Statin-induced Myopathy in Skeletal Muscle: the Role of Exercise

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Statins are widely used drugs to lower cholesterol levels and to reduce the risk of cardiovascular disease. However, it has been reported that statins are associated with adverse side effects of skeletal myopathy. Statin treatment can impair mitochondrial function and induce apoptosis in skeletal muscle in both human and animal models. Ubiquinone plays an essential role in transferring electrons in the mitochondrial electron transfer chain for oxidative phosphorylation. However, statin treatment reduces ubiquinone levels in the cholesterol synthesis pathway, which may be associated with mitochondrial dysfunction. In addition, reactive oxygen species (ROS) production and apoptosis induced by statins may provide cellular and molecular mechanisms in skeletal myopathy. Exercise is the most effective therapy to prevent metabolic and cardiovascular diseases. However, whether exercise provides a benefit to or exacerbation of statin-induced myopathy in skeletal muscle remains poorly investigated. This review will briefly provide a comprehensive summary regarding the effects of statins on skeletal myopathy, and discuss the potential mechanisms of statin-induced myopathy and the role of exercise in statin-induced myopathy in skeletal muscle.

Key Words: Statins, Myopathy, Exercise, Skeletal muscle

INTRODUCTION

3-hydroxy-3-methylgutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are cholesterol-lowering drugs which work by blocking the rate-limiting step in the cholesterol synthesis pathway (Fig. 1). Statins are the most frequently and widely used medication in the treatment of cardiovascular disease, diabetes, and cancer to reduce cholesterol levels (e.g., LDL-cholesterol) by inhibiting the formation of mevalonate (a precursor to cholesterol), ubiquinone (coenzyme Q), and other compounds [1,2]. Although statins have a number of beneficial effects including a lipid-lowering effect, improved endothelial function, anti-inflammation, and insulin sensitivity [1,3], statins, particularly lipophilic statins (e.g., simvastatin, atorvastatin, cerivastatin, and lovastatin), also cause adverse side effects in skeletal muscle ranging from mild to moderate muscle fatigue, weakness, and pain to fatal rhabdomyolysis [4-6]. In fact, considering that the occurrence of less adverse side effects is not reported, the incidence of statin-induced myopathy may be 5-10%, and concerns about the safety of statins on skeletal muscle are expected to increase [7]. However, the underlying mechanisms by which statins induce skeletal muscle side effects have not been clearly determined. Therefore, this review primarily focuses on statin-induced myopathy and the potential mechanisms of statin-associated myopathy. In addition, this review provides an overview of the role of exercise in statin-induced myopathy.

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EFFECTS OF STATINS ON SKELETAL MYOPATHY

Statins, widely prescribed cholesterol-lowering drugs for the treatment of dyslipidemia and cardiovascular disease, are associated with skeletal muscle-related complaints or myopathies. Apoptosis is programmed cell death that is highly regulated and executed via the activation of caspase dependent or independent signaling. In general, apoptosis plays an important role in governing development, growth, and repair in cells [8]. However, excessive apoptosis may be associated with dysfunction, disease, and myopathy in skeletal muscle. It has been reported that statin treatment can induce apoptosis in skeletal muscle in both human [9-12] and rodent [13-16] models. For example, simvastatin treatment (5 μM) during 48 hours increased protein levels of proapoptotic protein Bax and apoptosis marker TUNEL-positive nuclei in primary human skeletal muscle cells [12]. Furthermore, Kobayashi et al. [11] showed that cerivastatin treatment (100 μM) during 24-72 hours elevated apoptosis in rhabdomyosarcoma cells from human subjects.

Mitochondria play a central role in regulating homeostasis as well as inducing apoptosis in skeletal muscle. Therefore, mitochondrial dysfunction is associated with the increase in the susceptibility to apoptosis and oxidative stress in skeletal muscle. Previous studies showed that statins might impair mitochondrial function in the skeletal muscles of humans [17-23] and animals [15,24], leading to myopathy. For example, patients with hypercholesterolemia taking simvastatin (80 mg/day) for 8 weeks displayed a decrease in mitochondrial respiratory chain enzyme and citrate synthase activities [20]. Stains also inhibit the synthesis of ubiquinone (coenzyme Q10), a major electron carrier in the mitochondrial respiratory chain [5,17]. However, statin treatment does not appear to consistently affect mitochondrial function in the whole body. Chung et al. [25] showed that fat oxidation and respiratory exchange ratio (RER) did not change in patients with hypercholesterolemia taking atorvastatin (40 mg/day) for 8 weeks. Table 1 summarizes the effects of statins on the whole body and skeletal myopathy.

POTENTIAL MECHANISMS OF STATIN-INDUCED MYOPATHY

Although numerous studies on statin-associated myopathy have been reported in animals and humans, the molecular
| Subject or animal | Sex | Types of statins (doses) | Treatment | Duration | Tissues | Results | References |
|-------------------|-----|--------------------------|-----------|----------|---------|---------|------------|
| Patients with hypercholesterolemia | Both | Simvastatin 80 mg/day | Oral intake | 2-4 years | Muscle biopsy | ↓ Muscle strength | Phillips et al., 2002 [18] |
| Healthy subjects | - | Simvastatin (30 μM) | Cell culture | 24 hours | Primary skeletal muscle cells from muscle biopsy | ↑ Apoptosis | Sacher et al., 2005 [9] |
| Healthy subjects | Male | Simvastatin (200 μM) | Fiber incubation | Acute | Muscle biopsy (quadriceps) | ↑ Mitochondrial membrane depolarization | Sirvent et al., 2005 [19] |
| Patients with hypercholesterolemia | Both | Simvastatin 80 mg/day | Oral intake | 8 weeks | Muscle biopsy (quadriceps femoris) | ↓ Respiratory chain enzyme | Paiva et al., 2005 [20] |
| Patients with heart disease | - | Simvastatin (5 μM) | Cell culture | 96 hours | Cardiac myocytes | ↓ Mitochondrial membrane depolarization | Demyanets et al., 2006 [10] |
| Healthy subjects | - | Cerivastatin (100 μM) | Cell culture | 24-72 hours | Rhabdomyosarcoma cells | ↑ Apoptosis | Kobayashi et al., 2007 [11] |
| Patients with hypercholesterolemia | Both | Simvastatin (80 mg/day) | Oral intake | 8 weeks | Muscle biopsy (quadriceps) | ↓ Mitochondrial DNA | Schick et al., 2007 [21] |
| Patients with hypercholesterolemia | Female | Atorvastatin (40 mg/day) | Oral intake | 8 weeks | Whole body | ↓ RER & anaerobic threshold | Chung et al., 2008 [25] |
| Patients with hypercholesterolemia | Both | Simvastatin (10-80 mg/day) | Oral intake | 4 months | Muscle biopsy (vastus lateralis) | ↓ Fat oxidation | Hübä et al., 2011 [22] |
| Patients with statin-induced myopathy | Both | Simvastatin (20 mg/day) | Oral intake | 24-48 months | Muscle biopsy (deltoid) | ↑ ROS | Bouitbir et al., 2012 [23] |
| Healthy subjects | Male | Simvastatin (5 μM) | Cell culture | 48 hours | Primary skeletal muscle cells from muscle biopsy | ↓ Oxidative phosphorylation | Kwak et al., 2012 [12] |
mechanisms of statin-induced myopathy have not been completely elucidated. A variety of hypotheses regarding potential mechanisms of statin-induced myopathy have been proposed to gain insight into myopathy in skeletal muscle, including (a) deficiency of ubiquinone, (b) reactive oxygen species (ROS) production, and (c) induction of apoptosis.

Ubiquinone is located in the mitochondrial respiratory chain, where it plays an essential role in transferring electrons from complex I and II to complex III as well as superoxide (O$_2^-$) free radicals. In particular, superoxide is generated in the electron transport chain by enzymes such as HCO$_3^-$ and HCO$_3^-$ reductase. Mitochondrial dysfunction is involved in the production of ROS and the generation of superoxide anions (O$_2^-$) in the electron transport chain. Mitochondrial dysfunction can lead to oxidative stress and apoptosis in skeletal muscle cells.

In addition, it has been suggested that statin-induced myopathy is associated with apoptosis in skeletal muscle. Apoptosis is a form of programmed cell death that is characterized by the activation of a series of enzymes and gene expression. Apoptosis is induced through three major apoptotic signaling pathways, which may be an essential factor causing statin-induced myopathy. These pathways include the extrinsic pathway, the intrinsic pathway, and the death receptor pathway. In general, apoptosis is induced by an increase in oxidative stress and apoptosis is one of the major processes involved in the pathogenesis of statin-induced myopathy.
pathways: the (a) mitochondrial-driven pathway, (b) cytokines/Fas-driven pathway, and (c) endoplasmic reticulum (ER)/Ca²⁺-driven pathway [31]. However, statin-induced apoptosis in skeletal muscle may be mitochondrial-mediated as indicated by an increase in Bax, release of cytochrome c, active caspase-9, and caspase-3 by statin treatment [12,30]. In particular, the increase in ROS (e.g., O₂⁻ and H₂O₂) generation with statin treatment may play an important role in opening the mitochondrial permeability transition pore (mPTP), which results in caspase dependent (e.g., cytochrome c and caspase-9) or independent (e.g., apoptosis inducing factor [AIF] and EndoG) apoptosis in skeletal muscle (Fig. 3), suggesting that statin-induced oxidative stress triggers mitochondrial-mediated apoptosis. For example, Kwak et al. [12] demonstrated that simvastatin treatment induced apoptosis as well as oxidative stress in differentiated skeletal muscle cells.

**ROLE OF EXERCISE IN STAIN-INDUCED MYOPATHY: FRIEND OR FOE?**

Exercise is regarded as one of the most cost effective ways to prevent metabolic and cardiovascular diseases and is recommended to patients as a lifestyle intervention to sup-
### Table 2. Effects of exercise on statin-induced myopathy

| Subject or animal | Sex | Types of exercise (Duration) | Types of statins (doses) | Duration of statin treatment | Tissues | Results | References |
|-------------------|-----|------------------------------|--------------------------|-----------------------------|---------|---------|-----------|
| Healthy subjects  | Male| Acute eccentric treadmill exercise (1 hour) | Lovastatin (40 mg/day)   | 30 days                      | Serum   | ↔ CK    | Reust et al., 1991 [38] |
| Healthy subjects  | Both| Acute maximal treadmill exercise | Lovastatin (20 mg/day)   | 4 weeks                      | Serum   | ↔ CK    | Thompson et al., 1991 [39] |
| Healthy subjects  | Male| ↓Acute downhill treadmill walking (45 min) ↓Acute biceps curl exercise (10 RM, 4 sets) | Lovastatin (40 mg/day)   | 5 weeks                      | Serum   | ↓ Downhill treadmill: ↑ CK ↓ Biceps exercise: ↔ CK | Thompson et al., 1997 [33] |
| Healthy subjects  | Male| Acute eccentric contractions (30 min) | Atorvastatin (80 mg/day)  | 4 weeks                      | Muscle biopsy (vastus lateralis) | ↑ Ubiquitin proteasome pathway & catabolism | Urso et al., 2005 [34] |
| Patients with hypercholesterolemia | Both| Endurance and resistance exercise (10 weeks) | Rosuvastatin (10 mg/day) | 20 weeks                      | Serum   | ↔ CK    | Coen et al., 2009 [40] |
| Athletes with hypercholesterolemia | Both| Acute marathon | All statins (various doses) | 6 months                      | Plasma  | ↑ Statin-related muscle injury (CK) | Parker et al., 2012 [35] |
| A healthy subject | Male| Acute aerobic exercise (1 h 42 min) | Simvastatin (10 mg/day)  | 6 months                      | Blood   | ↔ Lipoprotein & white blood cell concentrations  | Semple, 2012 [41] |
| Obese subjects   | Both| Aerobic exercise (12 weeks) | Simvastatin (40 mg/day)  | 12 weeks                      | Whole body  ↓Cardiorespiratory fitness ↓ Muscle citrate synthase activity | Mikus et al., 2013 [36] |
| Rats              | Female| Treadmill exercise (2 weeks) | Cerivastatin (0.5, 1.0 mg/kg/day) | 2 weeks                      | Muscles | ↑ Muscle damage | Seachrist et al., 2005 [37] |
| Mice              | Male| Wheel running (4 weeks) | Cerivastatin (1 mg/kg/day) | 2 weeks                      | Whole body  ↓ Statin-associated force loss & increased fatigability | Meandor and Huey, 2011 [42] |
plement drug therapy. However, the benefit/risk of exercise with statin therapy has not been thoroughly investigated. To date, the effects of exercise frequency, intensity, time or type on the risk of statin-induced myopathy have not been well studied. Most studies of the interactions of exercise and statin therapy include an acute/single exercise and indirect measures of muscle damage (i.e., blood creatine kinase [CK] levels). In contrast to statin-induced myopathy, chronic exercise training has the potential to counteract statin-induced side effects in skeletal muscle. For example, endurance exercise training increases mitochondrial biogenesis and mitochondrial respiration, and decreases oxidative stress and apoptosis in skeletal muscle [32].

However, previous studies have shown inconsistent findings regarding the effects of exercise on statin-induced myopathy. While some studies reported that exercise seemed to increase the risk of statin-induced myopathy [33-37], others suggested that exercise did not affect statin-induced myopathy [33,38-42]. For example, 12 weeks of aerobic exercise training in combination with simvastatin (40 mg/day) decreased cardiorespiratory fitness and muscle citrate synthase activity in obese subjects [36]. In addition, 2 weeks of treadmill exercise increased muscle damage in rats taking cerivastatin (0.5-1.0 mg/kg/day) for 2 weeks [37]. In contrast, 10 weeks of endurance and resistance exercise training did not affect serum CK in hypercholesterolemic patients taking rosuvastatin (10 mg/day) for 20 weeks [40]. Furthermore, Meador and Huey [42] showed that 4 weeks of wheel running exercise with cerivastatin treatment (1 mg/kg/day) for 2 weeks prevented statin-associated force loss and increased fatigability in mice, suggesting that exercise prior to statin treatment can protect against statin-induced muscle dysfunction. Table 2 shows a summary of studies examining the effects of exercise on statin-induced myopathy in human and animal models.

CONCLUSIONS

Statins are common cholesterol-lowering drugs for treating cardiovascular disease. However, adverse side effects of statins include skeletal muscle myopathy. Although the mechanisms of statin-induced skeletal myopathy have not been determined, the mechanisms may be associated with ubiquinone deficiency, oxidative stress, and apoptosis. However, the underlying molecular and cellular mechanism by which statins affect mitochondrial function and apoptosis in skeletal muscle remains unknown. Furthermore, it is not clear whether exercise exacerbates statin-associated myopathy in skeletal muscle. Therefore, further studies of patients taking statins with different kinds of exercise are warranted to develop new strategies for statin-associated mitochondrial dysfunction and apoptosis leading to skeletal myopathy.

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