Statins, Exercise, and Exercise Training*

Paul D. Thompson, MD,† Beth Parker, Ph.D‡
Hartford, Connecticut

Statins are life-saving medications and so effective that some have suggested they be added to the drinking water to “fluorinate” the vascular bed against atherosclerotic disease. But statins, both in research models and clinically, can have deleterious effects on skeletal muscle. The most serious side effects are myositis and rhabdomyolysis manifested by marked elevations in creatine kinase and associated, in several studies, with variants in the hepatic organic anion transporter protein SLC01B1 (1). These variations result in reduced statin hepatic uptake and expose more of the periphery and skeletal muscle to the drug. Rhabdomyolysis is extremely rare in the absence of concomitant medications such as gemfibrozil, cyclosporine, human immunodeficiency virus protease inhibitors, azole antifungals, and macrolide antibiotics that increase statin blood and muscle levels (2).

The mechanisms mediating statin myopathy are unclear, but possibilities include decreased sarcolemmal or endoplasmic reticulum cholesterol, reduced production of prenylated proteins including the mitochondrial electron transport protein coenzyme Q10, reduced fat catabolism, vitamin D deficiency, and inflammation (2). Increasingly, interest has focused on altered cellular energy use and mitochondrial dysfunction, with the dysfunction activating pathways leading to muscle atrophy (6–8).

This issue of the Journal presents results from an exercise training study that further implicate altered mitochondrial function in statin-associated muscle dysfunction. Mikus et al. (9) randomized previously sedentary, statin-naïve adults with at least 2 risk factors for metabolic syndrome to 12 weeks of supervised, aerobic exercise training alone (n = 19) or in combination with 40 mg of simvastatin (n = 18). Maximal oxygen uptake, expressed either as an absolute value or relative to body weight, increased 10% with training in the exercise-only group, but only 1.5% in the exercise-and-simvastatin group (p < 0.01 for interaction). Citrate synthase activity, a measure of muscle mitochondrial content obtained from vastus lateralis biopsies in 12 exercise-plus-simvastatin and 17 exercise-only subjects, increased 13% following exercise training in the exercise-only subjects but decreased 4.5% in the exercise-plus-simvastatin subjects (p < 0.05 for interaction). There were also changes in skeletal muscle mitochondrial complexes I, II, III, and IV with exercise.

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From the †Cardiology Division, Hartford Hospital, Hartford, Connecticut; and the ‡Department of Health Sciences, University of Hartford, Hartford, Connecticut. Funded in part by National Institutes of Health grants #RO1HL081893, #1RO1HL098085, and #RC1 AT005836. Dr. Thompson has received grant and research support from GlaxoSmithKline, Genoma, Novartis, Roche, sanofi-aventis, Regeneron, Esperion, and Amarin; has served as a consultant for Astrazeneca, Amgen, Regeneron, Merck & Co., Inc., Roche, Genoma, Abbott, Lupin, Runners World, Genzyme, sanofi-aventis, GlaxoSmithKline, and Esperion; has received speaking honoraria from Merck, Abbott, Astrazenea, GlaxoSmithKline, and Kowa; owns stock in General Electric, JA Wiley Publishing, Johnson & Johnson, and Abbott; and has served as a legal consultant on cases involving cardiac complications of exercise and statin myopathy. Dr. Parker has reported that she has no relationships relevant to the contents of this paper to disclose.

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training alone, but no changes with exercise training and statin treatment.

Exercise training studies are difficult because they require a large time commitment from both the subjects and the investigators, but this trial was well done by a research group known for their expertise in exercise physiology. The design would have been enhanced by double-blinding with the use of a placebo medication. This becomes particularly relevant given data suggesting that statin-treated subjects overestimate the effects of statins on skeletal muscle (5). It would also be useful to know if the training intensity was similar in the two groups. We have observed a reduction in spontaneous physical activity levels in individuals over age 55 years treated with atorvastatin (5). Knowing whether the statin-treated subjects exercised less intensely in the Mikus et al. (9) trial would indicate if statins reduced the training stimulus itself or if they reduced the physiological response to a similar training stimulus.

These results are not good news for clinicians trying to convince physically active patients to stay on statins, but other studies have also suggested that statins affect the skeletal muscle response to exercise and exercise training. Only 20% of 22 professional soccer players with familial hypercholesterolemia were able to tolerate any of the 5 statins then available (10). The incidence of statin muscle complaints in PRIMO was 14.7% in those subjects who practiced some intense form of sport, but only 10.8% in less active individuals (4). The creatine kinase increase after exercise is greater in individuals randomized to lovastatin 40 mg daily (11) and in Boston marathoners treated with statins than in runners not on these medications (12). Statins also reduce the increase in atrogin-1 gene expression that occurs after eccentric exercise (13). Atrogin-1 is a key component of the ubiquitin proteasome pathway and participates in catabolizing muscle protein. Down-regulation of atrogin-1 after exercise suggests a reduced ability to clear damaged muscle protein that could contribute to the muscle complaints reported in physically active subjects (13). The results reported by Mikus et al. (9) add to the evidence that statins affect the ability of skeletal muscle to adapt to the stress of exercise training.

These results also raise additional questions about the statin effect. Is the reduction in the exercise training response limited to aerobic exercise training, or do statins also affect the muscle’s response to resistance training? Is the effect limited to individuals with baseline alterations in glucose metabolism and risk factors for metabolic syndrome such as those who participated in this study? Do statins reduce exercise capacity in physically active patients, or do they only reduce the exercise-training response in previously inactive subjects? A recent cross-sectional analysis of over 10,000 patients indicates that both statin use and increased physical fitness are separately associated with reduced mortality, but that there is an additive benefit of the combination such that physically active patients treated with statins demonstrate the lowest risk for premature mortality (14). Are the advantageous effects of improving physical fitness reduced by concomitant statin therapy? The benefits of statins clearly outweigh their risks, but there are few studies on the effects of statins on physical activity, in physically active subjects, and on the physiological response to exercise training.

Mikus et al. (9) should be congratulated for a study that further implicates the mitochondria in statin-related muscle dysfunction. Their paper provides novel data that answer some, but raises more, questions about the interaction of physical activity and exercise with statin therapy.

Reprint requests and correspondence: Dr. Paul D. Thompson, Cardiology Division, Hartford Hospital, 80 Seymour Street, Hartford, Connecticut 06102. E-mail: pthomps@harthosp.org.

REFERENCES


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