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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). Stains 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 stain-induced myopathy.

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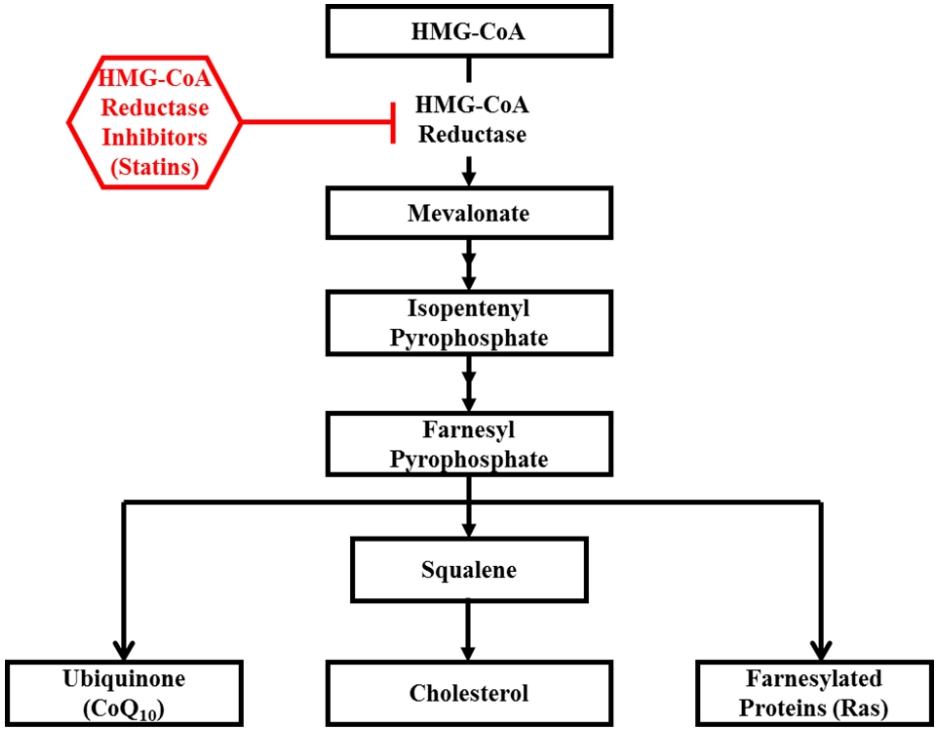

Fig. 1. Cholesterol synthesis pathway and inhibition of statins.

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

Table 1. Effects of statins on whole body and skeletal myopathy

Subject or animal	Sex	Types of statins (doses)	Treatment	Duration	Tissues	Results	References
Patients with hypercholesterolemia	Both	Simvastatin Pravastatin Fluvastatin	Oral intake	8 weeks	Serum	↓ Ubiquinone ↑ Lactate/pyruvate ratio	Pinieux et al., 1996 [17]
Patients with hypercholesterolemia	Both	Simvastatin (80 mg/day) Lovastatin (40 mg/day) Atorvastatin (20 mg/day)	Oral intake	2-4 years	Muscle biopsy	↓ Muscle strength ↓ Cytochrome oxidase activity	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 ↑ Cytoplasmic Ca^{2+}	Sirvent et al., 2005 [19]
Patients with hypercholesterolemia	Both	Simvastatin (80 mg/day)	Oral intake	8 weeks	Muscle biopsy (quadriceps femoris)	↓ Respiratory chain enzyme ↓ Citrate synthase activity	Paiva et al., 2005 [20]
Patients with heart disease	-	Simvastatin (5 μM)	Cell culture	96 hours	Cardiac myocytes	↓ Mcl-1(inhibitor of apoptosis) ↔ Bax ↑ DNA fragmentation	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 ↓ LDL	Schick et al., 2007 [21]
Patients with hypercholesterolemia	Female	Atorvastatin (40 mg/day)	Oral intake	8 weeks	- Whole body - Plasma	↔ RER & anaerobic threshold ↔ Fat oxidation	Chung et al., 2008 [25]
Patients with hypercholesterolemia	Both	Simvastatin (10-80 mg/day) Atorvastatin (10-80 mg/day)	Oral intake	4 months	Muscle biopsy (vastus lateralis)	↓ Oxidative phosphorylation	Hubal et al., 2011 [22]
Patients with statin-induced myopathy	Both	Simvastatin (20 mg/day) Atorvastatin (20 mg/day)	Oral intake	24-48 months	Muscle biopsy (deltoid)	↑ ROS ↓ mRNA of SOD1,2	Bouitbir et al., 2012 [23]
Healthy subjects	Male	Simvastatin (5 μM)	Cell culture	48 hours	Primary skeletal muscle cells from muscle biopsy	↓ O_2 consumption ↑ $O^{\cdot -}_2$ & H_2O_2 ↑ Apoptosis	Kwak et al., 2012 [12]

Table 1. Continued

Subject or animal	Sex	Types of statins (doses)	Treatment	Duration	Tissues	Results	References
Rats	Male	Atorvastatin (100 μM)	Cell culture	24 hours	Vascular smooth muscle cells	↑ Apoptosis	Guijarro et al., 1998 [13]
Rats & Humans	-	Cerivastatin (50, 100 nM)	Cell culture	24 hours	- L-6 cells - Human (fetal thigh) myotubes	↑ Apoptosis	Johnson et al., 2004 [14]
Rats	Male	Fluvastatin (20 mg/kg/day) Atorvastatin (10 mg/kg/day)	Oral intake	2 months	Muscle biopsy (EDL, TA)	↑ Myoglobinemia	Pierno et al., 2006 [26]
Mice	Both	Lovastatin (100 mg/kg/day)	Oral intake	15 days	Mitochondria from muscle and liver	↑ Mitochondrial permeability transition	Velho et al., 2006 [24]
Rats	-	Cerivastatin (100 μM) Fluvastatin (100 μM) Atorvastatin (100 μM) Simvastatin (100 μM)	Cell culture	24 hours	L-6 cells	↑ Cell death (apoptosis) ↓ Mitochondrial membrane potential ↓ O_2 consumption & beta-oxidation	Kaufmann et al., 2006 [15]
Rats	Female	Simvastatin (88 mg/kg/day)	Oral intake	12 days	Muscle biopsy (biceps femoris)	↑ Necrosis ↑ PDK4 & MAFbx	Mallinson et al., 2012 [16]

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 associated with oxidative phosphorylation and energy production [27]. In addition, ubiquinone acts as a potent antioxidant in the inner mitochondrial membrane by scavenging free radicals [28]. However, it has been shown that statins reduced levels of ubiquinone in muscle and blood (Fig. 2). The rationale of statin-induced decrease in ubiquinone is the fact that statins can inhibit the biosynthesis of ubiquinone as well as cholesterol in the cholesterol synthesis pathway as shown in Fig. 1. For example, blood and muscle concentrations of ubiquinone were decreased after short- and long-term treatment with statins [20,29], which suggests that deficiency of ubiquinone in mitochondria may impair cellular respiration resulting in skeletal myopathy and that supplementation with ubiquinone may be an appropriate therapy to counteract adverse side effects of statin treatment.

Impaired mitochondrial function is involved in the production of oxidative stress in cells. Most oxidative stress, such as ROS, is generated in the mitochondria. In particular, superoxide ($O_2^{\cdot -}$) free radicals are generated from complex I (mainly) and complex III in the electron transport system and changed to hydrogen peroxide (H_2O_2). It has been recently reported that statin treatment increased oxidative stress in human skeletal muscle cells [12] and fibers [23] (Fig. 3). For example, we recently found that simvastatin treatment induced mitochondrial oxidative stress as indicated by increases in $O_2^{\cdot -}$ and H_2O_2 production as well as impaired oxygen consumption supported by complex I substrates (glutamate + malate) [12].

In addition, it has been suggested that statin-induced myopathy is associated with apoptosis in skeletal muscle [5,9,12,30]. As mentioned above, statins induce apoptosis in skeletal muscle, which may be an essential factor causing myopathy experienced by patients taking stains. In general, apoptosis is induced through three major apoptotic signaling

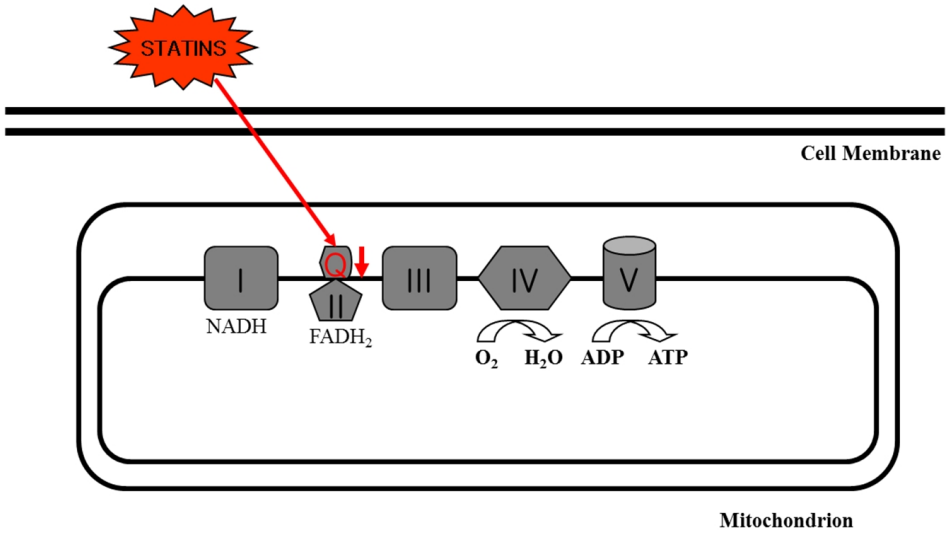

Fig. 2. Ubiquinone (Q) inhibition by statins in the mitochondrial electron transfer chain.

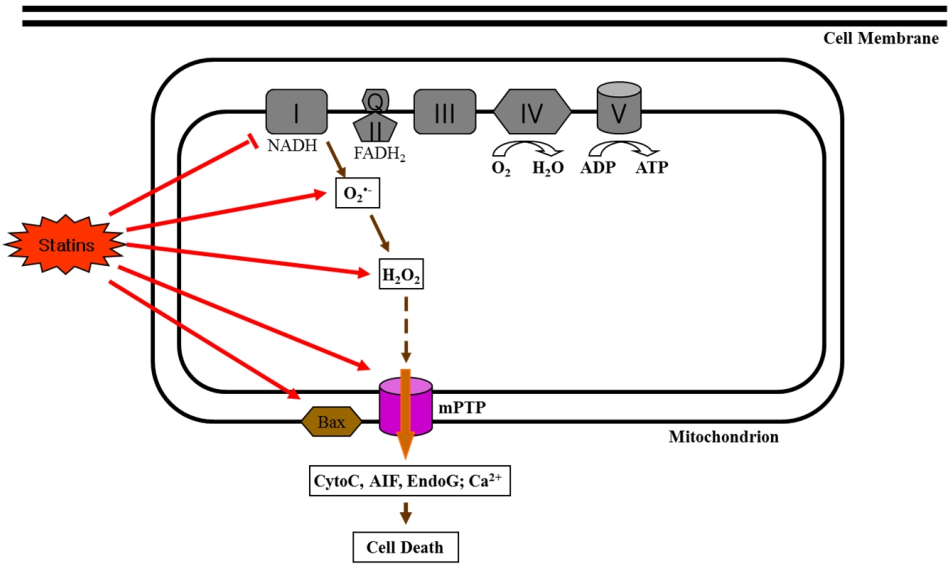

Fig. 3. Effects of statins on reactive oxygen species (ROS) production and apoptotic signaling.

pathways: the (a) mitochondrial-driven pathway, (b) cytokines/Fas-driven pathway, and (c) endoplasmic reticulum (ER)/Ca^{2+}-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.*, $O_2^{\cdot -}$ and H_2O_2) 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 -Muscle biopsy (vastus lateralis)	↓ 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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