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EDITORIAL COMMENT

A Novel Mechanism to Explain Statin-Associated Skeletal Muscle Symptoms*

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The first commercially available statin, lovastatin, was approved by the US Food and Drug Administration in 1987. The first cases of lovastatin-associated rhabdomyolysis were reported in cardiac transplant patients in 1988 (1,2). Reports of increased creatine kinase (CK) levels associated with exercise were reported in 1990 (3). Thus, one would think that by 2019 we would definitively know what physiological mechanisms cause statin-associated muscle symptoms (SAMS), how exercise affects SAMS and vice versa, and why statins affect skeletal, but not cardiac, muscle. But we do not. There is not even consensus that statins cause SAMS in the absence of overt muscle damage as evidenced by increased CK levels (4,5).

In this issue of *JACC: Basic to Translational Science*, Lotteau et al. (6) present a series of elegant studies examining the mechanisms producing SAMS, an explanation of why skeletal and not cardiac muscles are affected, and new evidence on the interaction of exercise and statin treatment. A full description of the protocols used to develop and support this hypothesis is beyond the scope of this editorial but we present here the salient points.

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It is well known that statins inhibit the rate-limiting enzyme in the mevalonate-cholesterol pathway, but inhibition of this pathway has other effects such as reducing the production of various isoprenoids. Some of these isoprenoids increase nitric oxide synthase activity, thereby increasing nitric oxide production. Reducing nitric oxide by inhibiting the mevalonate-cholesterol pathway can increase both reactive nitrogen species (RNS) and reactive oxygen species (ROS), and atorvastatin is known to increase the generation of ROS (7). RNS and ROS can cause the ryanodine receptor 1 (RyR1) to dissociate from its stabilizing protein, FKB12 (FK506 binding protein [calstabin]). RyR1 releases calcium (Ca^{2+}) from the sarcoplasmic reticulum into the cytosol, thus initiating muscle contraction. Dissociating FKPB12 from RyR1 increases Ca^{2+} leakage from the sarcoplasmic reticulum, producing spontaneous Ca^{2+} release events called Ca^{2+} sparks. Ca^{2+} sparks are observed in other human muscle diseases, including muscular dystrophy and malignant hyperthermia. Bidirectional Ca^{2+} fluxes occur between the sarcoplasmic reticulum and mitochondria and thus increased cytosolic Ca^{2+} increases mitochondrial Ca^{2+}, which increases mitochondrial ROS production. Consequently, Lotteau et al. (6) propose that this dissociation of RyR1 from FKPB12 causes SAMS by initiating a cascade of deleterious effects related to increased cytosolic and mitochondrial Ca^{2+}. Stains can initiate the process in skeletal but not cardiac muscle because cardiac muscle has better antioxidant

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protection against RNS and ROS activity and because RyR2 is the dominant cardiac RyR and may be less susceptible to dissociation from FKBP12.

What evidence do Lotteau et al. (6) provide to support this hypothetical chain of events? They show that Ca^{2+} sparks in muscle fibers from statin-treated rats are more frequent, last longer, and are of greater amplitude, indicating a greater Ca^{2+} leak. They note that sparking has not been observed previously with in vivo statin treatment but also note that previous statin studies used permeabilized muscle fibers, a process requiring magnesium, which could inhibit RyR1 function. Indeed, the present investigators did not observe Ca^{2+} sparking when they repeated their studies using permeabilized, instead of intact, muscle fibers. They also did not observe any Ca^{2+} sparks in cardiac muscle from statin-treated animals.

They further showed that statin treatment decreases FKBP12 binding to RyR1 in both biopsy-obtained, human vastus lateralis and rat type II muscle fibers (6). Type II muscle fibers are mitochondrial poor and primarily glycolytic, and some (8), but not all (9), rodent research suggests that this fiber type is most vulnerable to statin muscle injury. There was robust dissociation of FKBP12 from RyR1 in the 13 statin-treated patients compared with control subjects matched with their number, age, and sex, which is noteworthy given the variability in the statin-treated subjects' ages (range 48 to 71 years). Dissociation of FKBP12 from RyR1 not only increases spontaneous Ca^{2+} leaking but also promotes protein degradation and programmed cell death. Evidence for programmed cell death was provided by increases in the proapoptotic enzyme caspase-3, as well as a marked increase in terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) nuclei, in skeletal muscle from both humans and rats treated with statins. Evidence that nitric oxide and superoxide production play a role in this process was provided by the observation that administration of a nitric oxide synthase inhibitor, N(ω)-nitro-L-arginine methyl ester (L-NAME), eliminated the differences in Ca^{2+} spark frequency and duration between the rat control and statin-treated muscle fibers. Differences in Ca^{2+} spark frequency and duration between statin-treated and control rat muscle fibers were also eliminated when the statin-treated fibers were treated with the superoxide dismutase/peroxynitrite scavenger Mn(III)tetrakis(1-methyl-4-pyridyl)porphyrin (MnTMPyP) and the mitochondrial-targeted superoxide dismutase mimetic (2-(2,2,6,6-tetramethylpiperidin-1-oxyl-4-ylamino)-2-oxoethyl)triphenylphosphonium chloride (mitoTEMPO). A role for increased cytosolic Ca^{2+} leading to increased mitochondrial Ca^{2+} was shown by the observation that Ca^{2+} spark frequency and duration were no longer different between muscle fibers from statin-treated and untreated rats when Ca^{2+} mitochondrial entry was inhibited by Ru360, an inhibitor of the mitochondrial Ca^{2+} uniporter. Consequently, this series of experiments provides strong support for the authors' proposed mechanism for SAMS.

Physical activity and exercise are generally believed to increase SAMS (10). We have documented increased CK levels after 45 min of downhill treadmill walking in a double-blind study of men randomly assigned to receive lovastatin 40 mg daily or placebo (11). We have also documented increased CK levels in runners taking statins completing the Boston Marathon versus nonstatin-treated control subjects (12). Both studies show that statins increase the muscle injury from exercise. Statins also seem to affect exercise-related mitochondrial adaptations to exercise training. Maximal oxygen uptake increased only 1.5% after 12 weeks of aerobic exercise training in subjects treated with simvastatin 40 mg daily but increased 10% in exercise-trained subjects not taking statins (13). Citrate synthase activity, a marker of muscle mitochondrial content, increased only 4.5% in the statin-treated subjects but 13% in the subjects not taking statins. A comparison of exercise performance and mitochondrial function in symptomatic ($n = 10$) and asymptomatic ($n = 10$) statin-treated subjects and untreated control subjects ($n = 10$) showed comparable exercise performance among the groups but a lower onset of exercise lactate accumulation, a crude measure of mitochondrial function, in both statin-treated groups (14). Muscle fatigue was measured by the rate of maximal force rise during electrical stimulation of the quadriceps muscle. Muscle contractile function was similar among groups after a single stimulus, but with repetitive stimuli, maximal force rise declined more rapidly in both statin-treated groups, consistent with a more rapid onset of muscle fatigue. Mitochondrial complexes II and IV were also reduced in the symptomatic statin-treated subjects compared with control subjects. Such results support the possibility that statins negatively affect exercise performance; documentation of this hypothesis is limited in part, however, because of the weak design of many exercise training studies (15).

In contrast to a possible negative effect of statins on exercise performance, Lotteau et al. (6) suggest a potential beneficial interaction between statins and exercise. These authors found no effect of statins on single-muscle fiber tetanic force production, and even a small increase in the statin-treated rats.

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Surprisingly, statin-treated rats with access to a running wheel ran farther than the control rats. Wheel running also prevented the statin-mediated dissociation of FKBP12 to RyR1, which reduced Ca2+ sparks and proapoptotic signaling. Rather than a deleterious interaction of statins and exercise, these results suggest 2 beneficial effects: statin-treated rats exercised more, and exercise reduced statin-associated deleterious muscle effects.

Neither concept would be an easy sell to clinicians who prescribe, or patients who use, statins. Statins are life-saving medications, but many patients who would benefit from statin treatment discontinue statin therapy because of real or perceived SAMS. Lotteau et al. (6) present an elegant series of studies suggesting how statins could affect skeletal muscle. Much more work is required to better define the relation of statins, muscle, and exercise performance, and how insights into the mediating mechanisms for SAMS can be used in clinical practice.

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