Creatine monohydrate enhances strength and body composition in Duchenne muscular dystrophy

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Abstract—*Objective:* To determine whether creatine monohydrate (CrM) supplementation increases strength and fat-free mass (FFM) in boys with Duchenne muscular dystrophy (DD). *Methods:* Thirty boys with DD (50% were taking corticosteroids) completed a double-blind, randomized, cross-over trial with 4 months of CrM (about 0.10 g/kg/day), 6-week wash-out, and 4 months of placebo. Measurements were completed of pulmonary function, compound manual muscle and handgrip strength, functional tasks, activity of daily living, body composition, serum creatine kinase and γ-glutamyl transferase activity and creatinine, urinary markers of myofibrillar protein breakdown (3-methylhistidine), DNA oxidative stress (8-hydroxy-2-deoxyguanosine [8-OH-2-dG]), and bone degradation (*N*-telopeptides). *Results:* During the CrM treatment phase, there was an increase in handgrip strength in the dominant hand and FFM ($p < 0.05$), with a trend toward a loss of global muscle strength ($p = 0.056$) only for the placebo phase, with no improvements in functional tasks or activities of daily living. Corticosteroid use, but not CrM treatment, was associated with a lower 8-OH-2-dG/creatinine ($p < 0.05$), and CrM treatment was associated with a reduction in *N*-telopeptides ($p < 0.05$). *Conclusions:* Four months of CrM supplementation led to increases in FFM and handgrip strength in the dominant hand and a reduction in a marker of bone breakdown and was well tolerated in children with DD.

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Duchenne muscular dystrophy (DD) is an X-linked progressive myopathy due to mutations within the dystrophin gene.[1] To date, there is no cure, and the only therapy that can slow disease progression is corticosteroids, which are usually associated with a number of significant side effects.[2,3] Therapies should target the known consequences of DD, including an increase in oxidative stress,[4] a reduction in protein synthesis,[5] and an increase in protein breakdown.[6]

Creatine is a guanidino compound that may confer therapeutic benefit in muscular dystrophy by increasing strength[7] and fat-free mass (FFM),[8] by its antioxidant properties,[9] by reducing protein breakdown,[10] and by enhancing sarcoplasmic reticulum calcium reuptake.[11] Creatine enhanced survival and attenuated calcium accumulation in primary myoblasts from both *mdx* mouse and DD muscle[11] and reduced necrosis and enhanced muscle mitochondrial function in *mdx* mice.[12]

The short-term (days to weeks) administration of creatine monohydrate (CrM) increased muscle strength in patients with a variety of neuromuscular disorders,[13] McArdle disease,[14] mitochondrial cytopathies,[15] and a heterogeneous group of patients with muscular dystrophy.[16] A recent pilot study in boys with dystrophinopathy showed an increase in strength and endurance of the arm flexors, an increase in bone density, and a reduction in a marker of bone breakdown (*N*-telopeptides).[17]

Given the uncertainties regarding the efficacy of CrM supplementation in specific subgroups of muscular dystrophy, we evaluated the effect of 4 months of CrM supplementation in 30 boys with DD using a randomized, double-blind, cross-over design. We hypothesized that DD patients would demonstrate a relative increase in FFM mass, a slowing of strength deterioration, or a slight increase in muscle strength after the 4-month trial of CrM as compared with placebo.

Methods. *Subjects.* Thirty-one boys were recruited from the Neuromuscular Clinic at McMaster University in Hamilton (n = 6) and from the Pediatric Neuromuscular Clinic at Bloorview MacMillan Children's Center and the Hospital for Sick Children in Toronto (n = 25). The mean age of the DD boys was 10 ± 3 years, their height was 129.2 ± 16.0 cm, and their weight was 35.3 ± 15.8 kg. None of the participants had been taking CrM supple-

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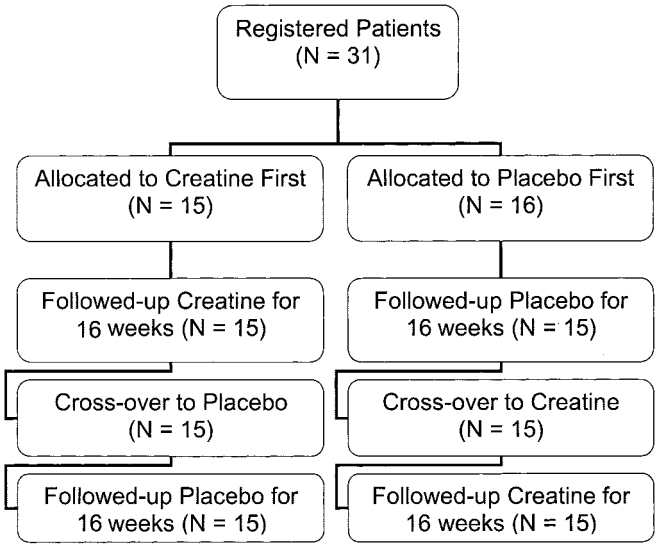

Figure 1. Study design. Each of the intervention phases was 4 months in duration, and the wash-out period was a minimum of 5 weeks.

ments for a minimum of 3 months prior to starting the study. Of those who started the trial (n = 31), one person dropped out within the first month of the study (randomized to placebo) because he did not like the taste and texture of the chewable tablets. The final analysis was based on the 30 children who completed both arms of the study (figure 1). A total of 15 of the boys were taking corticosteroids and had done so for at least 6 months before starting the trial (table 1). Thirteen of the children were taking deflazacort (about 0.9 mg/kg/day) and two were taking prednisone (about 0.75 mg/kg/day). Each participant had the diagnosis confirmed by clinical assessment, elevated serum creatine kinase (CK) activity, and detection of a pathogenic gene mutation in the dystrophin gene and/or absence of immunoreactivity using anti-dystrophin antibodies. Three of the 30 boys were dependent on a wheelchair for mobility. Fifteen of the children started the trial with the CrM phase and 15 with the placebo phase. The study received ethical approval from the Hamilton Health Sciences Corporation and the Bloorview MacMillan Children's Center Research Ethics Committees. All participants provided assent, and their parent or guardian provided informed written consent for participation.

Table 1 *Baseline participant characteristics*

Characteristics	Non–corticosteroid treated, n = 15	Corticosteroid treated, n = 15
Age, y	10.0 (0.8)	10.4 (0.8)
Weight, kg	35.7 (3.9)	34.9 (4.4)
Height, cm	127 (3.3)	131 (4.9)
Fat-free mass, kg	19.0 (1.4)	20.8 (1.4)
No. ambulatory	13	14
Total manual muscle strength score	118 (9.6)	124 (6.0)
Dominant handgrip strength, kg	6.8 (1.4)	7.1 (1.0)
Nondominant handgrip strength, kg	6.5 (1.5)	6.7 (1.0)
FVC, L	1.75 (0.18)	1.94 (0.13)
FEV_1, L	1.75 (0.29)	1.50 (0.15)
CK activity, U/L	10,614 (2,483)	8,079 (2,832)
Creatinine excretion, g/24 h	0.83 (0.11)	0.76 (0.12)

Values are means (SEM). All variables not significantly different.

FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 s; CK = creatine kinase.

The study used a randomized, double-blinded, placebo-controlled, cross-over design, with each participant receiving both treatment and placebo for 4 months, each with a minimum wash-out period of 6 weeks. The CrM supplementation consisted of a flavored tablet containing lemon flavoring, dextrose (about 500 mg/tablet), and pure CrM (1 g/tablet, Neotine; Avicena Group, Palo Alto, CA). Each child received a total of 2 to 5 tablets/day (2 to 5 g of CrM based on weight = 0.102 ± 0.027 g/kg/day) during the creatine condition and an identical number of similar-tasting placebo tablets during the placebo condition. Testing was completed before and after each of the 4-month interventions and included anthropometry (height, weight, and FFM; see below), pulmonary function testing, Activity Scale for Kids,[18] manual muscle testing and functional tasks,[19] isometric handgrip strength, a side effect questionnaire (filled out by parents), and venous blood sampling. At the end of each of the 4-month treatment periods, each subject completed a 24-hour urine collection (after 3 days of flesh-free diet) and a 3-day diet record (completed by parents 1 week before testing).

Strength testing, spirometry, and body composition. Manual muscle testing was performed by the same investigator for all visits. The standard grading system was used, and a "mega-score" (sum of left + right individual scores) was calculated as previously described.[3] All children were tested in the morning to avoid afternoon fatigue, and repeat testing of all subjects was done at approximately the same time of the day. All testing at the Toronto site was conducted by the same trained physiotherapist, and all testing at the McMaster site was conducted by the same master's degree–level kinesiologist. The two testers spent time together to ensure that the interrater reliability was within acceptable recommended guidelines, and each child was assessed by the same evaluator.[20] The test–retest correlation coefficient for each assessor over the 4-month placebo period for all subjects was >0.97. Maximal isometric handgrip strength was also determined using a handgrip dynamometer for the dominant and nondominant hands, with the grip position held constant between trials (Jamar; Sammons Preston, Bollingbrook, IL). The peak strength from three trials was taken as the peak handgrip strength. At the McMaster site, all children also performed handgrip testing with a custom-made force transducer device as previously described,[7,15] and the correlation with the Jamar was >0.98. Pulmonary function testing consisted of functional vital capacity and forced expiratory volume in 1 second using a spirometer (Koko; PDS Instrumentation, Louisville, CO).

Participants completed a whole-body dual-energy x-ray absorptiometry scan (Hologic QDR 4500A, Bedford, MA) for determination of FFM, percentage body fat, bone mineral content, and bone mineral density.

Functional tasks and questionnaires. Functional tests included time to walk or wheel 30 ft, climb four standardized stairs, stand from a supine position, and cut a 3 × 3–in square from an 8 × 11–in piece of paper with scissors.[3,21] All children also completed the Activity Scale for Kids questionnaire with assistance from their parents.[19]

Venous blood sampling and 24-hour urine collection. Whole blood was collected from the antecubital vein (with EMLA cream prior application; AstraZeneca, Wilmington, DE) into untreated evacuated tubes (Vacutainer; Becton Dickinson, Franklin Lakes, NJ), allowed to clot, and centrifuged at 1,200 *g* for 10 minutes. The serum was transferred into microcentrifuge tubes and frozen at −20 °C until subsequent analysis for CK activity, γ-glutamyl transferase (γGT) activity, and creatinine concentration at the central core laboratory facility at McMaster University Medical Center using a dry slide technology automated analyzer (Vitros 950; Ortho-Clinical Diagnostics, Rochester, NY). Twenty-four-hour urine collections were completed at the end of each of the 4-month trials on the day prior to testing. Urine creatinine was determined using a commercially available picric acid–based kit (kit 555-A; Sigma, St. Louis, MO). Urinary 8-hydroxy-2-deoxyguanosine (8-OH-2-dG) is a marker of DNA oxidative dam-

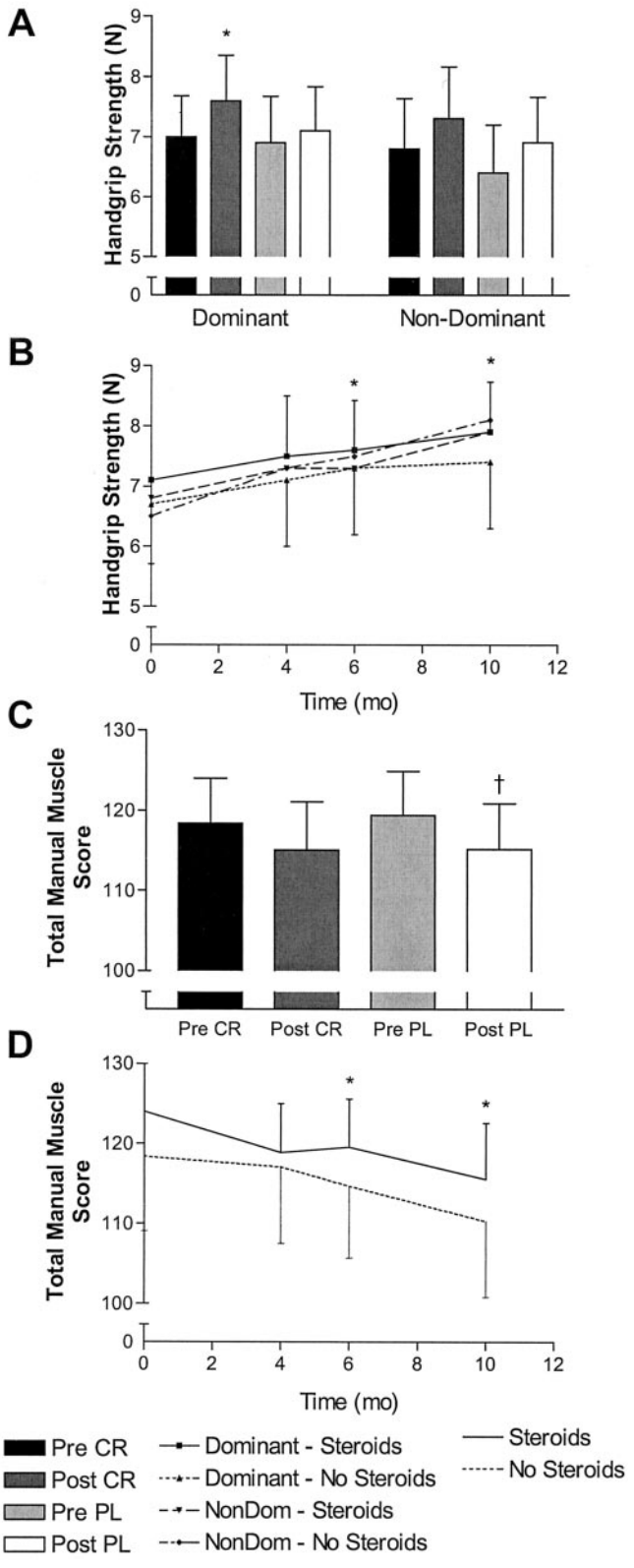

*Figure 2. Isometric handgrip strength values for the dominant and nondominant hands before and after creatine (CR)/placebo (PL) treatment (A) as well as throughout the duration of the study (B) in children who were concurrently taking corticosteroid treatment vs those who were not. Also shown are total manual muscle score values before and after creatine/placebo treatment (C) as well as throughout the duration of the study (D) in children who were concurrently taking corticosteroid treatment vs those who were not. In A and C, data were collapsed across corticosteroid treatment; in B and D, data were collapsed across creatine treatment. *p < 0.05, significantly different from pre or baseline; analysis of variance, Tukey highly significant difference post hoc. †p = 0.056, trend for a difference from pre; analysis of variance, Tukey highly significant difference, post hoc.*

age and was measured using an ELISA method as previously described.[4] The *N*-telopeptide excretion in urine is indicative of bone breakdown and was determined using an ELISA kit (Osteomark NT; Ostex International, Seattle, WA). Urinary 3-methylhistidine (3-MH) was determined using an amino acid analyzer (Beckman 6300, Palo Alto, CA). The 8-OH-2-dG, *N*-telopeptide, and 3-MH data were expressed relative to both creatinine and FFM, and the results were identical using either denominator.

Statistics. Data were assessed using two-way analysis of variance with corticosteroid treatment (±) as a between-group factor and CrM treatment as a repeated measures factor (all children received CrM and placebo). To determine whether the corticosteroids per se had an effect on any of the outcome variables over the course of the experiment (i.e., over the longer period of 9.5 to 10 months), we also examined the data from the first to the last measurement, irrespective of CrM administration. A Tukey post-hoc test was used to determine pairwise differences. All tests were two tailed except for the following urinary tests, where we made the following a-priori hypotheses based on previous data: CrM treatment and corticosteroid use would reduce oxidative stress (8-OH-2-dG)[9] and bone breakdown (*N*-telopeptides)[17] (one tailed). All data in tables, figures, and text are given as means ± SEM. A value of $p \leq 0.05$ was considered significant.

Results. *Strength testing and functional scales.* There was an increase in grip strength of the dominant hand only during the CrM trial ($p < 0.05$) (figure 2). Handgrip strength increased over time when both groups were collapsed across treatment and arm at 6 months ($p < 0.05$) (see figure 2). A strong trend toward a reduction of global compound manual muscle strength was observed ($p = 0.056$) only during the placebo trial (see figure 2). As expected, total manual muscle testing score decreased across time (collapsed across trial) by 6 months ($p < 0.05$) (see figure 2). There were no significant effects of CrM or corticosteroid treatment on pulmonary function measures (NS) (table 2), functional tasks, or activities of daily living scales (NS) (see table 2).

Body composition. There was an increase in FFM (+0.7 kg; $p < 0.05$) (figure 3) during the CrM treatment period, with no changes in bone density or content (data not shown). Corticosteroid treatment was not associated with any differential alterations in FFM, percentage body fat, or bone mineral content/density. The mean percentage body fat did not change consequent to CrM treatment (see figure 3) but was in the obese category for a total of 27% of non-corticosteroid-treated and 20% of corticosteroid-treated boys and in the overweight category for 20% of non-corticosteroid-treated and 40% of corticosteroid-treated boys (NS between groups).

Side effects and blood and urine measurements. There was no effect of either CrM or corticosteroid treatment on serum creatinine, CK, or γGT activity (NS; data not shown). Urinary creatinine was not influenced by CrM or corticosteroid treatment, and there was no change in calculated serum creatinine clearance (NS; data not shown). Corticosteroid use was associated with a lower 8-OH-2-dG/creatinine and *N*-telopeptide/creatine content ($p < 0.05$) (figure 4). CrM treatment resulted in a reduction of the *N*-telopeptide/creatinine

Table 2 *Pulmonary function, ASK, and functional tasks*

		Condition			
		Creatine		Placebo	
Parameters	n	Pre	Post	Pre	Post
Forced vital capacity, L	21	1.92 (0.11)	1.91 (0.13)	1.87 (0.10)	1.82 (0.10)
FEV_1, L	21	1.80 (0.12)	1.73 (0.14)	1.76 (0.13)	1.70 (0.13)
ASK survey score	19	76.0 (3.9)	74.3 (4.4)	75.5 (3.0)	79.3 (3.3)
Time to climb 4 stairs, s	18	5.9 (0.88)	6.9 (1.2)	5.7 (0.66)	6.0 (0.89)
Time to walk 30 ft, s	22	6.8 (0.55)	7.1 (0.55)	7.3 (0.67)	7.4 (0.64)
Time to cut 3 × 3–in square, s	27	27.3 (3.1)	24.2 (2.3)	29.9 (2.6)	24.5 (2.1)

Values are means (SEM). All values are not significantly different from each other.

FEV_1 = forced expiratory volume in 1 s; ASK = Activity Scale for Kids.

content ($p < 0.05$) (see figure 4). Neither CrM nor corticosteroid use influenced 3-MH/creatinine concentration in the urine (NS) (see figure 4).

Discussion. Evidence from in vitro experiments,[11] in vivo studies using *mdx* mice,[12] and shorter-term clinical trials[13,16] has suggested a role for CrM in the treatment of muscular dystrophy. A double-blind cross-over study of 15 boys with dystrophinopathy provided the first indication of a benefit from CrM in a specific type of muscular dystrophy.[17] The current findings support the beneficial effects from CrM supplementation (0.10 g/kg/day) over a 4-month period in a reasonably large and homogeneous group of boys with DD. Importantly, the beneficial effects were independent of corticosteroid use. Finally, the CrM was well tolerated, and there was no objective evidence of renal or liver dysfunction over the 4-month treatment period.

Corticosteroid treatment appears to result in a fairly rapid increase in global muscle strength in boys with DD, with the improvements maintained for months[3] to years.[22] The children in the current study had been on corticosteroid treatment for an average of 3.6 ± 1.6 years, and although the global muscle strength tended to be slightly greater (NS), the decline in strength over the approximately 10 months of the study was similar. The decline in global strength during the 4-month placebo phase tended to be greater (3.7%; $p = 0.056$) than for the decline during the CrM phase (2.8%; $p = 0.15$). Given that we could detect a significant decline in global muscle strength only after about 6 months in the current trial, it is possible that a longer treatment would have yielded a significant result. The results of this study and several others suggest that the rate of decline in the compound manual muscle testing score after the first few months is less attenuated by corticosteroid use.[2,3,22] Consequently, the fact that the trend toward a greater decline in strength during the placebo phase was independent of corticosteroid use implied that CrM has the potential to improve strength over and above that conferred by corticosteroids. In combination with our recent findings that CrM attenuated corticosteroid-induced growth retardation in growing rats,[23] these findings are potentially of therapeutic benefit for the many growing children with DD who are taking corticosteroids.

CrM treatment was associated with a significant

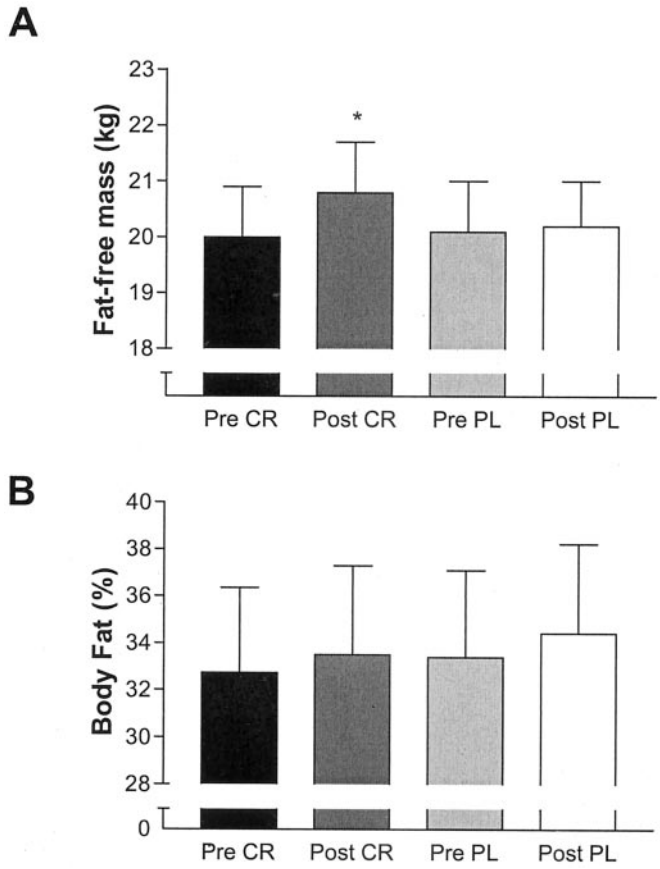

Figure 3. Fat-free mass (A) and body fat percentage (B) before and after creatine (CR)/placebo (PL) treatment (collapsed across corticosteroid treatment). *p < *0.05, significantly different from pre; analysis of variance, Tukey highly significant difference post hoc.*

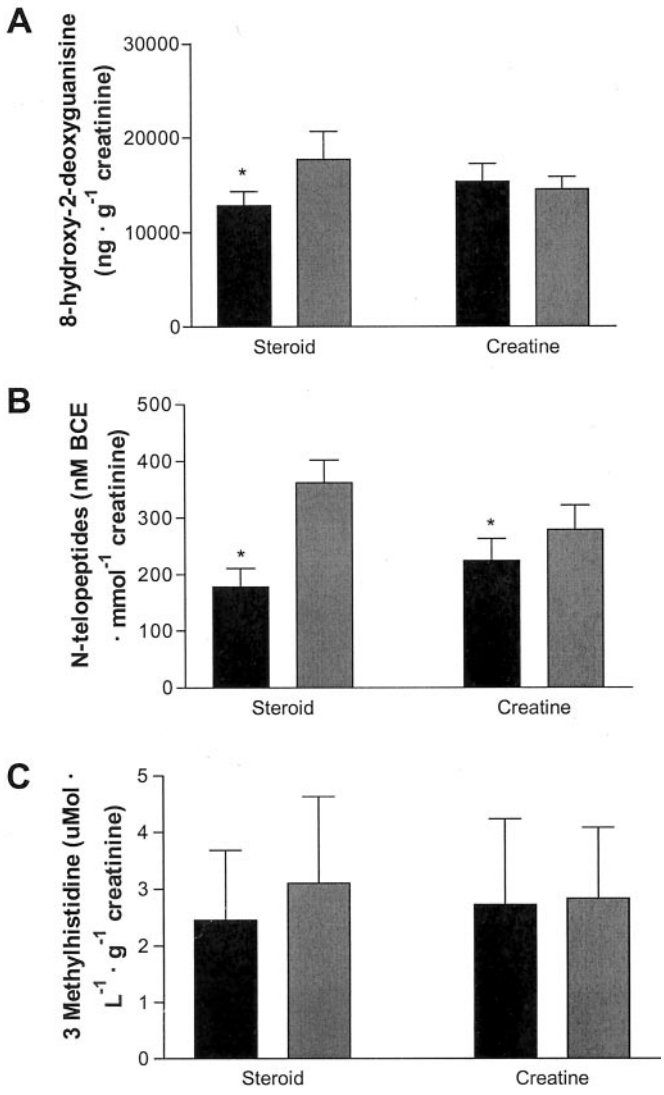

Figure 4. 8-Hydroxy-2-deoxyguanisine (A), N*-telopeptides (B), and 3-methylhistidine (C) in children who were on corticosteroid (steroid) treatment vs those who were not (collapsed across creatine treatment) (darker columns = + steroid) as well following the creatine/placebo phase of the trial (collapsed across corticosteroid treatment) (darker columns = + creatine).* *p $<$ *0.05, significant main effect for treatment; analysis of variance, Tukey highly significant difference post hoc. BCE = bone collagen equivalents.*

increase in handgrip strength in the dominant hand. The ability to detect such a difference likely reflects the inherently increased sensitivity of objective testing with a dynamometer as compared with the ordinal values obtained from manual muscle testing.[20] In contrast to global muscle strength, handgrip strength increased significantly with age, likely reflecting normal childhood growth and the fact that the finger flexors are affected later in the course of DD. Our findings support those from a recently reported smaller clinical trial that found an increase in maximal objective muscle strength of elbow flexors over time in 15 children with dystrophinopathy.[17] Another study reported benefits in objective muscle strength from CrM supplementation in pediatric patients with muscular dystrophy.[16] The fact that the CrM-mediated increase was significant only in the dominant hand is consistent with the fact that muscle contraction is important for creatine transport[24] and to enhance muscle strength and mass gains.[25,26]

Although one study found that CrM improved the neuromuscular symptom score in children with muscular dystrophy,[16] we did not find any effect using a pediatric-specific activity scale or in functional tasks. This likely represents the fact that these measurements are inherently less sensitive than objective muscle strength testing, and an impact on these variables will require larger sample sizes and longer treatment durations. Together, the existing evidence provides support for larger and longer-term studies of CrM therapy in DD; possibly greater gains could be realized with regular therapeutic exercise as a co-intervention.[25-27]

The beneficial effects of CrM seen in the current study occurring independently of corticosteroid therapy are important for two reasons: First, some physicians and families are reluctant to place children on corticosteroids owing to the known side effects, and until now, there were no proven alternative adjunctive therapies. Second, given that the CrM had an effect in children who were already deriving the known benefits of corticosteroid therapy in DD,[2,3] there may be an additive effect. In addition, our group has recently reported that the co-administration of CrM with corticosteroid treatment prevented growth retardation and increased type II muscle fiber area in growing rats.[23] Although the duration and size of the current study were likely underpowered to detect such an effect, future studies with larger sample size and for longer durations should be completed to see whether CrM can attenuate the growth retardation effects of corticosteroids in children with DD.

The attenuation of muscle strength loss with the CrM treatment was co-temporal with an increase in FFM and no change in fat mass. Given that the majority of the boys were already in the obese or overweight range, the latter finding is important. The positive relationship between FFM and strength is encouraging, for muscle mass is the greatest determinant of muscle strength and muscle is, by far, the largest component of FFM. Although an increase in intracellular water could also explain the increase in FFM following the CrM intervention,[8] an increase in water would not be expected to influence strength directly. The exact mechanism behind the positive effect of CrM on FFM is unclear, although our group has found a reduction in amino acid oxidation and whole-body protein breakdown after acute CrM supplementation in young men.[10] Based on previous work using 3-MH excretion as an indicator of myofibrillar protein breakdown in boys with DD,[5,28,29] we used this noninvasive indicator and did not find any significant effect from CrM treatment. We did find a similar reduction in 3-MH associated with corticosteroid use

to that reported previously in a longitudinal study,[28] although our values also did not reach significance. It will be difficult to determine the potential mechanism(s) of how CrM may alter protein metabolism for a change in FFM of about 700 g over a 4-month period could occur with any one of an infinite combinations of changes in protein synthesis and degradation that would be less than the variance in any currently available measurement method.[5,10,28,29]

An important novel finding in the current study was the fact that corticosteroid treatment was associated with a lower excretion of 8-OH-2-dG. The 8-OH-2-dG/creatinine ratio is a marker of oxidative DNA damage, and this has been shown to be elevated in DD patients as compared with myotonic dystrophy and healthy control subjects.[4] There are several other reports of increased oxidative stress in DD,[30-32] and a recent study showed that green tea extract improved skeletal muscle structure and function in *mdx* mice owing to an antioxidant effect.[33] Corticosteroids can attenuate ischemia/reperfusion-induced oxidative stress in skeletal muscle[34] and inhibit superoxide production.[35] Although CrM has antioxidant properties,[9] we did not find any reduction in oxidative stress in the current study. The lack of a reduction in serum CK activity from CrM or corticosteroid treatment may appear not to support the strength and antioxidant effects; however, our group has not found a correlation between the degree of CK activity elevation and direct histologic measurements of muscle damage.[36]

Our results support the findings that CrM supplementation is well tolerated and without significant serologic alterations in healthy young men and women[7,8,10,37,38] and in patients with a variety of myopathies.[14-17] We and others have found that plasma creatinine content increases up to 15% owing to an increased rate of appearance to the nephron, yet there is no effect on creatinine clearance.[8,37–39] Furthermore, longer-term studies (up to 5 years) have not found evidence for renal dysfunction with CrM administration.[37]

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