Effect of Oral Creatine on Muscle Metabolism of Duchenne Muscular Dystrophy (DMD) by Phosphorus MRS

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OBJECTIVE
To compare the levels of phosphorus metabolites in patients with Duchenne muscular dystrophy (DMD) and controls and to evaluate the effect of oral creatine supplementation versus placebo on muscle energetics using 31PMRS and correlation of changes in muscle strength and functional level.

INTRODUCTION
DMD is an X-linked recessive disease which occurs due to deficiency of dystrophin; an important component of muscle cytoskeleton. It is the most common form of muscular dystrophy affecting 1 in 3300 live male births. In spite of extensive research in humans and mdx mouse models no satisfactory therapeutic approach has been developed. In DMD patients, low phosphocreatine (PCr) / phosphorus (Pi) and PCr / Adenosine tri phosphate (ATP) ratios have been reported using 31P MRS of skeletal muscle in vivo1. In vitro results also reported significant reduction in the concentration of total creatine and several other metabolites in DMD patients compared to normal subjects2. In literature few studies reported a positive effect of creatine supplementation in DMD patients which is encouraging albeit with different dose, duration and outcome measures3-5. A recent randomized, double blind placebo controlled trial failed to demonstrate a statistically significant effect of creatine on muscle strength though a disease modifying effect of creatine was noticed in younger patients (< 7 years age)5. We therefore designed the present study to investigate the effect of oral creatine monohydrate supplementation versus placebo on muscle metabolism using 31PMRS and correlation of changes in muscle strength and functional level in a large cohort of patients.

METHODOLOGY
A total of 33 patients [(mean age, 7.2(1.5) yrs)] and 8 age and sex matched control subjects were recruited for the study. Institute ethics committee approved the study. A randomized, placebo controlled trial of 5 grams/day of creatine monohydrate supplementation for 8 weeks was conducted and phosphorus metabolite ratios using 31PMRS, manual muscle strength (MMT) score and functional status were evaluated at baseline and after 8 weeks follow-up. 31P MRS experiments on calf muscle were performed using surface coil at 1.5 T (Sonata, Siemens, Germany). Means of metabolite ratios between groups were compared by unpaired t-test and categorical variables by Chi-square/Fisher exact test. Differences between the metabolite ratios on MRS and MMT scores between groups were analyzed by analysis of covariance adjusting for age, stunting and the corresponding baseline variable. Functional grade at end point between groups was compared by McNemar’s χ2 test and parental response of treatment effect between groups by Fisher’s exact test. A value of p<0.05 was considered statistically significant.

RESULTS
At baseline the PCr/Pi and the PCr/βATP ratio was lower in DMD patients compared to controls which was statistically significant (p<0.0001). The PDE/PCr ratio was significantly higher in DMD patients compared to controls (p=0.0006). The αATP/PCr ratio was higher in DMD patients compared to controls (p=0.0002). Creatine supplementation resulted in increased PCr /Pi ratio measured in right calf (p=0.03) but statistically insignificant changes in PCr/β ATP, PDE/PCr and αATP/PCr ratios. Creatine supplementation also results in changes in MMT score versus placebo (p=0.04) but no significant change in functional scale. A greater proportion of parents on creatine reported subjective improvement versus worsening on placebo (p=0.02). Creatine was found to be well tolerated and safe.

DISCUSSION
Our results showed significantly lower PCr/Pi and PCr/βATP ratio while significantly higher αATP/PCr and PDE/PCr ratio in DMD patients compared to controls indicating lower stores of muscle phosphocreatine and altered cellular energetics in DMD. As ATP has been found to be comparable in DMD patients and controls the difference in above ratios may be interpreted as due to the difference in muscle phosphocreatine levels. Our results showed that the PCr/Pi ratio is improved in DMD patients after creatine supplementation suggesting an improvement in muscle energy metabolism. In normal healthy subjects, creatine consumption for 2 weeks has been found to improve the muscle phosphocreatine stores on 31P MRS and to improve performance in high-intensity intermittent exercises. A statistically significant decrease in the MMT scores in the placebo group and a marginal increase in MMT in creatine group was detected suggesting improvement in muscle strength on creatine supplementation. In a previous study of creatine on muscular dystrophy patients including patients with DMD a favorable response was elicited from patients who received creatine3-5. Since the mean age of DMD patients in the present study was 7.2 years when DMD patients are known to have linear decrease in muscle strength the preservation of strength in the creatine group might indicate a disease modifying effect of creatine monohydrate.

REFERENCES