Lovastatin Increases Exercise-Induced Skeletal Muscle Injury

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This study tested the hypothesis that exercise in combination with a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor produces greater creatine kinase (CK) elevations, an index of skeletal muscle injury, than exercise alone, using a double-blind, placebo-controlled design. Fifty-nine healthy men aged 18 to 65 years with low-density lipoprotein cholesterol (LDL-C) levels greater than 3.36 mmol/L (130 mg/dL) despite diet therapy were studied. Subjects were randomly assigned to receive lovastatin (40 mg/d) or placebo for 5 weeks. Subjects completed 45 minutes of downhill treadmill walking (−15% grade) at 65% of their predetermined maximum heart rate after 4 weeks of treatment. During the subsequent week, they completed four 10-repetition sets of one-arm biceps curl exercise using 50% of their maximum capacity. CK levels were measured before exercise and daily for 4 and 5 days after the treadmill and biceps exercises, respectively. Age, body weight, and blood lipid and lipoprotein levels were similar in lovastatin and placebo groups. Resting CK levels were 33% higher in the lovastatin group before treatment ($P < .05$), but were not significantly altered by lovastatin. CK levels were 62% and 77% higher ($P < .05$) in the lovastatin group 24 and 48 hours after treadmill exercise after adjusting for initial CK differences. There were no significant CK differences between lovastatin and placebo groups after biceps curl exercise. We conclude that HMG-CoA reductase inhibitors exacerbate exercise-induced skeletal muscle injury.

MUSCLE SORENESS and elevations in serum creatine kinase (CK) have been reported in hypercholesterolemic patients receiving the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors lovastatin[1] and simvastatin.[2] In addition, rhabdomyolysis with renal failure has occurred in some patients receiving lovastatin in combination with cyclosporine,[3] nicotinic acid,[4] erythromycin,[5] and gemfibrozil.[6]

Marked increases in CK levels following physical exertion have also been reported in some patients receiving lovastatin,[7,8] fluvastatin,[9] and simvastatin,[10] and one case report[11] linked lovastatin and exercise to rhabdomyolysis and acute renal failure. However, it is uncertain if HMG-CoA reductase inhibitors exacerbate exercise-induced muscle injury, because exercise alone can injure skeletal muscle and elevate CK levels.[12,13] This effect is greater after eccentric exercise whereby force is generated as the muscle lengthens,[14] and CK release after eccentric exercise is routinely used as a model to study exercise-induced muscle injury.[14]

We recently examined the possibility that lovastatin augments CK levels in hypercholesterolemic patients following standard treadmill exercise testing.[7] We were unable to document increases in mean CK levels with exercise, but two individuals had substantial CK elevations only during the combination of lovastatin and exercise. These preliminary findings suggest that lovastatin may increase the susceptibility for muscle injury after moderate exercise in certain patients, and raise the possibility that exercise might produce greater CK release in individuals treated with HMG-CoA reductase inhibitors. Consequently, the present study tested the hypothesis that exercise in combination with lovastatin administration produces greater CK elevations than exercise alone, using two exercises with a large eccentric component, downhill walking and the biceps curl.

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SUBJECTS AND METHODS

Subjects and Study Design

This randomized, double-blind, placebo-controlled trial was conducted at Duke University and the University of Pittsburgh. The study protocol was approved by the Biomedical Institutional Review Boards at each center, and written informed consent was obtained from all participants before the study. Participants were required to be physically inactive men who exercised less than once per week during the preceding 6 months, to consume on average fewer than two alcoholic beverages per day, and to be free of any chronic medical conditions requiring medication use. Women were not recruited, because of the possible protective effects of estrogens on exercise-induced muscle injury.[14] Lipid-lowering medications (HMG-CoA reductase inhibitors, niacin, fibrates, and resins), probucol, and supplemental vitamins were discontinued 6, 12, and 4 weeks, respectively, before study entry and for the duration of the protocol. Potential subjects were invited for a blood lipid determination and were required to have a fasting low-density lipoprotein cholesterol (LDL-C) level of at least 3.36 mmol/L (130 mg/dL), total cholesterol less than 7.76 mmol/L (300 mg/dL), triglycerides less than 4.52 mmol/L (400 mg/dL), and CK less than 250 IU/L.

Subjects with a fasting LDL-C of at least 3.36 mmol/L (130 mg/dL) on the screening sample were instructed to adhere to an American Heart Association (AHA) step 1 diet for 4 weeks and began taking a placebo pill at bedtime. Subjects returned to the clinic after the 4-week diet, and two fasting blood samples were obtained 1 week apart for LDL-C determination. If the two LDL-C concentrations differed by more than 12%, a third LDL-C measurement was performed. To avoid including subjects with marked lipid variability, the three samples could not differ by more than 18%. The mean of the two closest LDL-C measurements was used in the analysis. Participants were required to maintain an LDL-C level greater than 3.36 mmol/L (130 mg/dL) after consuming the AHA step 1 diet to continue in the study. Height and weight were measured, and body mass index (BMI) was calculated (weight in kilograms divided by height in meters squared) as an estimate of obesity.

One hundred ninety-nine men were screened, of whom 79 (44%)

were eligible and agreed to participate. An additional 20 men were disqualified because their blood lipid levels no longer qualified for drug treatment after the diet (n = 19) or because of elevated transaminase levels (n = 1). Consequently, 59 men were randomized to receive lovastatin (40 mg/d) or an identical placebo at bedtime for 5 weeks.

Four weeks after randomization, subjects performed a maximal exercise treadmill test using the Bruce protocol to test for exercise-induced cardiac ischemia and to determine maximum heart rate. Subjects then rested 30 minutes before performing the downhill walking protocol. To determine the downhill treadmill speed, subjects walked for approximately 5 minutes at 0% elevation to determine a speed that elicited 65% (±5%) of their predetermined maximum heart rate. Subjects then walked at this speed downhill (−15% grade) for three 15-minute periods with 5 minutes of rest between exercise bouts.

One week after the treadmill test, the subjects' one-repetition maximum (1RM) with one arm for the biceps curl was determined using the nondominant arm. To perform the biceps curl, subjects were seated with legs apart and the elbow placed on the inner aspect of the ipsilateral thigh. The 1RM was defined as the maximum weight that could be lifted for one repetition. Subjects subsequently performed four sets of 10 repetitions at 50% of 1RM. Subjects were required to lower the weight slowly after each curl to maximize the eccentric stress. Assistance was provided if needed during the concentric (lifting) phase of the exercise, but the subject controlled the weight during the eccentric (lowering) phase. A 2-minute rest period was allowed between sets of biceps curls.

Fasting blood samples were obtained before the treadmill test to determine posttreatment CK and lipid levels. CK was determined in samples obtained before and daily for 4 days after the treadmill exercise and for 5 days after the biceps curl exercise. Sera for CK determination was separated from whole blood within 1 hour and stored at −70°C until analysis. All CK values for an individual subject were analyzed in a single autoanalyzer run.

Laboratory Analyses

Blood lipid and CK analyses were performed at a central laboratory located at the University of Pittsburgh, Pittsburgh, PA. Samples obtained at Duke University Medical Center were shipped on dry ice to the central laboratory for CK analysis. Total CK activity was determined using the Kodak Ektachem Clinical Chemistry Slide (Eastman Kodak, Rochester, NY). Total cholesterol was also determined by Kodak Ektachem Clinical Chemistry Slide (Eastman Kodak). Triglycerides were determined using an enzymatic method based on determination of glycerides in serum after blanking for free glycerol (Boehring Diagnostics, Indianapolis, IN). High-density lipoprotein cholesterol (HDL-C) was determined using magnetically enhanced reagent containing dextran sulfate. LDL-C was calculated using the Delong modification of the Friedewald formula.[15]

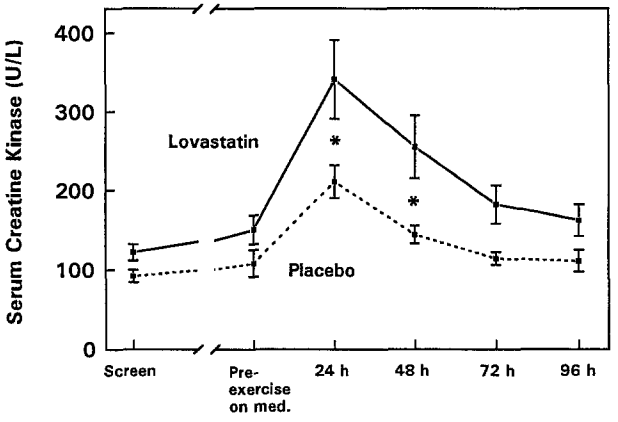

Fig 1. Serum CK levels (U/L) before treatment (screen), after 4 weeks of lovastatin or placebo (pre-exercise on med.), and daily for 4 days after downhill walking. *$P < .05$.

Table 1. Subject Characteristics at Baseline in the Lovastatin and Placebo Treatments

Characteristic	Lovastatin (n = 22)	Placebo (n = 27)
Age (yr)	39.4 ± 2.4	37.7 ± 1.7
Body weight (kg)	89. ± 3.8	83.4 ± 2.0
BMI (kg/m²)	28.6 ± 1.1	27.0 ± 0.6
CPK (U/L)†	122 ± 10	92 ± 8*

NOTE. Values are the mean ± SE. Significance levels were determined with an unpaired *t* test.

Abbreviation: CPK, creatine phosphokinase.

*$P < .05$.

†Statistical analysis performed on transformed values.

Statistical Analyses

The comparability between study centers of subject characteristics and CK responses to exercise was first assessed by examining the treatment-by-center interaction in an ANOVA with treatment, study center, and their interaction as the model effects. Since there were no significant differences between study centers, data were pooled for all subsequent statistical analyses.

The comparability of treatment groups before randomization was assessed with unpaired *t* tests. Changes in blood lipids and lipoproteins after the placebo and lovastatin treatments were compared with unpaired *t* tests. Because pretreatment CK levels were significantly higher in subjects randomized to the lovastatin group, we adjusted CK values before and after exercise for baseline CK levels using analysis of covariance. Logarithmic transformation of CK was used in analyses to normalize the distribution. Nontransformed values are presented in the tables and text. All probability values are based on two-tailed tests. Results are presented as the mean ± SE.

RESULTS

Of 59 men randomized into the study, five were disqualified because they had exercise stress tests suggestive of coronary ischemia, and one was disqualified because he consumed more than two alcoholic beverages per day during the protocol. Two subjects in the lovastatin group were excluded from statistical analysis because their increase in CK greatly exceeded that of the other subjects, and two controls were excluded because of missing baseline CK values. Thus, 49 men, 22 in the lovastatin group and 27 in the placebo group, form the basis of the present report. Eighty-eight percent of the participants were caucasian, 8% were African-American, and 4% were of another racial descent. Baseline age, weight, and BMI were similar in subjects randomized to the lovastatin and placebo treatments (Table 1).

Table 2. Lipid and Lipoprotein Levels at Baseline and Change After 4 Weeks of Lovastatin and Placebo Treatment

	Lovastatin		Placebo	
Variable	Baseline	Change	Baseline	Change
Cholesterol (mg/dL)				
Total	225 ± 5	−48 ± 4†	228 ± 5	7 ± 4
LDL	152 ± 4	−45 ± 4†	160 ± 4	3 ± 4
HDL	44 ± 2	2 ± 1	41 ± 1	2 ± 1
Triglycerides (mg/dL)	153 ± 14	−29 ± 10*	159 ± 13	0 ± 7

*$P < .05$ and †$P < .0001$ for difference between treatments.

Table 3. Creatine Phosphokinase Levels (mean ± SE, U/L) Before and for 4 Days After Treadmill Exercise in the Lovastatin and Placebo Treatments

	Before	After			
		24 h	48 h	72 h	96 h
Lovastatin	150 ± 18	341 ± 50*	255 ± 40*	182 ± 24†	162 ± 20
Placebo	108 ± 17	211 ± 21	144 ± 11	114 ± 8	111 ± 14

NOTE. Significance levels were determined with analysis of covariance using screening CPK as a covariate. Statistical analyses were performed on logarithmically transformed CPK values.

*$P < .05$.

†$P = .088$.

Lipids and Lipoproteins

Baseline triglyceride and total cholesterol, LDL-C, and HDL-C levels were similar in subjects randomized to the lovastatin and placebo treatments (Table 2). As expected, total cholesterol and LDL-C levels also decreased significantly during lovastatin treatment, but not during placebo. Triglycerides decreased more in the lovastatin group compared with the placebo group. HDL-C levels were unaltered during the lovastatin and placebo regimens.

Exercise Parameters

Subjects in the lovastation and placebo groups exercised at similar heart rates during the downhill treadmill walking exercise (119 ± 2 and 120 ± 1 beats per minute, respectively). The weight used during the biceps curl exercise was 8.91 ± 0.36 kg in the lovastatin group and 8.09 ± 0.27 kg in the placebo group. None of these differences was statistically significant.

Creatine Phosphokinase Levels

Average serum CK values before treatment were 33% higher ($P < .05$) in subjects randomized to lovastatin. Consequently, the significance of all subsequent CK values was analyzed after adjusting for pretreatment CK using analysis of covariance. CK levels increased by 23% during lovastatin treatment, and by 17% during the placebo condition (P = NS for difference between conditions). CK levels increased after treadmill exercise in both subject groups, but mean CK concentrations were 62% and 77% higher 24 and 48 hours after exercise, respectively, in lovastatin versus placebo subjects ($P < .05$; Table 3 and Fig 1). Mean CK values also increased after the biceps curl exercise in both subject groups. The mean CK increase in both treatment groups was approximately 10 times greater than that produced by downhill walking. The increase in CK tended to appear earlier in the lovastatin group. CK levels were 128% and 75% higher 24 and 48 hours, respectively, after biceps exercise in the lovastatin group, but were lower than in the placebo group at 96 and 120 hours after exercise. None of these differences were significantly different between treatment conditions (Table 4 and Fig 2).

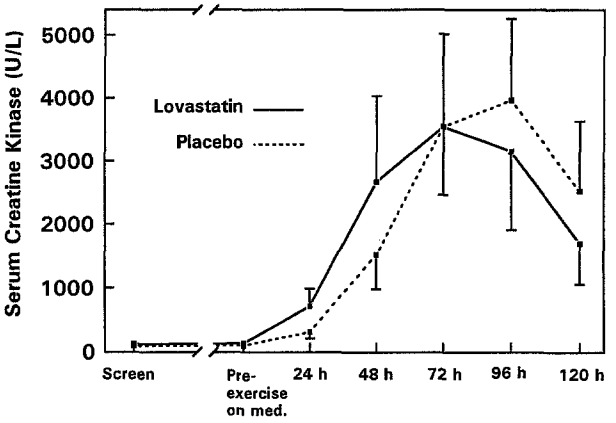

Fig 2. Serum CK levels (U/L) before treatment (screen), after 5 weeks of lovastatin or placebo (pre-exercise on med.), and daily for 5 days after one-arm biceps curl exercise.

DISCUSSION

The present report documents that compared with placebo, the HMG-CoA reductase inhibitor lovastatin increases mean CK levels after eccentric exercise in healthy young men with LDL-C levels greater than 3.36 mmol/L (130 mg/dL). Men receiving lovastatin had mean CK levels at least 62% higher than in men receiving placebo 24 and 48 hours after downhill walking or biceps curl exercise. However, only the difference after downhill walking was statistically significant, probably because of the larger variability in CK values in the lovastatin group after the biceps exercise.

These results confirm several case reports[8-11] and at least three smaller studies[16-18] suggesting that HMG-CoA reductase inhibitors exacerbate exercise-related muscle injury. These results contrast with other reports,[18,19] including one from our own group,[7] that failed to document greater CK levels in patients receiving lovastatin. A larger sample size in the present study plus several methodological differences may explain these contrasting results. The present study used exercises with a large eccentric component, whereas our prior study used standard treadmill testing. Eccentric exercise is known to produce a marked elevation of CK levels and is used as a model of exercise-induced muscle injury.[14] In addition, the present study used a parallel as opposed to a crossover design. CK

Table 4. Creatine Phosphokinase Levels (mean ± SE, U/L) Before and for 5 Days After Biceps Curl Exercise in the Lovastatin and Placebo Treatments

	Before	After				
		24 h	48 h	72 h	96 h	120 h
Lovastatin	135 ± 13	716 ± 276	2,671 ± 1,361	3,551 ± 1,472	3,150 ± 1,242	1,697 ± 641
Placebo	102 ± 11	314 ± 100	1,520 ± 537	3,551 ± 1,088	3,964 ± 1,297	2,527 ± 1,108

NOTE. Significance levels were determined with analysis of covariance using screening CPK as a covariate. Statistical analyses were performed on logarithmically transformed CPK values. There were no significant differences between treatments.

levels after eccentric exercise are markedly attenuated for 10 weeks and possibly as long as 6 months following a single exercise session.[20,21] Consequently, studies using a crossover design may have attenuated any increase in CK during the second exercise test, thereby reducing the ability to detect significant differences. We did not include a premedication exercise challenge in the present study, to avoid attenuating CK release after exercise during medication or placebo. In addition, only men were recruited in the present study because of observations that CK release after comparable levels of exercise is less in women, and the possibility that estrogen may reduce the efflux of intracellular proteins during injury.[14]

We cannot readily explain why lovastatin did not increase CK levels after the biceps curl exercise if HMG-CoA reductase inhibitors consistently increase exercise-induced muscle injury. However, CK levels were considerably higher after arm exercise, so it is possible that the biceps curl alone maximized muscle injury and obscured any medication effect.

A limitation of the present study is that subjects assigned to lovastatin by chance had initial CK values that were 33% higher than in subjects assigned to placebo. Random treatment assignment and double blinding were maintained throughout the study, so the only plausible explanation for these initial differences in CK levels is chance. Subjects assigned to lovastatin were slightly heavier and had a slightly greater BMI, but these small differences in body size are unlikely to account for CK differences. Others[17,18] have suggested that CK elevations after exercise are more marked in subjects with higher pretreatment CK values. This raises the possibility that subjects with higher baseline CK may be predisposed to drug-induced CK elevations after exercise.[17] We adjusted all subsequent CK levels for pretreatment CK values using an ANCOVA, but we cannot exclude the possibility that lovastatin subjects were innately different from the controls prior to the intervention. However, this seems unlikely, given the random-assignment, double-blind study design.

The mechanism by which HMG-CoA reductase inhibitors injure skeletal muscle is not defined. The reductase product, mevalonic acid, is a precursor for key cellular cofactors such as ubiquinone and dolichol, as well as cholesterol. Attention has centered on ubiquinone, also known as coenzyme Q, since a disruption of its role in mitochondrial electron transport might predispose to muscle injury. During clinical treatment with HMG-CoA reductase inhibitors, serum levels of coenzyme Q are reduced. However, the reductions are probably simply commensurate with reduced plasma LDL, which is the major plasma carrier for this lipid-soluble molecule.[22] Human biopsy studies have shown normal muscle tissue levels of coenzyme Q following treatment with HMG-CoA reductase inhibitors, but the biopsies were obtained only under resting conditions and not after exercise.[23]

Animal models of HMG-CoA reductase inhibitor–induced muscle injury suggest that type II, or white, muscle fibers are primarily affected.[24,25] Type II fibers are predominantly glycolytic and contain fewer mitochondria than type I, or red, fibers. In situations where carbohydrate for glycolysis is depleted, such as exercise, any disruption of mitochondrial function could compromise energy production and cellular function. Indeed, Smith et al,[25] in a rat model of HMG-CoA reductase inhibitor–induced muscle injury, noted that glycogen-depleted fibers appeared most vulnerable to injury. Coenzyme Q administered intraperitoneally failed to prevent muscle injury in this rat model. In contrast, several case reports suggest that coenzyme Q supplementation might reverse exercise-induced muscle injury related to lovastatin treatment[8] and mitochondrial dysfunction after simvastatin therapy.[26] Coenzyme Q administration also reduced CK levels in rats immediately after downhill treadmill running,[27] but had no effect on CK levels 40 hours after exercise. To our knowledge, coenzyme Q has not been examined in studies of exercise-induced muscle injury in man.

HMG-CoA reductase inhibitors are widely and effectively used to decrease LDL-C. Clear cases of myopathy, generally defined as muscle symptoms plus CK elevations greater than 10 times the upper limit of normal, related to these agents are rare, but whether lesser degrees of muscle injury are more common is unknown. Our intent in performing the present study was to examine the possibility that exercise-induced muscle injury could be used as a model of this problem. Such a model would facilitate comparison of different HMG-CoA reductase inhibitors and comparison of risk in different patient groups, as well as evaluation of possible preventive measures. The present results demonstrate that lovastatin treatment plus eccentric exercise increases CK levels more than exercise alone, and suggest that such exercise may be a possible model for examining the rare skeletal muscle injury that occurs without physical exertion in patients receiving HMG-CoA reductase inhibitors.

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