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Original Article

Creatine supplementation does not alter the creatine kinase response to eccentric exercise in healthy adults on atorvastatin

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BACKGROUND: Serum creatine kinase (CK) levels are higher after eccentric, muscle-damaging exercise in statin-treated patients. This could contribute to the increased statin-associated muscle symptoms reported in physically active individuals.

OBJECTIVE: We tested the hypothesis in this pilot study that creatine (Cr) monohydrate supplementation would reduce the CK response to eccentric exercise in patients using statins to determine if Cr supplementation could be a strategy to mitigate statin-associated muscle symptoms in physically active individuals.

METHODS: Healthy, nonsmoking men (n = 5) and women (n = 14) were randomized to Cr monohydrate = atorvastatin 80 mg + 10 g Cr monohydrate (n = 10, age = 60 ± 7 years) or to placebo (PL) = atorvastatin 80 mg + PL (n = 9, age = 52 ± 6 years). After 4 weeks of treatment, subjects performed 45 minutes of eccentric exercise (downhill walking at a −15% grade). Serum CK levels, muscle soreness (visual analog scale after two squats), and muscle pain severity and interference (using the brief pain inventory) were measured before and after 4 weeks of treatment, and then for 4 consecutive days after downhill walking. Vitamin D, or serum 25(OH)D, was also measured at baseline.

RESULTS: The PL group was younger ($P = .01$) but not otherwise different in blood lipids, vitamin D, CK, muscle visual analog scale, and pain scores before (all $P > .21$) or after (all $P > .12$) treatment. CK increased in all subjects after downhill walking ($P < .01$), but neither the relative peak change (expressed as group mean difference with 95% confidence intervals: 43.52% [−196.41, 283.45]) nor the absolute peak change (67.38 U/L [−121.55, 256.31]) relative to baseline was different between groups ($P = .46$ and .71, respectively). A similar lack of treatment effect was observed for muscle soreness (11.03 mm [−9.49, 31.55]), pain severity (0.77 pts [−0.95, 2.50]), and pain interference (1.02 pts [−1.25, 3.29]) with P-values for group comparisons = 0.27, 0.36, and 0.35, respectively. However,

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subjects with "insufficient" Vitamin D < 30 ng/mL (n = 10) had an ~2-fold greater CK increase with eccentric exercise (nominal *P*-value = .04) than subjects with higher vitamin D levels.

CONCLUSION: Cr monohydrate did not reduce CK increases after exercise in statin-treated subjects. We did observe that low vitamin D levels are associated with a greater CK response to eccentric exercise in statin-treated subjects.

Introduction

Hydroxy-methyl-glutaryl coenzyme A reductase inhibitors (statins) are well tolerated by the majority of patients, although they produce a range of statin-associated muscle symptoms (SAMS) such as pain, cramps, weakness, and stiffness in an estimated 5% of adults.[1,2] The incidence of SAMS may be higher in physically active individuals,[3,4] and some studies have found that serum creatine kinase (CK) levels are elevated to a greater extent after eccentric, muscle-damaging exercise in patients treated with statins than those not taking statins.[5,6] These findings suggest that statins increase susceptibility to exercise-induced skeletal muscle injury. Although eccentric exercise and muscle damage are normal components and responses of any routine exercise, an exaggerated CK response to exercise may be one mechanism underlying SAMS, particularly in adults routinely engaging in higher levels of physical activity.

There are few strategies to reduce SAMS other than changing the statin or reducing the statin dose. Two popular putative therapies, vitamin D and coenzyme Q10 supplementation, have produced equivocal results in clinical studies.[7,8] Skeletal muscle uses creatine (Cr) monohydrate to form Cr phosphate, a critical cellular energy source during intense exercise. Cr supplementation reduces CK levels following eccentric exercise in healthy men.[9] A genetic variant that reduces muscle Cr storage and availability has been associated with a decreased risk of SAMS,[10] but to our knowledge, only one study has directly investigated whether CR supplementation reduces SAMS in humans. CR supplementation reduced myopathy scores during statin therapy compared to statin use alone. A major problem in evaluating treatments for SAMS is the low prevalence of documented SAMS in patients with complaints[11,12] and the absence of any diagnostic markers for SAMS.[11–14] Consequently, we used an eccentric exercise model where statins exaggerate muscle damage to evaluate if Cr supplementation reduced the exaggerated CK response to eccentric exercise noted previously.[6,15] We hypothesized that Cr monohydrate supplementation would reduce the CK response to downhill walking in subjects treated for 4 weeks 80 mg of atorvastatin daily.

Methods

Study overview

Nineteen healthy, nonsmoking men and postmenopausal women (aged 40–70 years) were randomized in a double-blind fashion to one of two treatment groups: (1) atorvastatin 80 mg + 10 g Cr monohydrate (n = 10); or (2) atorvastatin 80 mg + placebo (n = 9) for 4 weeks. Subjects had no chronic conditions requiring medical treatment, did not participate in regular exercise > 2 d/wk, were not dieting, consuming <2 alcoholic beverages/d or using medications or supplements such as Cr monohydrate, coenzyme Q10, muscle-building protein or anabolic supplements, or other medications or substances known to increase SAMS risk with statin therapy. Subjects were also not currently taking statins or any other cholesterol-lowering drugs when they were recruited, although 5 reported previous statin use in the past. Subjects were phoned weekly to reinforce compliance and inquire about muscle symptoms. Subjects performed our standard downhill walking protocol after 4 weeks of treatment.[6,16] Serum CK levels and assessments of subjective muscle soreness and pain were measured before treatment, after 4 weeks of treatment, and daily for 4 days after downhill walking (Fig. 1). Subjects continued to take their statin and treatment for the 4 days following the exercise. Blood lipids were measured before and after treatment. Vitamin D was measured before treatment. The study was approved by the Hartford Hospital and University of Connecticut Institutional Review Boards in concordance with guidelines established in the Declaration of Helsinki.

Physical exam and medical history

Subjects' medical history and present and prior medications, blood pressure, heart rate (HR), height, weight, and waist circumference were measured and subjects underwent a physical exam at baseline. Qualified subjects were provided a 5 week supply of study drug and instructed to take the treatment every night with the evening meal.

Assessment of self-reported physical activity level

Subjects were queried about routine physical activity using the Paffenbarger Physical Activity Questionnaire,[17] at baseline and after 4 weeks of drug treatment.

Downhill walking

After 4 weeks of drug treatment, subjects performed a maximal treadmill test using the Bruce Protocol to determine maximum HR. After resting 30 minutes, they