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The Effect of Creatine Monohydrate Supplementation with Resistance Training on Liver Responses in Sedentary Males

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Abstract: This study evaluated the effects of long-term creatine monohydrate supplementation and resistance training on indices of liver disruption in previously sedentary males. Liver integrity was assessed by determining serum Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) activities before and after the supplementation and training. 20 non-athletic males (age 22.25 ± 2.02 years; weight 71.55 ± 4.72 Kg; height 171.92 ± 5.98 Cm) were randomly divided into two groups [training-creatine (n=10), training-placebo (n=10)] within a double-blind design. Both groups participated in resistance training and completed the 8 weeks weight training protocol. The creatine group consumed 250 ml creatine monohydrate supplementation solution (0.07 g/kg/day, creatine) and the placebo group consumed (0.07 g/kg/day, of wheat flour) during the training protocol. Venous blood samples were obtained 24h before the beginning protocol and 48 h after last session. Serum ALT and AST activities were measured by auto-analyzer system. Data was statistically analyzed by dependent and independent t-test at significance level P=0.05. There were no significant differences in serum ALT and AST activities before and after training in either the creatine training (P=0.102 and P=0.086 respectively) and placebo training groups (P=0.265 and P=0.769 respectively). Moreover, there were no significant differences in ALT or AST activities between creatine training and placebo groups before or after the 8 week protocol (P=0.519 and P=0.844 respectively). This observation suggests that 8 weeks resistance training period along with creatine monohydrate ingestion does not have adverse effects on these hepatic cellular damage indices.

Key words: Hepatic Enzymes · Creatine supplementation · Resistance Training

INTRODUCTION

Phosphocreatine plays a central role in the maintenance of power output in high intensity exercises. Depletion of muscle phosphocreatine during intense exercise is associated with the onset of muscle fatigue during such exercises [1]. Many studies have shown that oral creatine supplementation increases total creatine and creatine phosphate content in human skeletal muscle [2-7]. Increasing the phosphocreatine content of muscle through creatine monohydrate (CrM) supplementation has been demonstrated to increase subjects' work output during intermittent bouts of anaerobic activity [1,8-11]. Studies also suggest that creatine (Cr) supplementation can increase the concentrations of both creatine and phosphocreatine in skeletal muscle which may provide the means necessary for improved strength by an increase in muscle mass when combined with resistance training [12].

So far, Cr supplementation`s biochemical [13], physiological [13], ergogenic [14] and therapeutic [15,16] roles have been extensively investigated. In the last 20 years, Cr has become a very popular dietary supplement [17,18] and despite its widespread use, there is little evidence concerning possible side effects [19-21]. There has been scrutiny of possible adverse effects of creatine supplementation on renal function, however little research has been done of possible effects of creatine supplementation on hepatic function.

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Juhn and Tarnopolsky (1998) [22] and Kreider *et al.* (1998) [23] in their research articles relating to renal function stated a direct need for investigations into the effects of creatine on hepatic function. Poortmans and Francaux's (2000) [24] review of the health related literature surrounding creatine supplementation found two research abstracts, two research manuscripts and the authors' unpublished data as the only sources of information regarding blood markers of hepatic function in healthy individuals and athletes.

One retrospective study examining a wide variety of serum markers of health did include some measures of relevance to hepatic function [25]. This study found no relationship between Cr supplementation and these markers but also proposed that further studies be conducted to add weight to their conclusions. Robinson *et al.* (2000)[26] examined selected hematologic and serum chemistry indices in healthy subjects and found only serum creatinine to be significantly and reversibly affected by supplementation. Whereas some studies did not report any alteration in renal and hepatic function after Cr supplementation [27,28], others have suggested that Cr may speed up renal and hepatic disease progression [28-30]. Liver diseases have presented a broad variability in several human and animal studies, as well as in the criteria used to categorize the severity of hepatotoxicity [31]. Plasma levels of hepatic enzymes, such as ALT and AST are considered valuable for detecting toxic effects on the liver [32].

The present study specifically investigated the relationship of serum markers of hepatic stress during strength training while supplementing with Cr in non-trained males during intense resistance training.

MATERIAL AND METHODS

Subjects: Twenty non-trained healthy male students with no history of participation in any regular exercise training regimen were recruited for this study. None were taking any drugs. They were also required to be free of any creatine supplement for at least one month prior to training. The meal program was the same for all subjects one week before and throughout the research period. After receiving oral and written information about the study plans and procedures, subjects signed an informed consent form. The experimental protocol was approved by the local university ethics committee and all subjects were informed of the risks and purposes of the study before their written consent was obtained. Following the familiarization session, the subjects were randomly divided into creatine monohydrate training (CrMT) and placebo training (PT) groups by a double-blind way. Table 1 gives the physical and training characteristics of the subjects at the start of the study.

Table 1: Anthropometric data for the CrMT and PT groups. Data are means (±SD).

Variable	Creatine Monohydrate+Training	Placebo+Traning
Age (years)	22.30 (1.94)	22.20 (2.20)
Height (cm)	171.25 (5.34)	172.60 (6.12)
Weight (kg)	72.5 (4.69)	70.60 (4.81)
BMI	24.72 (1.64)	23.69 (1.28)
%FAT	22.37 (4.75)	21.63 (3.08)

Determination of Resistance Training: At least one week before the first training session, two groups subjects were thoroughly familiarized with the implemented exercise tests and all subjects` 1RM were measured by the following formula [33]:

$$1RM = \frac{weigh\ Load\ Amount(kg)}{[1.0278 - (Number\ of\ repetitions \times 0.0278]}$$

After all pre-test data was collected; two groups were instructed to take creatine monohydrate and placebo supplements and to continue with the prescribed work-out program. The most important concept of this study was that the subjects were not to deviate from their regular work out program or daily diet under any circumstances. Any alteration in these two variables could result in their removal from the study. The subjects were asked to continue with their program for 8 weeks, 3 times a week with training daily sessions of 90 minutes.

Throughout the supplementation period, the subjects performed a regular resistance-training program, which consisted of a free-weight bench press, leg press, barbell curl, reverse grip cable press-down, standing cable reverse fly and dumbbell lateral raise based on each subject's 1RM and consisted of 3 sets of 10 repetitions at 75% of 1RM and subjects rested for 60-90 sec between repetitions and for 1-3 minutes between sets. No progression was built into the program and subjects continued using the same resistance throughout the study. This would allow for assessment at the end of the 8 week protocol that would be reflective primarily of ALT and AST activity in serum, primarily from liver sources and not potentially complicated by ALT or AST due to possible muscle damage or disruption as all muscle damage or adaptation would have been resolved by this time.

Creatine Monohydrate Supplementation: In order to obtain baseline values of alanine aminotransferase (ALT) and aspartate aminotranferase (AST), all subjects abstained from any creatine supplementation for one month prior to the beginning of the testing protocol. This duration was chosen as Hultman *et al.* (1996) [6], indicated a return of intracellular creatine levels to baseline after a 30 day period of no supplementation [34]. Pure creatine monohydrate (Nutrasense, Shawnee, KS) was distributed to the entire CrMT group prior to the initiation of the study. The CrMT group consumed 250 ml creatine monohydrate supplementation solution (0.07 g/kg/day, creatine) during training protocol. The placebo group received wheat flour (0.07 g wheat flour /kg body mass/day) during training protocol. Both groups were instructed to ingest the supplement and wheat flour along with 250 ml grape juice [35,36].

All daily doses were taken orally and were monitored by the research coordinator to insure proper supplementation. On training days the subjects were instructed to consume a portion of their daily dose within one hour of completing their training session. None of the subjects were vegetarians and all reported consuming a varied diet which remained consistent throughout the study.

Blood Sampling and Enzymatic Measurements: A standard 10 mL serum tube (Vacutainer SST, Becton-Dickinson, Franklin Lakes, NJ) of blood was acquired from the forearm vein, 24 hours before the beginning of training program and 48 hours after the ending of training program at 8 a.m. Each subject and each sample was assigned a unique identification number and the code key remained confidential until all analyses were completed.

The enzyme assays were then completed for blood alanine aminotransferase (ALT) and aspartate aminotransferase (AST) using autoanalyser (Hitachi 917 Automate; Mannheim, Germany) and Roche Diagnostic's reagents (Mannheim, Germany).

Statistical Analysis: The results were expressed as mean ± SEM. Independent samples t-test was used to determine differences between CrMT and PT groups' plasma ALT and ALS concentrations means. Additionally, differences within the two groups for plasma ALT and ALS concentrations means were determined using paired samples t-test. Data in text and figures are given as the mean ± sem. P = 0.05 was considered statistically significant. All data was analyzed by using SPSS for windows software version 16.0 (SPSS Inc, Chicago, IL).

RESULTS

There were no age, height, weight; BMI and %fat differences between the CrMT and placebo group subjects (Table 1). All 20 subjects completed the 8 week training period and the data from all subjects were included in the analyses. Figure 1 indicates the comparison of the of serum ALT and AST concentrations between CrMT and PT groups.

At the end of the week 8, the mean ALT and AST concentrations of creatine monohydrate supplementation group were not significantly different from the levels found before the start of the study (p=0.102 and p=0.086).

Similarly the levels of serum ALT and AST activities of the placebo group at the end of the wk 8 training were not significantly different from the before training levels (p=0.265 and p=0.769).

Additionally, independent samples t-test between the two training groups showed that there were no significant differences between ALT concentrations before or after training protocol (p=0.519 and p=0.486) between groups. Similarly AST concentrations between the two training groups were not significantly different before or after the training protocol (p=0.844 and p=0.431).

DISCUSSION

This study demonstrates that an 8 week period of the creatine monohydrate supplementation ingestion along with light resistance training does not result in increased serum ALT and AST levels as indicative of hepatic tissue damage in previously untrained males. ALT and AST measurements serve as clinical indicators of hepatic, myocardial, or skeletal muscle necrosis [34]. Concentrations of these enzymes must increase 10-200 folds in order to become clinically relevant markers of malfunction or disease [34,37].

Oral Cr supplementations in humans and rats has been proven to increase physical performance [14,21,38] and some studies have demonstrated benefits in certain pathological conditions [21,39,40]. So, the Cr supplementation has become popular among athletes due to a performance-enhancing potential. However, as an available and legal product, it can be easily purchased in nutrition stores or supermarkets and the potential effect on muscle mass enhancement among untrained and/or among non-healthy people may represent a major concern, because its side effects have not been well established [21].

The results of this study suggest that the specific enzymes that can mark hepatic stress (ALT and AST) are not significantly affected when creatine monohydrate is supplemented with modest training in previously untrained males. These data support previous findings of Almada *et al.* [41], Earnest *et al.*[42], Mihic *et al.* [43], Robinson *et al.* [26], Schilling *et al.*[25] and Waldron *et al.* [34] who found no significant changes in hepatic associated serum enzyme levels with creatine supplementation. These data are also consistent with Poortmans and Franceaux's [24] review of existing literature that concluded that there were no deleterious effects to an athlete's health from creatine supplementation.

However, in exercised and exercised plus Cr supplemented group following 1 week of training, Souza *et al.* [21] observed an increased level of AST when compared to the Control groups. These results could be attributed to muscular alterations and not necessarily to Cr supplementation, since other studies demonstrate that physical exercise in initial periods of adaptation can generate muscular damage, characterized by plasma AST elevation [44,45]. The present study examined the effects of Cr supplementation after 8 weeks and no progression in training intensity or duration was used. Hence it is likely that muscular damage or adaptation would not contribute to any serum ALT or AST activity changes seem in at the end of this training period and any possible changes in ALT or AST activities could be attributed to liver sources alone. Since no such changes were seen, it is likely that 8 weeks of Cr supplementation combined with modest resistance training had no adverse effect on liver function as determined by these measures.

Although we have no measured intramuscular Cr content it is possible to speculate that exercise training could protect against kidney and liver alterations, by increasing Cr accumulation by skeletal muscles during exercise training, resulting in a decreased Cr accumulation and/or turnover in the kidneys and liver.

Overall, the results of the current study showed that resistance training at 75% of 1RM load, three times a week with training sessions of 90 minutes combined with recommended doses of Cr supplementation will not alter specific indicators of liver damage following the 8 week training program. However, it should be noted that the findings of the current study may only be applicable to a CrM supplementation at "recommended" doses used in this study.

CONCLUSION

Our data adds to the existing body of knowledge supporting the safety of creatine monohydrate supplementation over a period of weeks to months.

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REFERENCES

1. Rossiter, H.B., E.R. Cannell, P.M. Jakeman, 1996. the Effect of Oral Creatine Supplementation on the 1000-m Performance of Competitive Rowers, J. Sports Sci., 14: 175-179.
2. Febbraio, M.A., T.R. Flanagan, R.J. Snow, S. Zhao and M.F. Carey, 1995. Effect of creatine supplementation on intramuscular TCr, metabolism and performance during intermittent, supramaximal exercise in humans. Acta Physiologica Scandinavica, 155: 387-395.
3. Greenhaff, P.L., K. Bodin, K. Soderlund and E. Hultman, 1994. Effect of oral creatine supplementation on skeletal muscle phosphocreatine resynthesis. American J. Physiol., 266: 725-730.
4. Greenhaff, P.L., A. Casey, A.H. Short, R.C. Harris, K. Soderlund and E. Hultmann, 1993. Influence of oral creatine supplementation on muscle torque during repeated bouts of maximal voluntary exercise in man. Clinical Sci., 84: 565-571.
5. Harris, R.C., K. Soderlund and E. Hultman, 1992. Elevation of creatine in resting and exercised muscle of normal subjects by creatine supplementation. Clinical. Sci., 83: 367-374.
6. Hultman, E., K. Söderlund, J.A. Timmons, G. Cederblad and P.L. Greenhaff, 1996. Muscle creatine loading in men. J. Applied Physiol., 81(1): 232-237.
7. Van Loon, L.J.C., A.M. Oosterlar, F. Hartgens, M.K.C. Hesselink, R.J. Snow and A.J.M. Wagenmarkers, 2003. Effects of creatine loading and prolonged creatine supplementation on body composition, fuel selection, sprint and endurance performance in humans. Clinical Sci., 104: 153-162.

8. Balsom, P.D., B. Ekblom, K. Sonderlund and B. Sjodin, 1993. Creatine supplementation and dynamic high intensity intermittent exercise. Scandinavian J. Medicine Science in Sport, 3: 143-149.
9. Balsom, P. and B. Sjödin, 1995. Skeletal Muscle Metabolism During Short Duration High Intensity Exercise: Influence of Creatine Supplementation. Acta Physiologica Scandinavica, 154: 303-310.
10. Greenhaff, P.L., 1995. Creatine and its Application as an Ergogenic Aid, International J. Sport Nutrition, 5: 100-110.
11. Flanagan, P.M., M. Foley, T. Rossiter, 2004. Oral Creatine Supplementation and Short-Term Dynamic Power Production in Healthy Young Men, Presented to the Royal Academy of Medicine in Ireland, Conference of Human Sciences, Trinity College Dublin, 2004.
12. Bembeni, M.G., M.S. Witten, J.M. Carter, K.A. Eliot, A.W. Knehans and D.A. Bemben, 2010. The effects of supplementation with creatine and protein on muscle strength following a traditional resistance training program in middle-aged and older men. The J. Nutrition, Health and Aging, 14(2): 155-159.
13. Greenhaff, P.L., 1997. The nutritional biochemistry of creatine. The J. Nutritional Biochemis., 11: 610-618.
14. Bemben, M.G. and H.S. Lamont, 2005. Creatine supplementation and exercise performance: recent findings. Sports Med., 35: 107-125.
15. Gualano, B., G.G. Artioli, J.R. Poortmans and A.H. Lancha Junior, 2009. Exploring the therapeutic role of creatine supplementation. Amino Acids. Mar. 1. [Epub ahead of print].
16. Vieira, R.P., A.C. Duarte, R.C. Claudino, A. Perini, A.B. Santos, H.T. Moriya, F.M. Arantes-Costa, M.A. Martins, C.R. Carvalho and M. Dolhnikoff, 2007. Creatine supplementation exacerbates allergic lung inflammation and airway remodeling in mice. American J. Respiratory Cell and Molecular Biology., 37: 660-667.
17. Bird, S.P., 2003. Creatine supplementation and exercise performance: a brief review. J. Sports Science and Med., 2(4): 123-132.
18. Maughan, R.J., D.S. King and T. Lea, 2004. Dietary supplements. J. Sports Sci., 22: 95-113.
19. Bizzarini, E. and L. De Angelis, 2004. Is the use of oral creatine supplementation safe? The J. Sports Medicine and Physical Fitness, 44: 411-416.
20. Poortmans, J.R., A. Kumps, P. Duez, A. Fofonka, A. Carpentier and M. Francaux, 2005. Effect of oral creatine supplementation on urinary methylamine, formaldehyde and formate. Medicine and Science in Sports and Exercise, 37: 1717-1720.
21. Souza, R.A., H. Miranda, M. Xavier, R.A. Lazo-Osorio, H.A. Gouvea, J.C. Cogo, R.P. Vieira and W. Ribeiro, 2009. Effects of high-dose creatine supplementation on kidney and liver responses in sedentary and exercised rats. J. Sports Science and Med., 8: 672-681.
22. Juhn, M.S. and M. Tarnopolsky, 1998. Potential side effects of oral creatine supplementation: A critical review. Clinical J. Sport Med., 8: 298-304.
23. Kreider, R.B., M. Ferreira, M. Wilson, P. Grindstaff, S. Plisk, J. Reinardy, E. Cantler and A.L. Almada, 1998. Effects of creatine supplementation on body composition, strength and sprint performance. Medicine and Science in Sports and Exercise, 30(1): 73-82.
24. Poortmans, J.R. and M. Francaux, 2000. Adverse effects of creatine supplementation, fact or fiction? Sports Med., 30(3): 155-170.
25. Schilling, B.K., M.H. Stone, A. Utter, J.T. Kearney, M. Johnson, R. Coglianese, L. Smith, H.S. O'Bryant, A.C. Fry, M. Starks, R. Keith and M.E. Stone, 2001. Creatine supplementation and health variables: a retrospective study. Medicine and Science in Sports and Exercise, 33(2): 183-188.
26. Robinson, T.M., D.A. Sewell, A. Casey, G. Steenge and P.L. Greenhaff, 2000. Dietary creatine supplementation does not affect some haematological indices, or indices of muscle damage and hepatic and renal function. British J. Sports and Med., 34(4): 284-8.
27. Taes, Y.E., J.R. Delanghe, B. Wuyts, J. VanDeVoorde and N.H. Lameire, 2003. Creatine supplementation does not affect kidney function in an animal model with pre-existing renal failure. Nephrology Dialysis Transplantation, 18(2): 258-264.
28. Tarnopolsky, M.A., J.M. Bourgeois, R. Snow, S. Keys, B.D. Roy, J.M. Kwieeien and J. Turnbull, 2003. Histological assessment of intermediate and long-term creatine monohydrate supplementation in mice and rats. American J. Physiology. Regulatory, Integrative and Comparative Physiol., 285: 762-769.
29. Edmunds, J.W., S. Jayapalan, N.M. Dimarco, M.H. Saboorian and H.M. Aukema, 2001. Creatine supplementation increases renal disease progression in Han:SPRD-cy rats. American J. Kidney Diseases, 37: 73-78.

30. Ferreira, L.G., C. De Toledo Bergamaschi, M. Lazaretti-Castro and I.P. Heilberg, 2005. Effects of creatine supplementation on body composition and renal function in rats. Medicine and Science in Sports and Exercise, 37(9): 1525-1529.
31. Nunez, M., 2006. Hepatotoxicity of antiretrovirals: incidence, mechanisms and management. J. Hepatol., 44: 132-139.
32. Boada, L.D., M. Zumbado, S. Torres, A. Lopez, B.N. Diaz-Chico, J.J. Cabrera and O.P. Luzardo, 1999. Evaluation of acute and chronic hepatotoxic effects exerted by anabolic-androgenic steroid stanozolol in adult male rats. Archives of Toxicol., 73: 465-472.
33. Bompa, T.O., 1999. Periodization: Theory and Methodology of Training. 4th Ed.,
34. Waldron, J.E., J.W. Pendlay, T.G. Kilgore, G.G. Haff, J.S. Reeves and J.L. Kilgore, 2002. Concurrent creatine monohydrate supplementation and resistance training does not affect markers of hepatic function in trained weightlifters. J. Exercise Physiol., 5(1): 57-64.
35. Cooke, M., 2005. The effects of nutritional supplementation on regeneration of muscle function after damage. A dissertation submitted in total fulfillment of the requirements of the degree of Doctor of Philosophy. Faculty of Health, Engineering and Science Victoria University Footscray Park Campus: Victoria, Australia.
36. Santos, R.V., R.A. Bassit, E.C. Caperuto and L.F. Costa Rosa, 2004. The effect of creatine supplementation upon inflammatory and muscle soreness markers after a 30km race. Life Sci., 75(16): 1917-24. PMID: 15306159.
37. Henry, J.B., 1984. Clinical Diagnosis and Management by Laboratory Methods 17th Edition. Philidelphia W.B. Saunders Company.
38. Kreider, R.B., 2003. Effects of creatine supplementation on performance and training adaptations. Molecular and Cellular Biochemistry, 244: 89-94.
39. Bender, A., D.P. Auer, T. Merl, R. Reilmann, P. Saemann, A. Yassouridis, J. Bender, A. Weindl, M. Dose, T. Gasser and T. Klopstock, 2005. Creatine supplementation lowers brain glutamate levels in Huntington's disease. J. Neurol., 252: 36-41.
40. Jeong, K.S., S.J. Park, C.S. Lee, T.W. Kim, S.H. Kim, S.Y. Ryu, B.H. Williams, R.I. Veech and Y.S. Lee, 2000. Effects of cyclocreatine in rat hepatocarcinogenesis model. Anticancer Res., 20: 1627-1633
41. Almada, A., T. Mitchell and C. Earnest, 1996. Impact of chronic creatine supplementation on serum enzyme concentration. *FASEB* J., 10: A790 (abstract).
42. Earnest C., A. Almada and T. Mitchell, 1996. Influence of chronic creatine supplementation on hepatorenal function. FASEB J., 10: A790 (abstract).
43. Mihic, S., J.R. MacDonald, S. McKenzie and M.A. Tarnopolsky, 2000. Acute creatine loading increases fat-free mass, but does not affect blood pressure, plasma creatinine, or CK activity in men and women. Medicine and Science in Sports and Exercise, 32(2): 291-96.
44. Peake, J., K. Nosaka and K. Suzuki, 2005. Characterization of inflammatory responses to eccentric exercise in humans. Exercise Immunology Rev., 11: 64-85.
45. Van Der Meulen, J.H., H. Kuipers and J. Drukker, 1991. Relationship between exercise-induced muscle damage and enzyme release in rats. J. Applied Physiol., 71: 999-1004.