

Effect of Statins on Skeletal Muscle: Exercise, Myopathy, and Muscle Outcomes

Beth A. Parker^{1,2,3} and Paul D. Thompson^{1,2}

¹Division of Cardiology, Henry Low Heart Center, Hartford Hospital, Hartford; ²School of Medicine, University of Connecticut, Farmington; and ³Department of Health Sciences, University of Hartford, West Hartford, CT

PARKER, B.A. and P.D. THOMPSON. Effect of statins on skeletal muscle: exercise, myopathy, and muscle outcomes. *Exerc. Sport Sci. Rev.*, Vol. 40, No. 4, pp. 188–194, 2012. *Statins are effective in reducing low-density lipoprotein cholesterol and cardiac events but can produce muscle side effects. We have hypothesized that statin-related muscle complaints are exacerbated by exercise and influenced by factors including mitochondrial dysfunction, membrane disruption, and/or calcium handling. The interaction between statins, exercise, and muscle symptoms may be more effectively diagnosed and treated as rigorous scientific studies accumulate.* **Key Words:** cholesterol-lowering medication, muscle strength, aerobic capacity, myalgia, vitamin D, HMG CoA reductase inhibitor

INTRODUCTION

Hydroxy-methyl-glutaryl (HMG) coenzyme A (CoA) reductase inhibitors or statins are the most effective medications for managing elevated concentrations of low-density lipoprotein cholesterol (LDL-C). These drugs also offer one of the most effective strategies in reducing cardiovascular disease and have been documented to reduce cardiac events in both coronary artery disease (CAD) patients (21) and in previously healthy subjects (3). Statins are so effective that they are presently the most prescribed drugs in the United States and the world.

Treatment guidelines based primarily on serum LDL-C levels were established by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III in May 2001 (5). These guidelines suggest an LDL-C treatment goal of less than 100 mg·dL⁻¹ for patients with established vascular disease, diabetes, or a calculated 10-yr CAD risk of more than 20%. Several recent clinical trials support even lower LDL-C goals for many patients. The Heart Protection Study (HPS) observed a 23% reduction in CAD events among 20,536 high-risk patients treated with simvastatin 40 mg·d⁻¹ for 5 yr (17). A similar percent reduction in cardiac events was seen in the 6793 patients whose baseline LDL-C was less than 116 mg·dL⁻¹. Moreover, an NCEP update stated that an LDL-C goal of less

than 70 mg·dL⁻¹ is “a reasonable clinical strategy” for patients at very high risk of CAD and that older persons also benefit from LDL-C reduction. Recently published results from the JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) Trial indicate that healthy individuals without hyperlipidemia but with elevated high-sensitivity C-reactive protein levels benefit from a reduction in the incidence of major cardiovascular events after several years of treatment with 20 mg rosuvastatin (22). These collective results suggest that increasing numbers of patients, including the elderly and those with low initial LDL-C levels, will be treated with larger doses of the more potent statins. Indeed, the Centers for Disease Control and Prevention reported that from 2005 to 2008, approximately 25% of U.S. adults older than 45 yr reported using a prescription statin drug in the last 30 d, a roughly 10-fold increase over 1988 to 1994 (Fig. 1).

MUSCLE SIDE EFFECTS ASSOCIATED WITH STATIN TREATMENT

Statins are extremely well tolerated by most patients but can produce a variety of muscle-related complaints in some individuals. The most serious risk of these drugs is rhabdomyolysis with acute renal failure and even death. This risk was emphasized by the withdrawal of cerivastatin in August 2001 after the drug was associated with approximately 100 rhabdomyolysis-related deaths. Fortunately, clinically important rhabdomyolysis with statins is rare, with an overall reported incidence of fatal rhabdomyolysis of 1.5 deaths per 10⁶ prescriptions (27). Unfortunately, statins are much more frequently associated

Address for correspondence: Beth Parker, Ph.D., 80 Seymour St, Hartford Hospital, Hartford, CT 06012 (E-mail: bparker03@hartosp.org).

Accepted for publication: July 26, 2012.

Associate Editor: LaDora V. Thompson, Ph.D.

0091-6331/4004/188-194

Exercise and Sport Sciences Reviews

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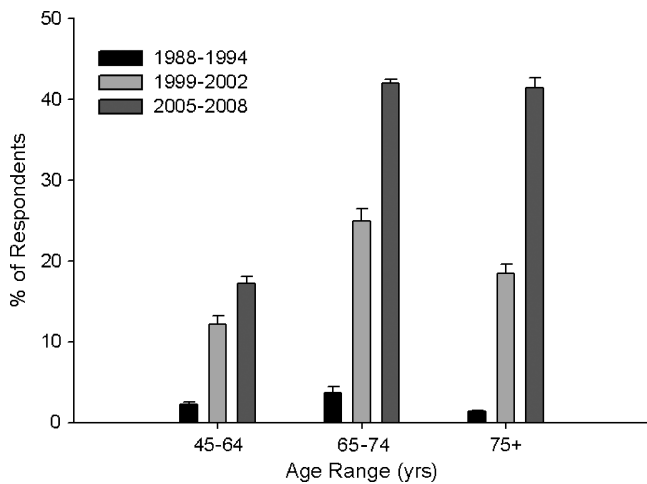


Figure 1. Trends in statin drug use among adults in the United States are shown by age group (aged 45–64, 65–74, and 75+ yr) over three age ranges (1989–1994, 1999–2002, and 2005–2008). Data are self-report data (group means \pm SEM) from the National Health and Nutrition Examination Survey, with “statin use” defined as taking a prescription statin during the past 30-d period.

with “mild muscle complaints,” including myalgia, cramps, and weakness. Myalgia can occur with or without creatine kinase (CK) elevations, a serum marker of muscle damage. The reported incidence of myalgia during therapy with the more powerful statins has varied from 1% in pharmaceutical company reports (20) to 25% (19) of patients. It is impossible to discern the true incidence of mild muscle complaints because these problems typically are not examined in pharmaceutical-sponsored trials and because of study design. In the HPS, for example, subjects were not randomized to simvastatin or placebo until they had successfully tolerated simvastatin 40 mg for a 5-wk introductory period (17), and most trials report muscle symptoms only when CK values exceeded 10 times upper limits of normal.

Recent clinical reports, however, have confirmed clinicians’ suspicions that statins frequently produce muscle symptoms. Among 7924 patients treated with high-dose statins, 11% developed muscle symptoms, 4% had symptoms severe enough to interfere with daily activities, and 0.4% were actually confined to bed with their symptoms (2). We and others have suggested various approaches to managing statin myalgia, but this management often requires withdrawal of these life-saving medications.

EFFECTS OF STATINS ON MUSCLE STRENGTH AND AEROBIC PERFORMANCE

Muscle weakness also is a clinically acknowledged complication of statin use in some individuals. Data from direct assessments of muscle weakness (*i.e.*, strength testing) and statins are limited and have produced inconsistent conclusions. We recently published a review summarizing the six published articles documenting the effect of statins on skeletal muscle strength in humans (12). To our knowledge, Phillips *et al.* (19) were the first to examine the association of statins and muscle strength in four subjects (2 women aged 76 and 66 yr; 2 men

aged 66 and 62 yr) with symptoms of statin myopathy despite normal CK levels. These authors noted reductions of 10% to 40% in hip abduction strength. Similarly, another study documented statin-induced myopathic proximal weakness in patients with neurological disease. Authors used a prospective cohort design to examine the effect of statin therapy on muscle function, muscle mass, and fall risk in 774 individuals, aged 50 to 79 yr, participating in the Tasmanian Older Adults Cohort Study. Statin users at 2.6 yr of follow-up had significantly lower mean leg strength than statin nonusers at follow-up, and muscle strength and quality decreased significantly in those who reported statin use at baseline and follow-up when compared with all other patients. Interestingly, both muscle strength and quality were significantly decreased in statin users at baseline and follow-up compared with those who stopped statin therapy, although the latter group was small ($n = 11$). Such results suggest that statins decrease muscle strength in older individuals and that this decrease is reversible with treatment cessation. Conversely, a larger cross-sectional study of statin users versus nonusers found slightly improved performance on a sit-to-stand chair test (a measure of proximal muscle strength) with statin use in older community-dwelling adults, suggesting that low-dose statin therapy improved strength in an asymptomatic cohort. Still other studies have shown no effects of high-dose statin therapy on handgrip, upper body, and leg muscle strength.

There also are sparse data on the effects of statins on aerobic exercise performance; again these findings were covered in our recent review on the topic (12). One study provided atorvastatin 5 to 10 mg to five healthy middle-aged men (54 ± 10 yr) and one woman. Exercise results in these subjects were compared with results from nine men and two women who developed muscle complaints plus CK elevations during statin alone ($n = 6$), statin and fibrate ($n = 3$), or statin and niacin ($n = 2$) therapy. There was no effect of statin therapy on maximal oxygen uptake ($\dot{V}O_{2max}$), a measure of aerobic fitness, in the normal patients, but $\dot{V}O_{2max}$ was significantly lower in the myopathic patients, a finding the authors attributed to these patients’ physical inactivity because of their myopathy. Interestingly, the resting respiratory exchange ratio ($RER = \dot{V}CO_2/\dot{V}O_2$) increased with statin therapy in the normal subjects (0.75 ± 0.02 to 0.86 ± 0.06) and also was elevated in the myopathic patients off statin therapy (0.90 ± 0.07). RER decreases with fat oxidation and increases as carbohydrate is used as fuel but is a crude measure of these processes. The authors interpreted their findings as showing that statins impair fat metabolism in healthy patients and that patients with statin myopathy have a pretreatment abnormality in fat metabolism that is exacerbated by statin therapy leading to the muscle complaints. There was no apparent change in the onset of lactate accumulation or “anaerobic threshold” during the exercise test, however, which argues against an alteration in exercise fat metabolism with statin treatment. One additional study of 195 noninsulin diabetics noted a 6% increase in resting RER (0.78 to 0.83), which the authors attributed to improved glucose metabolism with statin treatment, but exercise parameters were not measured in that study.

By contrast, several studies have found no evidence of an effect of statins on aerobic exercise performance. For example, $\dot{V}O_{2max}$ and RER did not change in 10 patients after 12 wk of

simvastatin therapy ($80 \text{ mg}\cdot\text{d}^{-1}$), suggesting that short-term high-dose statin therapy does not impair aerobic capacity or alter substrate metabolism in older asymptomatic patients. Other investigators observed that $\dot{V}\text{O}_{2\text{max}}$ increased by $29\% \pm 6\%$ in a group of hypercholesteremic and physically inactive subjects simultaneously treated with $10 \text{ mg}\cdot\text{d}^{-1}$ rosuvastatin and undergoing 10 wk of exercise training. These results suggest that statins do not eliminate the aerobic training response, but this study did not include an untreated exercise-trained control group, so data must be interpreted with caution. Moreover, in clinical populations, such as adults with heart failure and claudication, statin therapy improves average walking distance and/or pain-free walking time. Cumulatively, therefore, these equivocal results suggest that despite their documented myopathic effects, the effects of statins on muscle strength and aerobic exercise performance are unclear.

STATIN-RELATED COMPLAINTS ARE EXACERBATED BY EXERCISE

We have hypothesized that statin-related muscle complaints may be exacerbated by exercise based on several reports indicating that athletes and/or physically active individuals are less likely to tolerate statin therapy. This was based on our observation in 1990 of 36 participants in a clinical trial comparing the lipid effects of fluvastatin versus lovastatin. Four individuals developed CK elevations, an index of muscle injury, and each elevation was associated with recent physical exertion. One subject, who had not habitually exercised, performed a weightlifting workout and presented with severe muscle pain and a CK level 100 times the upper limit of normal (29). Furthermore, Sinzinger and O'Grady (26) monitored statin use and muscle side effects in 22 professional athletes with familial hypercholesterolemia. Only 20% of these top athletes ultimately tolerated statin therapy despite multiple trials with multiple medications. Similarly, Bruckert *et al.* (2) observed more muscle symptoms in physically active individuals than sedentary individuals. The incidence of muscle pain with statin therapy increased with the level of physical activity from 10.8% in those engaging in leisure-type physical activity to 14.7% in those regularly engaging in vigorous activity, suggesting that statin-associated muscle side effects are provoked by physical activity. The muscle pain prevented even moderate exertion during everyday activities in 38% of the patients with myalgia on statins.

We then tested this hypothesis directly in a double-blind, placebo-controlled study of 59 healthy men aged 18 to 65 yr with LDL-C levels greater than $130 \text{ mg}\cdot\text{dL}^{-1}$ (31). Subjects were randomly assigned to lovastatin ($40 \text{ mg}\cdot\text{d}^{-1}$) or placebo for 5 wk. Subjects completed 45 min of downhill treadmill walking (-15% grade) at 65% of their predetermined maximum heart rate after 4 wk of treatment. CK levels were measured before exercise and daily for 4 d after the treadmill exercise. CK levels were 62% and 77% higher in the lovastatin group 24 and 48 h after treadmill exercise after adjusting for initial CK differences between groups at baseline (Fig. 2). Although CK levels may not fully correlate to the degree of muscle injury, these data support that HMG-CoA reductase inhibitors exacerbate exercise-induced skeletal muscle injury.

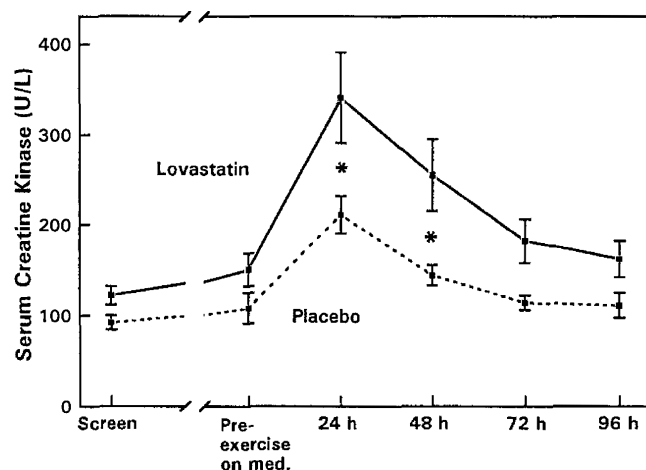


Figure 2. Serum creatine kinase (CK) levels (in units per liter) in men treated with $40 \text{ mg}\cdot\text{d}^{-1}$ lovastatin ($n = 22$) or placebo ($n = 27$) before treatment (screen), after 4 wk of lovastatin or placebo (preexercise on medication), and daily for 4 d after downhill walking. * $P < 0.05$. (Reprinted from (31). Copyright © 1997 Elsevier. Used with permission.)

A subsequent study examined the CK response to downhill walking in subjects treated with low and high doses of atorvastatin to determine whether statin-induced elevations in muscle damage are dose dependent (11). Seventy-nine healthy men with LDL cholesterol more than $100 \text{ mg}\cdot\text{dL}^{-1}$ were discontinued from statin medications for 6 wk and randomly assigned to atorvastatin 10 mg ($n = 42$) or 80 mg ($n = 37$) for 5 wk. Similar to the previous study, subjects completed 45 min of downhill treadmill walking (-15% grade) at 65% of their predetermined maximum heart rate in the fifth week of treatment. Leg muscle soreness and plasma CK were measured daily for 4 d after the exercise. CK and muscle soreness increased above preexercise levels in all subjects after the exercise, with no differences in the CK response between the high- and low-dose treatment groups at any time point. We thereby concluded that exercise can increase CK levels with even low-dose statin therapy. It is possible, however, that downhill walking may not be sufficiently sensitive to detect dose-dependent differences in the effects of statin therapy on eccentric exercise-induced muscle damage.

We have confirmed that eccentric exercise during statin therapy does increase CK levels more than exercise on placebo in our most recent study conducted at the 2011 Boston Marathon (18). The Boston race course drops approximately 440 ft, despite the notorious Newton hills, so includes a lot of eccentric exercise. We measured total CK in 37 statin-using athletes (29 men and eight women) and 43 controls (30 men and 13 women) running the race. Subjects were on a variety of statin medications and doses. Venous blood samples were obtained the day before and within 1 h and 24-h after the race. The exercise-related increase in CK 24 h after exercise, adjusted for changes in plasma volume, was greater in statin users than controls (Fig. 3). Notably, there was no relationship between statin potency and the changes in CK immediately and 24 h after exercise, although increases in CK at both finish and 24 h after the race measurements were directly related to age in the statin users. We concluded that statins increase exercise-related muscle injury, and the susceptibility

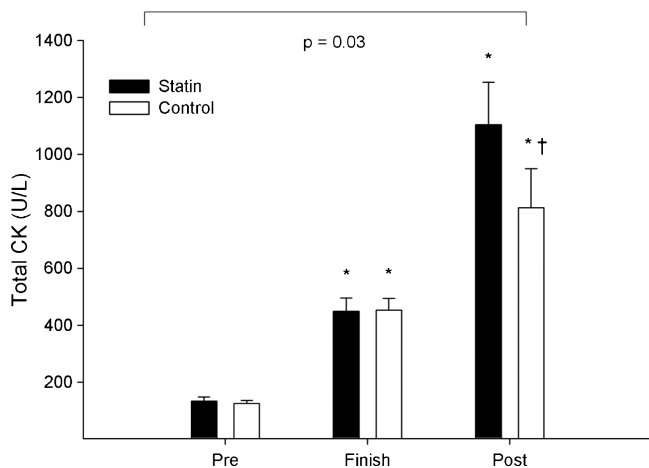


Figure 3. Group means (\pm SD) of total creatine kinase (CK) before (Pre), immediately after (Finish), and 24 h after the 2011 Boston Marathon (Post) in 37 individuals treated with statins and in 43 non-statin-treated controls, including the P value for the group \times time interaction. *Significant effect change relative to the baseline (pre) value at $P < 0.05$ within each group; †Significant difference between groups at $P < 0.05$. (Reprinted from (18). Copyright © 2012 Elsevier. Used with permission.)

to exercise-induced muscle injury with statins does not appear to be dose dependent but does increase with age. Age increases serum and ultimately muscle concentrations of statins and is considered a risk factor for skeletal muscle myopathy. Therefore, it is plausible that age magnifies the effect of statins on exercise-associated elevations in CK because of the same mechanism by which age increases the risk of myopathy.

It should be noted that other studies have failed to confirm greater increases in CK levels after eccentric (18,28) exercise during statin treatment possibly because of small sample sizes and the use of a crossover design and/or repeated bouts of exercise. It is known, for example, that a single exercise session protects the muscle from subsequent injury during the next several months, so that crossover designs and/or those with multiple bouts of exercise may obscure any effect of statin treatment (4). In support of this hypothesis, Meador

and Huey (16) recently published a study showing that 2 wk of prior run training prevented cerivastatin-associated force loss and increased fatigability in mice.

MECHANISMS OF EXERCISE-ASSOCIATED DAMAGE

Sustained muscular contraction during periods of glycogen depletion and reduced adenosine-5'-triphosphate availability result in membrane permeability and fiber damage, permitting muscle enzyme efflux that is proportional to the duration and intensity of the exercise. There are several mechanisms by which statins could amplify this process (Fig. 4).

The most popular but largely untested theory for statin myopathy at rest and during exercise is depletion of intramuscular CoQ10 producing mitochondrial dysfunction, subsequent abnormal muscle energy metabolism, and, ultimately, symptoms. We have recently summarized the data linking CoQ10 to statin myopathy (15). Serum CoQ10 levels decrease during statin therapy, but CoQ10 is transported in lower density lipoprotein particles, and its decrease is commensurate with decreases in blood cholesterol. This suggests that the decrease in serum CoQ10 is caused by a reduction in transport particles. CoQ10 levels do not decrease during ezetimibe and cholestyramine therapy, however, despite reductions in LDL levels, so it is possible that the effect of statins on CoQ10 is independent of their reductions in transport particles. Muscle biopsy studies have failed to detect consistent reductions in muscle CoQ10 levels, although one study in statin-naive subjects found microscopic evidence of statin myopathy and reductions of 30% in intramuscular CoQ10 levels in subjects treated with simvastatin 80 mg for 8 wk. Another report noted muscle CoQ10 levels 2 to 4 SD below normal in 50% of patients with statin myopathy.

Similarly, there is emerging animal and human evidence for a disruption in mitochondrial function with statin therapy. Bouitbir *et al.* (1) recently characterized mitochondrial function and reactive oxygen species (ROS) production in skeletal muscle after exhaustive exercise in atorvastatin-treated rats relative to untreated rats. At rest, ROS levels were increased by

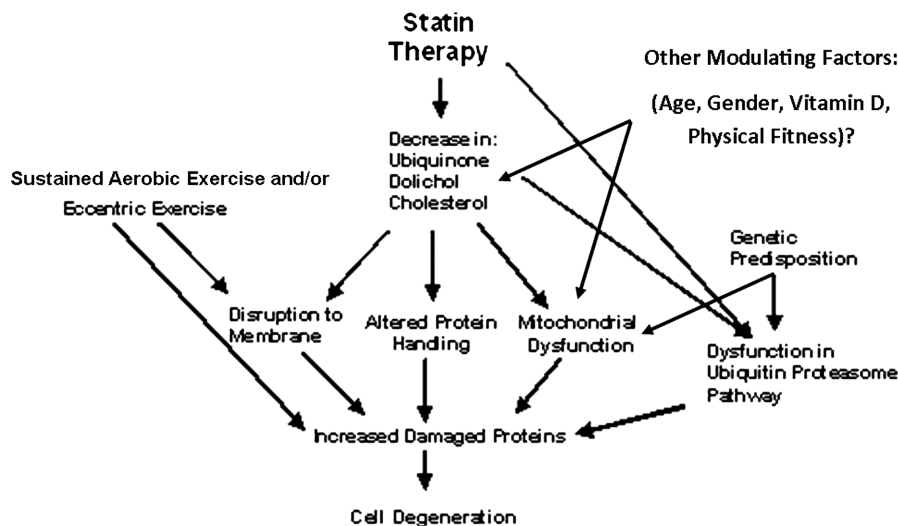


Figure 4. A schematic diagram of the potential mechanisms by which statin therapy and exercise result in skeletal muscle damage.

60% in the plantaris muscle of atorvastatin versus control rats; the difference was even more pronounced (226% increase with atorvastatin) after exhaustive exercise. Moreover, atorvastatin treatment reduced the distance covered during exhaustive exercise, and this correlated to a 39% decrease in maximal mitochondrial respiration observed relative to the control group. Similarly, phosphocreatine exercise recovery time after calf flexion exercise increased after 4 wk of statin therapy in 10 hypercholesteremic patients, suggesting again that statins impair mitochondrial oxidative function (34). The hypothesis that statins deleteriously affect mitochondrial function is supported by our observation that transcriptional patterns between statin myopathic and statin-tolerant subjects differ after eccentric leg exercise; symptomatic subjects treated with a statin exhibited decreased skeletal muscle gene expression for oxidative phosphorylation-related and mitochondrial ribosomal protein genes relative to asymptomatic subjects (9). Interestingly, mitochondrial gene expression also was different at baseline (before statin treatment) between subjects who had and had not previously tolerated statin therapy.

To our knowledge, only two small studies have administered CoQ10 to patients with statin myalgia but neither tested muscle injury after exercise, and these reports produced contrasting results. One study randomly assigned patients with previous statin myalgia and currently on statin treatment to low-dose CoQ10 (100 mg·d⁻¹, n = 18) or vitamin E (400 IU·d⁻¹, n = 14) for 30 d. Pain severity decreased by 40% and pain interference with daily activities decreased by 38% in the group treated with CoQ10, but neither pain severity nor pain interference with daily activities changed with vitamin E. Another study randomized 44 patients with statin myalgia to CoQ10 200 mg·d⁻¹ or placebo during upward dose titration of simvastatin from 10 to 40 mg·d⁻¹ but found no difference in myalgia score, adherence to simvastatin treatment, or the number of patients tolerating the highest simvastatin dose.

Alternatively, statins may modify the response of muscle to exercise stress by altering skeletal muscle membrane integrity as well as the actions of the ubiquitin proteasome pathway (UPP), protein folding, and catabolism, thereby disrupting the balance between cell degradation and repair. For example, the skeletal muscle membrane content is predominantly composed of phospholipids, which, if reduced by statin therapy, may exacerbate damage associated with bouts of exercise. Moreover, the UPP system is responsible for the recognition and degradation of many skeletal muscle proteins and is involved in conditions involving muscle mass loss such as cancer cachexia, diabetes, uremia, and sepsis. Atrogin-1, a component of the UPP system, is induced early in the atrophy process. We demonstrated marked reductions in atrogin transcription in a human exercise injury model of statin myopathy (32). In contrast, Hanai and colleagues (8) found increases in atrogin-1 expression in human skeletal muscle in patients with statin myopathy, and animal cells lacking atrogin-1 were resistant to statin myotoxicity. Consequently, the role of the UPP system in statin-induced myotoxicity is not defined. Furthermore, the factors activating this system are not clear and could involve changes in energy production. Statin therapy also may upregulate skeletal muscle apoptosis via activation of calpain (which stimulates programmed cell death), as has been observed in human muscle cells after treatment with simvastatin. More-

over, statin treatment results in repression of the antiapoptosis gene (*Birc4*) and activation of the proapoptosis gene (*Cflar*) in human muscle cells (35).

Finally, statin therapy could alter calcium handling such that calcium leaking from the mitochondria might impair sarcoplasmic reticulum calcium cycling. For example, 2 months' treatment of rats with fluvastatin and atorvastatin caused an alteration of calcium homeostasis, increasing resting cytosolic calcium up to 60% with the higher fluvastatin dose (13). Because animal research suggests that type II glycolytic muscle fibers are most vulnerable to statin-associated muscle injury after cervistatin treatment and treadmill exercise in female rats, carbohydrate depletion during exercise could make these fibers particularly susceptible to injury in humans as well. Differences in fiber type composition between individuals also may consequently impact muscle response to the combination of statin and exercise.

POTENTIAL MODIFIERS OF THE INTERACTION BETWEEN STATINS, SKELETAL MUSCLE, AND EXERCISE

We have recently reviewed the growing body of evidence suggesting that genetic factors increase an individual's susceptibility to statin myopathy (6). For example, a genome-wide scan conducted in 85 subjects with statin-induced myopathy yielded a single strong association of myopathy with the rs4363657 single-nucleotide polymorphism (SNP) located within *SLCO1B1*. *SLCO1B1* encodes the organic anion-transporting polypeptide OATP1B1, thereby regulating the hepatic uptake of statins. A recent investigation tested 110 patients with primarily statin-induced myopathies and noted that 10% of these patients had at least one abnormal allele for a gene affecting muscle metabolism. A more recent study of 190 patients with severe statin myopathy resulted in the identification of three SNPs in the eyes shut homolog (*EYS*) on chromosome 6, which may play a role in maintaining the structural integrity of skeletal muscle (10). We also have shown genetic variants predictive of muscular side effects in patients treated with statins. In a recent multisite study of 377 patients with statin-associated myalgia and 416 patients tolerant of statins, three candidate genes (*COQ2*, *ATP2B1*, and *DMPK*), representing pathways involved in CoQ10 synthesis, calcium homeostasis, and myotonic dystonia, respectively, were validated as markers for myalgia (25). A previous study found a relationship between statin myalgia and two polymorphisms in serotonergic genes, such that SNPs in the *HTR3B* and *HTR7* genes, rs2276307 and rs1935349, respectively, were significantly associated with the myalgia score of probable or definitive myalgia (23).

Similarly, there appears to be a genetic predisposition to non-exercise-induced CK increases during statin treatment because individuals homozygous for the cytochrome P450 (*CYP*)3A genetic variant (*CYP3A5**3) demonstrated greater serum CK levels than patients heterozygous for *CYP3A5**3 after atorvastatin treatment (33). We also screened for genetic associations with CK levels in 102 patients receiving statin therapy, finding that SNPs in the angiotensin II Type 1 receptor and nitric oxide synthase 3 genes were significantly associated with CK activity (24).

Because non-statin-treated individuals also show genetic susceptibility to exercise-induced muscle damage, we have hypothesized that the interaction between muscle side effects and damage, statin therapy, and exercise is likely to be influenced by expression of certain genetic variants. However, to the best of our knowledge, no data yet exist to directly confirm this hypothesis.

We also recently reviewed the relationship between vitamin D deficiency (commonly measured as 25 hydroxyvitamin D [25(OH)D] levels below $30 \text{ ng}\cdot\text{mL}^{-1}$) and statin myopathy (7). Cholesterol is used to synthesize 7-dehydrocholesterol, the precursor to vitamin D3 (cholecalciferol), endogenously. Interestingly, although it is expected that statin therapy would reduce both cholesterol and serum vitamin D, studies to date have shown that statin therapy either has no effect on vitamin D or, conversely, increases vitamin D levels in asymptomatic adults. Despite these latter findings, case reports, clinical anecdotes, and cross-sectional studies have linked vitamin D insufficiency to statin myopathy. For example, among 11 patients with statin myalgia prompting statin discontinuation, eight were vitamin D insufficient (25(OH)D, $<24 \text{ ng}\cdot\text{mL}^{-1}$) and three of these were severely deficient (25(OH)D, $<12 \text{ ng}\cdot\text{mL}^{-1}$). Six of the eight patients had complete resolution and two had significant improvement of myalgia for approximately 3 months, with cessation of the statin and vitamin D replacement ($1000\text{--}10,000 \text{ U}\cdot\text{d}^{-1}$); moreover, four of the six patients agreed to rechallenge with the same statin after vitamin D repletion and tolerated statin therapy for at least 6 months without myalgia. Another study of statin-treated patients noted that serum vitamin D levels at enrollment were lower in 128 patients with myalgia versus 493 asymptomatic patients. Of the 82 vitamin D-deficient patients with myalgia (vitamin D levels, $20.8 \pm 7.1 \text{ ng}\cdot\text{mL}^{-1}$), 38 were given vitamin D (ergocalciferol $50,000 \text{ U}\cdot\text{wk}^{-1}$ for 12 wk), with an increase in serum vitamin D from 20.4 ± 7.3 to $48.2 \pm 17.9 \text{ ng}\cdot\text{mL}^{-1}$ and resolution of myalgia in 35 (92%).

Molecular mechanisms of vitamin D action on muscle tissue include genomic and nongenomic effects via receptors present in and on muscle cells, and vitamin D deficiency alone can cause skeletal muscle myopathy as well as decreased muscle strength. There is presently no definitive evidence that vitamin D contributes to statin myalgia, but this possibility does warrant further scientific inquiry (7).

SUMMARY

Statin therapy, although well tolerated by most patients, can be associated with muscle-related side effects and may exacerbate CK release and presumably the skeletal muscle damage associated with eccentric exercise. However, gaps in physiological, molecular, mechanistic, and clinical knowledge regarding muscle effects of statin therapy remain substantial, with many unresolved issues and equivocal findings. Key questions include

- Are statin-induced muscle side effects a continuum from myalgia to rhabdomyositis and caused by similar mechanisms? This is an important question for clinicians who must decide whether or not continuing statin therapy in

subjects with myalgia increases the risk of life-threatening rhabdomyolysis.

- Should clinicians discontinue statin use for several days before endurance events especially if heat stress or other potential exacerbators of rhabdomyolysis may occur? The latter could be particularly important for older runners who appear more likely from our 2011 Boston Marathon to experience muscle injury.
- Can we develop better, more consistent, screening and testing techniques to assess individuals who may be at risk for myalgia, decreases in muscle strength and aerobic performance, and increased muscle damage with statin treatment? This could include genetic profiles designed to identify genes associated with statin muscle complaints.
- Are statin-associated muscle complaints altered by acute and chronic physical activity, and what other factors contribute to the relationship between statins and skeletal muscle function? Discrepant results regarding the effects of statins on muscle strength, aerobic performance, and CK levels after exercise suggest that multiple additional factors influence the effects of statins on skeletal muscle at rest and during exercise. To date, although evidence supports the hypothesis that acute and chronic resistance and aerobic exercise may exacerbate statin-associated muscle complaints in some individuals, there is a paucity of carefully controlled, adequately powered, rigorously designed studies to fully document this.
- Finally, can increases in CK associated with exercise and statin therapy be confirmed with more direct measurements of muscle damage in human subjects that also provide important information about underlying mechanisms, such as apoptosis, calcium handling, and oxidative stress? Most human studies on this topic have assessed non-invasive markers of muscle damage or assessed molecular and genetic pathways in resting skeletal muscle treated with statin therapy. There also are limited animal studies investigating statin-induced skeletal muscle damage with exercise.

A recent editorial in the *New England Journal of Medicine* emphasized the need for clinical trials in statin-intolerant patients (14). There is a similar need for large-scale trials investigating the effects of statins on skeletal muscle strength, aerobic performance, and exercise-induced muscle damage during a long-term duration of treatment in individuals with or without statin myalgia. To this end, we recently have completed data collection of an NHBLI-funded (STOMP [The Effect of STatins On Skeletal Muscle Function and Performance]) study assessing CK, exercise capacity, and muscle strength before and after atorvastatin 80 mg or placebo treatment for 6 months in 420 healthy statin-naive subjects (30). We believe that these emerging results will address several of the inconsistencies in the literature to date regarding impacts of statin therapy on muscle and aerobic outcomes. Nonetheless, with an aging population, ever-lowering LDL-C guidelines, and increasing numbers of statin prescriptions, research aimed at better elucidating the relationship among exercise, statin therapy, and skeletal muscle will be critical for refining treatment guidelines.

Acknowledgments

The authors acknowledge Amanda Augeri, Jeffrey Capizzi, Lindsay Lorson, and William Roman for assisting with work cited in this manuscript. Because of reference limitations, we could not cite the individual work covered in our previously published review papers (6,7,12,15). We acknowledge the work of all authors whose work was covered in those papers.

Funding for this work was received from NHLBI 5R01HL081893 (Thompson) and NHLBI R01HL098085 (Parker).

Beth A. Parker has no disclosures. Paul D. Thompson reports receiving research grants from the National Institutes of Health, GlaxoSmithKline, Anthera, B. Braun, Genomas, Roche, Aventis, Novartis, and Furiex; serving as a consultant for Astra Zenica, Furiex, Regeneron, Merck, Takeda, Roche, Genomas, Abbott, Lupin, Runners World, Genzyme, Sanofi, Pfizer, and GlaxoSmithKline; receiving speaker honoraria from Merck, Pfizer, Abbott, Astra Zenica, GlaxoSmithKline, and Kowa; owning stock in Zoll, General Electric, JA Wiley Publishing, Zimmer, J&J, Sanofi-Aventis and Abbott; and serving as a medico-legal consultant on cardiac complications of exercise, statin myopathy, tobacco, ezetimibe, and nonsteroids.

References

1. Bouitbir J, Charles AL, Rasseneur L, et al. Atorvastatin treatment reduces exercise capacities in rats: involvement of mitochondrial impairments and oxidative stress. *J. Appl. Physiol.* 2011; 111(5):1477–83.
2. Bruckert E, Hayem G, Dejager S, Yau C, Begaud B. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients—the PRIMO study. *Cardiovasc. Drugs Ther.* 2005; 19(6):403–14.
3. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA.* 1998; 279(20):1615–22.
4. Evans WJ, Meredith CN, Cannon JG, et al. Metabolic changes following eccentric exercise in trained and untrained men. *J. Appl. Physiol.* 1986; 61(5):1864–8.
5. Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *JAMA.* 2001; 285:2486–97.
6. Ghatak A, Faheem O, Thompson PD. The genetics of statin-induced myopathy. *Atherosclerosis.* 2010; 210(2):337–43.
7. Gupta A, Thompson PD. The relationship of vitamin D deficiency to statin myopathy. *Atherosclerosis.* 2011; 215(1):23–9.
8. Hanai J, Cao P, Tanksale P, et al. The muscle-specific ubiquitin ligase atrogin-1/MAFbx mediates statin-induced muscle toxicity. *J. Clin. Invest.* 2007; 117(12):3940–51.
9. Hubal MJ, Reich KA, De BA, et al. Transcriptional deficits in oxidative phosphorylation with statin myopathy. *Muscle Nerve.* 2011; 44(3):393–401.
10. Isackson PJ, Ochs-Balcom HM, Ma C, et al. Association of common variants in the human eyes shut ortholog (EYS) with statin-induced myopathy: evidence for additional functions of EYS. *Muscle Nerve.* 2011; 44(4):531–8.
11. Kearns AK, Bilbie CL, Clarkson PM, et al. The creatine kinase response to eccentric exercise with atorvastatin 10 mg or 80 mg. *Atherosclerosis.* 2008; 200(1):121–5.
12. Krishnan GM, Thompson PD. The effects of statins on skeletal muscle strength and exercise performance. *Curr. Opin. Lipidol.* 2010; 21(4):324–8.
13. Liantonio A, Giannuzzi V, Cippone V, Camerino GM, Pierno S, Camerino DC. Fluvastatin and atorvastatin affect calcium homeostasis of rat skeletal muscle fibers in vivo and in vitro by impairing the sarcoplasmic reticulum/mitochondria Ca²⁺-release system. *J. Pharmacol. Exp. Ther.* 2007; 321(2):626–34.
14. Maningat P, Breslow JL. Needed: pragmatic clinical trials for statin-intolerant patients. *N. Engl. J. Med.* 2011; 365(24):2250–1.
15. Marcoff L, Thompson PD. The role of coenzyme Q10 in statin-associated myopathy: a systematic review. *J. Am. Coll. Cardiol.* 2007; 49(23):2231–7.
16. Meador BM, Huey KA. Statin-associated changes in skeletal muscle function and stress response after novel or accustomed exercise. *Muscle Nerve.* 2011; 44(6):882–9.
17. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet.* 2002; 360(9326):7–22.
18. Parker BA, Augeri AL, Capizzi JA, et al. Effect of statins on creatine kinase levels before and after a marathon run. *Am. J. Cardiol.* 2012; 109(2):282–7.
19. Phillips PS, Haas RH, Bannykh S, et al. Statin-associated myopathy with normal creatine kinase levels. *Ann. Intern. Med.* 2002; 137(7):581–5.
20. PDR Staff. *Physicians' Desk Reference.* Montvale, NJ: Medical Economics; 2002, p. 56.
21. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet.* 1994; 344(8934):1383–9.
22. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N. Engl. J. Med.* 2008; 359(21):2195–207.
23. Ruano G, Thompson PD, Windemuth A, et al. Physiogenomic association of statin-related myalgia to serotonin receptors. *Muscle Nerve.* 2007; 36(3):329–35.
24. Ruano G, Thompson PD, Windemuth A, et al. Physiogenomic analysis links serum creatine kinase activities during statin therapy to vascular smooth muscle homeostasis. *Pharmacogenomics.* 2005; 6(8):865–72.
25. Ruano G, Windemuth A, Wu AH, et al. Mechanisms of statin-induced myalgia assessed by physiogenomic associations. *Atherosclerosis.* 2011; 218(2):451–6.
26. Sinzinger H, O'Grady J. Professional athletes suffering from familial hypercholesterolaemia rarely tolerate statin treatment because of muscular problems. *Br. J. Clin. Pharmacol.* 2004; 57(4):525–8.
27. Staffa JA, Chang J, Green L. Cerivastatin and reports of fatal rhabdomyolysis. *N. Engl. J. Med.* 2002; 346(7):539–40.
28. Thompson PD, Gadaleta PA, Yurgalevitch S, Cullinane E, Herbert PN. Effects of exercise and lovastatin on serum creatine kinase activity. *Metabolism.* 1991; 40(12):1333–6.
29. Thompson PD, Nugent AM, Herbert PN. Increases in creatine kinase after exercise in patients treated with HMG Co-A reductase inhibitors. *JAMA.* 1990; 264(23):2992.
30. Thompson PD, Parker BA, Clarkson PM, et al. A randomized clinical trial to assess the effect of statins on skeletal muscle function and performance: rationale and study design. *Prev. Cardiol.* 2010; 13(3):104–11.
31. Thompson PD, Zmuda JM, Domalik LJ, Zimet RJ, Stagers J, Guyton JR. Lovastatin increases exercise-induced skeletal muscle injury. *Metabolism.* 1997; 46(10):1206–10.
32. Urso ML, Clarkson PM, Hittel D, Hoffman EP, Thompson PD. Changes in ubiquitin proteasome pathway gene expression in skeletal muscle with exercise and statins. *Arterioscler. Thromb. Vasc. Biol.* 2005; 25(12):2560–6.
33. Wilke RA, Moore JH, Burmester JK. Relative impact of CYP3A genotype and concomitant medication on the severity of atorvastatin-induced muscle damage. *Pharmacogenet. Genomics.* 2005; 15(6):415–21.
34. Wu JS, Buettner C, Smithline H, Ngo LH, Greenman RL. Evaluation of skeletal muscle during calf exercise by 31-phosphorus magnetic resonance spectroscopy in patients on statin medications. *Muscle Nerve.* 2011; 43(1):76–81.
35. Yu JG, Sewright K, Hubal MJ, et al. Investigation of gene expression in C(2)C(12) myotubes following simvastatin application and mechanical strain. *J. Atheroscler. Thromb.* 2009; 16(1):21–9.