supplementation (e.g., 5 g, 4-6 times/day, for 2 or more days) significantly increased total creatine content of the quadriceps femoris muscle. It was further observed that the greatest uptake by skeletal muscle occurred in subjects with a low initial total creatine content (1). Several years later, Green and colleagues (2,3) demonstrated via analysis of muscle biopsy, urine, and plasma samples that ingesting 5 g of creatine monohydrate, followed 30 min later by ingesting 93 g of simple carbohydrate in solution four/day for 5 days resulted in an increase in muscle phosphocreatine, creatine, and total creatine compared to creatine ingestion alone. These researchers also found that creatine plus carbohydrate ingestion dramatically elevated insulin concentrations and glycogen synthesis. These findings led to the premise that creatine accumulation during creatine supplementation in humans appears to be mediated in part by insulin. Further investigation into this phenomenon has shown that ingesting 35 g of carbohydrate with each dose of creatine may promote greater training adaptations than ingesting creatine alone (4) and that the combination of carbohydrate and protein will also augment creatine retention (5). Though this phenomenon is interesting, it can be onerous to the athlete, as one would have to consume an extra 560–1,500 calories with creatine in order to promote these adaptations. Consequently, there has been interest in determining whether other nutritional interventions may augment creatine retention.

Since D-pinitol has been reported to have insulin-like properties (9,10), co-ingestion of D-pinitol with creatine may serve as a means of augmenting creatine retention without having to ingest large quantities of carbohydrate and/or carbohydrate and protein. However, since D-pinitol is a relatively new discovery, the optimal dosage necessary to enhance the insulin-sensitizing effects in humans is unknown. Results of this pilot study suggest that ingesting low-doses of D-pinitol during creatine loading (i.e., 2 x 0.5 g/day) may augment creatine retention. However, ingesting higher quantities (i.e., 4 x 0.5 g/d) does not appear to affect creatine retention. Although these findings appear to be contradictory, it is possible that feed-back/feed-forward mechanisms might exist that will either enhance or blunt the possible effects of D-pinitol depending on the amount supplemented to the diet. However, additional research is necessary to examine the effects of varying doses of D-pinitol on insulin sensitivity and creatine retention before conclusions can be drawn.

In summary, results of this pilot study indicate that co-administration of creatine monohydrate with low-doses of D-pinitol (0.5 g, twice/day) may offer a non-caloric means of augmenting whole body creatine stores. However, ingestion of a higher dose of D-pinitol (0.5 g, four/daily) did not enhance creatine retention. Additional research

is warranted to examine the possible influence that D-pinitol supplementation may have at varying doses on insulin sensitivity and whole body creatine retention.

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## ACKNOWLEDGMENTS

We would like to thank the subjects who participated in this study and the laboratory assistants in the Human Performance Laboratory at Arkansas State University who assisted in data acquisition and analysis. This study was funded in part by Humanetics Corporation (Minneapolis, MN) and MetaResponse Sciences (Laguna Niguel, CA). Investigators from Arkansas State collected, analyzed and interpreted data from this study and have no financial interest in the outcome of results reported. Presentation of results in this study does not constitute endorsement by the researchers or the institutions that they are affiliated of the nutrients investigated.

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