# Biomedical Science

## Lovastatin Use and Muscle Damage in Healthy Volunteers Undergoing Eccentric Muscle Exercise

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**We did a double-blind, placebo-controlled crossover study of 10 healthy young men taking no medications to determine if ingesting lovastatin is associated with more severe muscle damage after exercise. Five men in the first group took 40 mg of lovastatin daily for 30 days while those in the second group took an identical-appearing placebo. Each volunteer then walked downhill on a −14-degree incline on a treadmill at 3 km per hour for an hour. After a 2-week rest, the subjects were crossed over. Serial serum creatine kinase activity was measured immediately before and 8, 24, 48, 72, 120, and 144 hours after each treadmill session.**

**With each subject serving as his own control, peak mean serum creatine kinase activity (±SEM) following treadmill after lovastatin therapy was similar to that following placebo (168.4±25.8 U per liter versus 146.7±14.7 U per liter, respectively [$P=.9$]). With an $\alpha$ value of .05, we had greater than a 99% chance of detecting a difference in the rise of serum creatine kinase activity of 200 U per liter between groups. Our data suggest that lovastatin is not an independent risk factor for developing exercise-induced muscle damage using this model of exercise in our study population.**

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Preclinical studies examining the safety and efficacy of lovastatin use have found the incidence of elevated serum creatine kinase (CK) activity (reflecting muscle damage) to range from 0.5% to 2% in those taking the drug.[1,2] Several reports have since described mild to moderate myopathy and overt rhabdomyolysis in patients taking lovastatin for the treatment of hypercholesterolemia.[3-9] All of these later patients had also been taking other medications, including immunosuppressive agents, other cholesterol-lowering drugs, and antibiotics.

Muscle damage, including rhabdomyolysis and myoglobinuric renal failure, can also be seen after excessive exertion. Even normal exercise is accompanied by biochemical evidence of muscle damage such as increased serum CK activity and elevated serum myoglobin and uric acid concentrations.[10] A recent report suggested that exertional myopathy may be more likely to occur in patients taking lovastatin.[11] We report a double-blind, placebo-controlled crossover study in ten healthy men to examine the ability of lovastatin to raise serum CK levels after exercise.

### Subjects and Methods

Experimental subjects were ten 27- or 28-year-old nonsmoking white men who were within 20% of ideal body weight. They had no known medical illnesses and were taking no medications. Because untrained persons have greater rises in markers for rhabdomyolysis after exercise,[12-15] the volunteers were required to have not participated in any regular exercise program for at least four months before the study began.

After baseline physical examinations and routine chemistry studies, including the measurement of serum cholesterol levels and CK activity, subjects were randomly assigned to two groups of five men. Five men in group A took one 40-mg capsule of lovastatin daily, and five men in group B took an identical-appearing placebo capsule daily for a month. Both investigators and volunteers were blind as to the contents of the capsules.

At the end of the month, each subject walked downhill on a −14-degree incline at 3 km per hour for an hour on a treadmill. This was done to produce eccentric muscle contractions that have been shown to result in reproducible and more severe elevations in serum CK levels than concentric muscle exercise.[16] Blood specimens were drawn for the measurement of serum CK activity and cholesterol concentrations immediately before exercise and then for the measurement of serum CK levels at times 0 (immediately after the treadmill test), and 8, 24, 48, 72, 120, and 144 hours after the end of the treadmill exercise.

After a two-week period, the subjects were crossed over so that group A subjects took placebo and group B subjects took lovastatin for a month. Identical treadmill exercises and blood chemistry studies were then repeated.

Two-tailed, paired $t$ tests were used to compare serum cholesterol concentrations after placebo or lovastatin therapy with baseline values and to compare peak serum CK activity after exercise with baseline values obtained immediately before exercise. Using a doubling of the upper limits of serum CK activity and an $\alpha$ error of .05, ten subjects in each group provided a power of greater than .99 to detect a difference, if one existed—that is, $\beta < .01$.

### Results

Baseline serum cholesterol concentrations for all subjects ($5.1 \pm 0.55$ mmol per liter [$195.6 \pm 21$ mg per dl]; mean ± standard error of the mean [SEM]) did not fall signifi-

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**ABBREVIATIONS USED IN TEXT**

CK = creatine kinase
SEM = standard error of the mean

cantly after placebo therapy (decline of $0.85 \pm 0.58$ mmol per liter [$32.5 \pm 22.4$ mg per dl]; $P = .18$). After taking lovastatin for a month, serum cholesterol concentrations fell by a mean of $1.51 \pm 0.43$ mmol per liter ($58.2 \pm 16.4$ mg per dl; $P = .006$), indicating that subjects were compliant in taking their medication.

Following treadmill exercise after lovastatin was taken, mean serum CK values rose from a baseline of $113.6 \pm 14.9$ U per liter to a peak of $168.4 \pm 25.8$ U per liter ($P = .0001$). Following treadmill exercise after placebo was taken, CK values also rose significantly from a pretreadmill mean of $100.7 \pm 13.4$ U per liter to a mean peak of $146.7 \pm 14.7$ U per liter ($P = .02$). There was no statistical significance in the degree of rise of CK activity after lovastatin use as compared with placebo ($P = .9$). The order of drug administration (lovastatin versus placebo) appeared to have no influence on peak CK activity, indicating that a training effect from the first treadmill exercise did not influence the results obtained after the second exercise. Figure 1 represents the mean serum CK values at indicated times following the treadmill test. Because serum CK activity in individual subjects peaked at different times, the mean values reflected on the graph are not identical to those used for statistical analysis.

## Discussion

The literature contains several reports of muscle damage occurring both spontaneously and in response to exercise in patients taking lovastatin.[1-9,11] Most of these patients had been taking other medications as well, including other cholesterol-lowering drugs, immunosuppressive agents, and antibiotics. To our knowledge, this is the first study evaluating the effects of lovastatin as an independent risk factor for exercise-induced muscle damage.

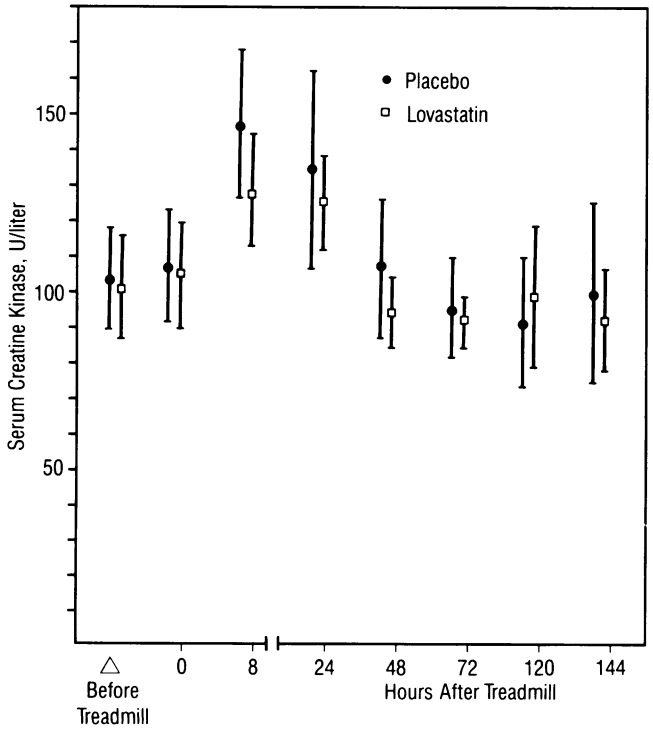


**Figure 1.**—In this graph of serum creatine kinase (CK) activity versus time, the pretreadmill values represent serum CK activity immediately before exercise and all other values are at times after the treadmill exercise was terminated. The values represent the mean ± a standard error of the mean.

We could not demonstrate a greater rise in serum creatine kinase activity induced by exercise in subjects taking lovastatin than in those taking placebo. Although our study population was biased toward a young, healthy cohort, age has not been reported to be a risk factor for exercise-induced rhabdomyolysis.[17] All other confounding variables such as race, sex, drug use, and training were controlled for.[17,18]

Serious muscle damage following exercise is commonly accompanied by hundreds-fold to thousands-fold elevations in serum CK activity.[19] With an $\alpha$ value of .05 in our study population, we had greater than a 99% chance of detecting a difference in the rise of serum CK activity of as little as 200 U per liter in response to exercise when lovastatin was taken as compared with placebo, if such a difference existed.

In a study of five normal untrained volunteers (two men, three women) ranging in age from 23 to 34 years, Newham and colleagues were able to show a greater rise in serum CK activity following identical eccentric exercise[16] than we found in our subjects. The smaller degree of rise we found may have been due to the fact that our subjects were in better physical condition. Our volunteers all were medical house staff who, although not involved in any regular exercise program, were accustomed to walking up and down stairs almost daily. Most likely, more severe eccentric exercise, such as longer treadmill walks, would result in greater CK rises in our subjects.

It could be argued that more severe exercise-induced muscle damage should have been induced in our patients to reflect CK rises typically seen after prolonged vigorous exercise. Without knowing the risk of severe exercise-induced muscle damage with lovastatin use, we did not want to produce more severe muscle damage for fear of exposing volunteers to undue risk. Furthermore, we did show significant and reproducible rises in serum CK activity reflecting muscle damage from exercise, and these were no greater after lovastatin use.

Although patients taking lovastatin often have coexisting factors predisposing them to rhabdomyolysis—such as poor nutrition, heart failure, alcoholism, and the use of other pharmaceutical agents—our data suggest that lovastatin is not an independent risk factor for the development of exercise-induced muscle damage in our study population. The possibility still exists that persons who may be more susceptible to exercise-induced myopathy or who undergo more severe exercise might have a greater degree of muscle damage when taking lovastatin. Our model may prove useful in determining which coexisting conditions increase the risk of exercise-induced rhabdomyolysis in such patients.

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## POEM WITHOUT A NAME

*Caminante, no hay camino*
*Se hace camino al andar.*

You come to me and say you're sorry
for the trouble you've brought to me:
the teacher whose changed face now frightens
children, the wife whose keys went through her cheeks*
so a child now lets her in,
the one who is missing who you will never bring to me,
and your own returning there to all these things.

So you must, you say, and I must
stay here and wonder who will bring which one of these
(of you) to me one day in this office where
I work and can only keep in my mind words
to keep the pictures out, words another doctor said,

(your brother, dead):
"It is no longer different for us now—
our work will not protect us long from grief
or love."

Remember, you did not bring
these things to me I looked
for you as I will look
for you and look

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*It is a common practice during interrogation in some Latin American countries for a person's housekeys to be passed through the cheeks.

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