Introduction

The sequelae of atherosclerotic vascular disease contribute significantly to the burden of illness in developed nations. In Canada an estimated 36% of all deaths result from cardiovascular disease (CVD). Among the various lipid-lowering medications the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, (HMGRI or “statins”) have emerged as the dominant class for the treatment of hypercholesterolemia. In addition to their ability to lower serum cholesterol by inhibiting a rate-limiting enzyme in the cholesterol biosynthetic pathway, statins have also been shown to target a variety of cellular processes that modify endothelial function, inflammatory responses, plaque stabilization and thrombogenesis. Relevant to these functions are the findings that acute statin therapy decreases the incidence of symptomatic ischemia in patients with acute coronary syndromes and may suppress recurrent transient ischemic attacks. These newly discovered properties make statins particularly attractive agents for the acute and long-term treatment of CVD because they target multiple pathways that ultimately converge in atherothrombotic events. The use of statins in the treatment of lipid-related disorders is therefore expected to rise.

Generally, the statins have a benign side-effect profile and are well tolerated. The most serious adverse effects arise from cell damage in liver and skeletal muscle. Increases in serum transaminases of hepatic origin are dose dependent and occur with a reported frequency of approximately 1%, whereas myotoxicity, defined as myalgias and elevated serum creatine kinase values (>10 times the upper limit of normal), occurs in 0.1% of patients. Although hepatotoxicity is more common, myotoxicity may pose a larger risk for sarcolemmal disruption (i.e., rhabdomyolysis) and can lead to myoglobinuria and acute renal failure. The incidence of myopathies is low, but the increasing use of statins implies that more physicians will encounter this clinical entity. Attempting to understand the pathophysiology of statins is of particular importance given the withdrawal of cerivastatin from the market in August 2001 owing to an unacceptable incidence of rhabdomyolysis and death. This review will consider the potential etiologies of statin myopathies in relation to altered cholesterol biosynthesis and muscle physiology.
**Pathophysiologic considerations**

*HMG-CoA reductase and statin biochemistry*

Unique among lipid-lowering drugs, statins impair cholesterogenesis by selectively targeting the rate-limiting enzyme, HMG-CoA reductase by reversible competitive inhibition. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an intermediate, which in turn gives rise to numerous metabolites (Fig. 1). Pharmacologic inhibition of HMG-CoA reductase results in reduced cholesterol synthesis and transcriptional upregulation of HMG-CoA reductase (i.e., impaired feedback inhibition) and may increase the expression of hepatic low-density lipoprotein (LDL) receptors. This increases the fractional catabolic rate of plasma LDL and therefore lowers serum cholesterol.

Hormonal control of HMG-CoA reductase is exerted by 4 agents: (1) glucagon, which opposes insulin’s transcriptional effect and phosphorylates the enzyme thereby reducing its activity; (2) thyroid...
hormone, which increases enzyme activity through enhanced transcription and mRNA stability; (3) glucocorticoids, which destabilize; and (4) estrogen, which stabilizes HMG-CoA reductase mRNA. Interestingly, hypothyroidism has been hypothesized to potentiate the myotoxic effects of statins. Although there have been no reports on myopathic interactions between glucocorticoids and statins, steroids may possibly contribute to muscle damage in organ transplant recipients receiving combination immunosuppressive and lipid-lowering therapy.

Five drugs — atorvastatin, fluvastatin, lovastatin, pravastatin and simvastatin — are currently marketed in North America; a sixth, cerivastatin, has recently been withdrawn. Lovastatin, pravastatin and simvastatin are all fungal derivatives and share the same hydronaphthalene ring structure. Simvastatin is a semi-synthetic methylated analogue of lovastatin. Pravastatin is a purified metabolite of mevastatin, the original HMG-CoA reductase inhibitor that was never marketed. Atorvastatin, cerivastatin and fluvastatin are synthetic. Each statin molecule has a moiety resembling hydroxymethylglutaric acid. The open, hydroxy acid, conformation is active whereas the closed, lactone, conformation is inactive. Hepatic hydrolysis at alkaline pH decyclizes and hence activates the lactone prodrugs lovastatin, atorvastatin and simvastatin.

Extensive first-pass metabolism limits the systemic bioavailability of the HMGRIs and accounts for the rapid clearance of statins, excepting atorvastatin. (Atorvastatin undergoes hepatic metabolism to active metabolites, which, together with the parent compound, have a half-life of about 15 hours.) The hepatic microsomal cytochrome P450 isoenzyme system (CYP) is responsible for the complex metabolism of the HMGRIs. After hydrolysis, the lactone prodrugs lovastatin, and simvastatin, and atorvastatin are primarily oxidized by CYP3A4. Fluvastatin is predominately (50%–80%) inactivated by CYP2C9, but recent evidence suggests that CYP3A4 and CYP2C8 also contribute to its biotransformation. Cerivastatin is also partially oxidized by CYP2C8. The multiple CYP isoenzyme pathways open to both cerivastatin and fluvastatin may afford increased protection against potential myotoxic interactions when coadministered drugs compete with or antagonize CYP isozymes.

Cholesterol biosynthesis and the isoprenoids

The inhibition of HMG-CoA reductase by the HMGRIs is approximately 14 steps and 9 to 10 enzymatic reactions removed from the terminal step(s) in cholesterologenesis (mediated by 7-dehydrocholesterol reductase and desmosterol reductase). Furthermore, mevalonic acid, the immediate product of HMG-CoA reductase, is a pivotal precursor intermediate which gives rise to the vital isoprenoids en route to cholesterol. It is not surprising, therefore, that inhibiting this important biosynthetic pathway causes pleiotropic metabolic consequences (Fig. 1).

Prenylation is a fundamental element of post-transcriptional lipid modification of proteins and other compounds and affects their function. Some of the known isoprenoids include the following: (1) isopentenyladenosine, required for transfer RNA synthesis; (2) dolichols, required for glycoprotein synthesis; (3) heme A, a polyisoprenoid component of the electron transport chain; and (4) ubiquinone, a polyisoprenylated quinoid cofactor of the electron transport chain, which accepts electrons from complexes I and II. The predominant form of coenzyme Q in human is coenzyme Q10, containing 10 isoprenoid units in the tail, whereas the predominant form in rodents is coenzyme Q9, with 9 isoprenoid units in the tail. The covalent addition of either farnesyl (15-carbon) or geranylgeranyl (20-carbon) isoprenoids to conserved cysteine residues on the C-terminus of important regulatory proteins enables both membrane association and protein–protein interactions. It is estimated that over 1% of mammalian cellular proteins are isoprenylated. Isoprenylated proteins have been implicated in smooth muscle cell migration and proliferation, and skeletal muscle cell growth and differentiation.

These conclusions were borne out of experiments in which statin treatment impaired cell development in culture, whereas the coapplication of mevalonate or its distal metabolites (i.e., farnesol or geranylgeraniol) reversed many of the inhibitory cellular effects of statins. The identification of prenylated proteins involved in signal transduction and cell cycle progression (i.e., laminin B, ras proto-oncogene, Rho-related proteins and the γ-subunit of heterotrimeric GTP-binding proteins) supports the dependency of these processes on the mevalonate pathway.
Statins and altered muscle physiology

Spectrum of myotoxic reactions to statin drugs

Various hypotheses have been proposed to explain the relationship between statin therapy and the spectrum of muscle dysfunction manifested by myalgia, myopathy and rhabdomyolysis. Although each demonstrates unique merits none has sufficiently elucidated the underlying pathophysiology, which remains speculative.39,42,44–46

Myalgias are clinically defined by any combination of muscle weakness, tenderness or pain either in a proximal or regional pattern. Clinically, patients often describe a cramping feeling in the muscle. The serum creatine kinase (CK) activity can be normal or only trivially elevated. In addition to myalgic complaints, patients with HMGRI-related myopathy may have CK activity values more than 10 times the upper limit of normal for a given reference laboratory (i.e., >2200 U/L for males and >1500 U/L for females).47 Light and electron microscopic histomorphometric features of statin-induced myopathy are listed in Table 1.48 Altered myofibre architecture with evidence of necrosis has been observed in experimental rodent models of statin myopathy, where exposure to suprapharmacologic doses accelerates myotoxicity,48,49 and in humans exposed to therapeutic doses.50–52

Rhabdomyolysis, an acute degeneration of skeletal muscle, is a potentially fatal condition due to the toxic effects of myoglobinemia/myoglobinuria on the renal tubules. Nephrotoxicity is largely mediated by the Fenton (Fe²⁺ + H₂O₂ → Fe³⁺ + OH⁻ + OH⁻) and Haber–Weiss (O₂⁻ + H₂O₂ → O₂ + OH⁻ + OH⁻) reactions as myoglobin provides ferrous iron, which serves as a catalyst for the generation of harmful reactive oxygen species. Interestingly, reactive oxygen species have also recently been implicated in the pathophysiology of contrast-agent-induced renal dysfunction,53–55 a condition in which N-acetylcysteine pre-supplementation (600 mg × 2 d) was shown to be nephroprotective.66 Whether the acute administration of antioxidants, at the onset of rhabdomyolysis, favourably alters the expression of renal damage is unknown but deserves investigation. Serum CK activity values are greatly elevated but cannot be used to differentiate rhabdomyolysis from myopathy. Possible complications arising from rhabdomyolysis and consequent acute tubular necrosis include hypocalcemia, hyperkalemia, metabolic acidosis, hyperuricemia, disseminated intravascular coagulation, cardiomyopathy and respiratory embarrassment.56

Ubiquinone and the development of statin myopathy

Much interest has focused on the role of ubiquinone in the development of statin myopathy.57–63 This potential etiology has biologic rationale as coenzyme Q10 is an essential cofactor of the electron transport chain.56 Coenzyme Q10 is a lipophilic compound composed of redox active quinoid moieties as well as essential for normal mitochondrial function.64,65

Table 1: Histomorphologic changes in mammalian skeletal muscle after pharmacologic doses of statins (lovastatin, 1 mg/g body weight for 30 days).

<table>
<thead>
<tr>
<th>Microscopy</th>
<th>Change</th>
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<tr>
<td>Light</td>
<td>Increased variability in fibre diameter</td>
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<td></td>
<td>Myofibre splitting</td>
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<td>Increased numbers of internal nuclei</td>
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<td>Perimysial fibrosis</td>
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<td>Coarsening of intermyofibrillar membranous network</td>
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<td>Clumping of intermyofibrillar membranous material</td>
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<td></td>
<td>Diffuse decrease in NADH dehydrogenase-staining in non-necrotic myofibres</td>
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<td>Myofibre necrosis with macrophage invasion</td>
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<td>Hypercontracted fibres</td>
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<td>Relative sparing of slow-twitch oxidative fibres with earlier involvement of fast-twitch glycolytic fibres</td>
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<td>Electron</td>
<td>2 types of mitochondrial alterations:</td>
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<td>• fragmented inner mitochondrial membrane (IMM) or absent or effaced mitochondrial cristae</td>
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<td>± replacement of cristae with fine granular material; outer mitochondrial membrane (OMM) intact</td>
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<td>• spared IMM and matrix; redundant and thickened OMM ± circular loops formed by OMM material</td>
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<td>M- yeastoid figures in degenerating mitochondrial membranes</td>
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<td></td>
<td>Dilated cisterns of the sarcoplasmic reticulum normal transverse tubules</td>
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<td></td>
<td>Increased presence of vacuoles</td>
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<td></td>
<td>Intermyofibrillar and subsarcolemmal accumulations of abnormal mitochondria</td>
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<td></td>
<td>Small zones of Z-band streaming</td>
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Adapted from Wacławik AJ, Lindal S, Engel AG. Experimental lovastatin myopathy. / Neuropathol Exp Neurol 1993;52:542-9. Biopsies were taken from Lewis rat gastrocnemius muscles on days 5, 10, 12, 14 and 30. Therefore, selected features from the above list were not observed in each animal. Longer treatment was associated with worsening disease.
as a hydrophobic prenylated tail that provides the physiochemical properties enabling mobility within the phospholipid bilayer of the inner mitochondrial membrane. Coenzyme Q10 is found in complexes I and II of the electron transport chain (ETC) where it undergoes 2 sequential 1 electron reductions by flavoproteins, first to the semiquinone radical and then to ubiquinol.6,35,36 Ubiquinol reduces cytochromes b and c of complex III and so provides the necessary electron carrier system for reduced nicotinamide adenine dinucleotide (NADH)- and reduced flavin adenine dinucleotide (FADH2)-linked substrates to aerobically generate ATP, the universal cellular energy currency. Coenzyme Q10 also serves as an important antioxidant in both mitochondria and lipid membranes.64,65 Apoptosis, which can be induced by statins in cultured myoblasts36,67 is inhibited by coenzyme Q10.68 Additionally, coenzyme Q10 decreases oxidative DNA damage in human lymphocytes.56 Further evidence of the potential utility of coenzyme Q10 for the treatment of statin myopathy derives from studies demonstrating both biochemical and clinical efficacy of quinone supplementation in patients with primary69–72 and secondary (i.e., cardiomyopathy)73–75 coenzyme Q10 deficiency states and other forms of mitochondrial disorders.76 Given the preponderance of evidence supporting the therapeutic efficacy of coenzyme Q10 in various conditions, the question is not whether coenzyme Q10 supplementation benefits patients who are ubiquinone-deficient, but whether statin therapy induces such a secondary deficiency state.

Shortly after the development of selective inhibitors of HMG-CoA reductase experimental evidence accrued demonstrating impaired ubiquinone synthesis in various cell types.77,78 Clinical reports describing the efficacy of coenzyme Q10 supplementation in patients with statin myopathy soon followed.79,80 The first case described a physically active 48-year-old physician who experienced fatigue and proximal myalgias and had elevated CK levels (1400 U/L) 2 to 3 weeks after starting lovastatin (20 mg OD). Despite withdrawal of the drug, his symptoms persisted for 6 months, at which time he began taking low-dose coenzyme Q10 (30 mg OD). Within a few days his symptoms abated, and he resumed strenuous activities without difficulty.80 The second case report described a 63-year-old woman who required hospital admission 8-months after starting simvastatin (20 mg OD) for a constellation of symptoms and laboratory abnormalities that resembled a MELAS (mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes) syndrome. Her clinical findings included diffuse muscle weakness, bilateral ptosis, external ophthalmoplegia, cognitive dysfunction and mild aphasia. Laboratory investigations revealed rhabdomyolysis (CK >20 000 U/L), hyperlacticacidemia (5.1 mmol/L; normal <2.2 mmol/L) and ragged-red fibres with abundant pleiomorphic mitochondria and a reduced muscle coenzyme Q10 concentration ([Q10]) (13.1 mg/g; normal 15.5–21.7 mg/g)81–83 on skeletal muscle biopsy. A 3-month trial of oral coenzyme Q10 (250 mg OD) ameliorated weakness and ophthalmoplegia, renormalized muscle [Q10] and eliminated ragged-red fibres.79 Interestingly, consecutive etofibrate and clofibrate treatment provoked a mitochondrial myopathy5 and valproate, an antiepileptic agent that inhibits mitochondrial fatty acid oxidation, reportedly triggered a MELAS syndrome in a woman who was later found to harbour the A3243G transition mutation.84 Although this 63-year-old did not have the A-to-G substitution at nucleotide 3243 it is quite conceivable that she harboured another defect since none of the other mutations (>50) were sought. These observations raise the possibility that pharmacologic inhibitors of mitochondrial metabolism may unmask latent mitochondrial dysfunction and manifest overt disease.

Coenzyme Q10 improved the lactate/pyruvate (L/P) ratios in some patients with mitochondrial myopathies and increased oxygen consumption in a patient with MELAS.76,85,86 Related to this, De Pinieux and colleagues,57 found increments in the L/P ratios of patients treated with statins compared to hyper- and normocholesterolemic controls (19.0 v. 15.9 and 13.1, respectively). The statin group was not supplemented with coenzyme Q10 to determine if blood lactate levels could be restored to normal. The high lactate levels were presumed to be secondary to a statin-induced alteration of ubiquinone biosynthesis and thus (ETC) function. Significantly, serum ubiquinone was lower in the statin group than the hypercholesterolemic controls but unchanged com-
pared to the healthy controls (0.75 v. 0.69 mg/L) who had normal L/P ratios. The etiologic importance of ubiquinone was therefore questionable.

Numerous investigations have confirmed that statins reduce serum ubiquinone concentrations. Circulating lipoproteins appear to be the predominant carrier proteins for ubiquinone in both animals and humans. Laaksonen and associates found reductions in serum and LDL ubiquinone approximately proportional to reductions in serum LDL cholesterol after 4 weeks of statin treatment. In contrast, another study found that whereas short-term (4-wk) statin treatment did not change serum ubiquinone-to-LDL ratios, long-term treatment (12 wk) caused a significant decrement in serum LDL (−25%) relative to serum coenzyme Q10 (−52%). Whether long-term statin treatment increases the likelihood of secondary ubiquinone deficiency is not entirely clear, but this seems unlikely as a subsequent study found no differences in serum ubiquinone-to-LDL ratios after 6 months of simvastatin therapy (i.e., 0.49 before v. 0.50 after). In fact, one study reported an elevated serum ubiquinone-to-LDL ratio after HMGRI treatment.

Of greater theoretical importance is the effect of statins on intramuscular coenzyme Q10 content for biosynthetic alterations in this tissue should provide a more precise index of deranged metabolism. Only one study has found depleted muscle ubiquinone, which appeared to be commensurate with the extent of muscle damage. Paradoxically, in the few muscle biopsy studies performed to date, ubiquinone concentrations were increased after HMGRI treatment in rodents and humans. These results suggest that HMGRIIs do not cause physiologically significant perturbations in muscle coenzyme Q10 synthesis. However, none of the patients in whom muscle biopsies were performed experienced any symptoms of myotoxicity. It is tempting to speculate that only those patients who express a latent mitochondrial diathesis or partial defect in coenzyme Q10 synthesis will become clinically symptomatic with the administration of statin drugs. This notion is supported by the finding that lovastatin while impairing the incorporation of [3H]acetate and [14C]tyrosine into ubiquinone failed to impair the activities of succinate-cytochrome c reductase and succinate dehydrogenase in murine neuroblastoma cells. Additionally, polarographic measurements of oxygen consumption in state 3 (i.e., electron transport chain saturation) and in an uncoupled state in both muscle homogenate and isolated mitochondria were normal. Therefore, even in the context of quantified decreases in ubiquinone synthesis mitochondrial respiration was preserved. However, this was an acute treatment effect in vitro and may not parallel chronic in vivo changes. Laaksonen and colleagues confirmed this with measurements of high-energy phosphates in skeletal muscle. Both ATP and creatine phosphate levels were unaffected by therapeutic doses of simvastatin. Recently, simvastatin treatment was associated with a reduction in blood ATP levels even though tissue ATP concentration ([ATP]) was not affected. Considering that muscle, by virtue of its mass and metabolic activity, is a major contributor to the blood ATP pool it is unclear what causes the fall in [ATP]. One possibility may be that statins cause membrane destabilization resulting in functional impairment of the ATP binding cassettes (i.e., ATP transport proteins) and decreased egress of ATP. Therefore, constrained ATP synthesis coupled with decreased membrane ATP transport may account for reduced blood [ATP] with paradoxically normal tissue [ATP]. This requires experimental confirmation.

Ubiquinone is an important antioxidant in biological systems. Statins reduce concentrations of lipophilic antioxidants (i.e., \( \alpha \)-tocopherol, \( \beta \)-carotene and lycopene) found in LDL particles. As with coenzyme Q10, this effect is thought to be mediated by a primary drop in serum lipoproteins. Lankin and associates found that pravastatin intensified in vivo free radical oxidation of LDL particles in patients with myocardial ischemia and that ubiquinone supplementation suppressed lipid peroxidation. Ischemia is a potent generator of free radicals and ubiquinone has been well described as an anti-ischemic cardioprotectant; therefore it is unclear to what extent exogenous coenzyme Q10 attenuated ischemia- or statin-related oxidative stress.

The contribution of ubiquinone to the development of statin myopathy is unclear. This is because definitive experiments correlating mitochondrial respiratory chain enzymology to muscle coenzyme [Q10]
and indices of oxidative stress (i.e., malondialdehyde, 8-iso-prostaglandinF₂α, 8-hydroxy-2′-deoxyguanosine) in patients with and without statin myopathy is lacking.

Effects of statins on membrane function and calcium regulation

Statins have been reported to affect skeletal muscle membrane physiology not only through changes in cholesterol content,⁹¹ which alters membrane fluidity,² but also through changes in (1) membrane electrical properties (which appears to be a secondary phenomenon),²,¹⁰⁴,¹⁰⁵ (2) Na⁺-K⁺ pump density,¹⁰⁶ (3) excitation-contraction coupling,¹⁰⁷ and (4) cell surface receptor signal transduction cascades.⁶⁶,¹⁰⁸ Fig. 2 provides a composite summary of the hypothetical multifactorial etiopathogenesis of statin-induced myotoxicity.

Fig. 2: A comprehensive schematic diagram of the proposed mechanisms of statin myopathy. Decreased chloride conductance (GCl⁻) potentially destabilizes membrane electrical potential and increases susceptibility to myotonic afterdepolarizations, which may elevate intracellular calcium ([Ca²⁺]i) through increased sarcoplasmic reticulum (SR) Ca²⁺ release. Furthermore, [Ca²⁺]i may be augmented from increased activity of the Na⁺-Ca²⁺ exchanger as a secondary response to increased intracellular [Na⁺], which accrues as a result of decreased Na⁺-K⁺ pump density. SR Ca²⁺ ATPase function may be impaired by statins therefore impairing the reuptake of free sarcoplasmic Ca²⁺. Statins induce the phosphorylation (P) of the γ1 subunit of phospholipase C (PLCγ1) causing phosphodiesterase activation and the conversion of phosphatidylinositol 4,5-bisphosphate (PIP) to diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP₃). Receptors on the SR for IP₃ mediate Ca²⁺ release (Note, the IP₃ receptors predominate in the junctional SR but are depicted in the longitudinal SR for clarity). Decrements in the membrane cholesterol-to-phospholipid (Chol/PL) ratio may also contribute to disruption of integral membrane protein function. Decreased synthesis of ubiquinone (Q10) may lead to both decreased ATP production and reduced free radical scavenging. E dysFx = energy dysfunction, ROS = reactive oxygen species.
Cholesterol’s role in membrane chloride conductance was first evidenced in patients treated with clofibrate who presented with acute muscular syndromes characterized by muscle cramping, weakness, stiffness and myopathic changes. Clofibrate produces electrophysiologic myotonia in rats, an effect completely attributable to a drug-induced decline in membrane chloride conductance. In experiments by Pierno and colleagues pravastatin was shown to have no effect on electromyographic activity or membrane chloride conductance whereas simvastatin caused dose-dependent reductions in the latter. Furthermore, decreased action potential amplitudes were recorded in simvastatin-treated rats, suggestive of decreased sodium channel function, and glybenclamide attenuated the increased potassium channel conductance, suggestive of reduced flux through the ATP-sensitive K+ channel. The latter finding was hypothesized to be attributable to decreased muscle ubiquinone and ATP, leading to channel opening; however, as discussed above, this remains inconclusive.

Sarcolemmal Na+–K+ ATPase activity is partly determined by the cholesterol environment in which it is expressed. Reductions in membrane cholesterol impair pump function whereas elevated cholesterol levels augment pump function. Lovastatin, through mechanisms unrelated to changes in membrane cholesterol, decreased sarcolemmal Na+–K+ ATPase density and pump current in skeletal and cardiac muscle. This was accompanied by a coordinated rise in sarcoplasmic Na+ concentration. Parenteral administration of mevalonate reversed these effects. Although unsubstantiated, increased intracellular Na+ could invoke Ca2+ influx via the Na+-Ca2+ antiport and cause myofibre necrosis or apoptosis.

Excitation-contraction coupling is the process by which a sarcolemmal action potential is propagated down the transverse tubules and converted into a calcium release signal through the interaction between L-type calcium channel dihydropyridine receptors and sarcoplasmic reticulum (SR) ryanodine receptors at the triadic junctions. A second messenger signal from inositol 1,4,5-trisphosphate (IP3) is also involved in modulating SR Ca2+ release in skeletal muscle. Simvastatin significantly reduced the mechanical threshold of rat skeletal muscle in a dose-dependent fashion. The voltage threshold for contraction is made more negative (closer to the resting potential) by any process, either physiologic or pharmacologic, that increases cytosolic Ca2+ concentration ([Ca2+]i). Either increased SR Ca2+ release or decreased SR Ca2+-ATPase (SERCA) activity can be responsible for elevated cytosolic [Ca2+]i. High concentrations of simvastatin in rat L6 myoblasts caused transient elevations in cytosolic [Ca2+]i and eventual membranolysis. Parallel findings were recorded in cultured rat skeletal muscle satellite cells superfused with simvastatin. In this study, neither mevalonic acid nor cholesterol could abolish simvastatin’s effect, and membrane lipid composition was unchanged, suggesting that the effect was not mediated through an inhibition of HMG-CoA reductase. Simvastatin caused similar increases in intracellular [Ca2+]i in cardiomyocytes. Recently, tyrosine phosphorylation of the γ1 subunit of phospholipase C (PLC) has been inculpated as a critical step in cell death signalling in L6 myoblasts. Tyrosine phosphorylation of PLC-γ1 stimulates catalytic activity, causing coordinated increments in IP3 and intracellular [Ca2+]i. Interestingly, aging is associated with decreased SERCA activity. Aging is also coupled to the accumulation of mitochondrial DNA mutations, leading to impaired ETC function and the generation of reactive oxygen and nitrogen species. The SERCA2 isoform appears to be relatively resistant to oxidative damage, whereas the fast-twitch isoform, SERCA1, is particularly vulnerable to oxidative modification at targeted cysteine residues. If statins do increase the oxidative burden in skeletal muscle, the SERCA1 protein may be susceptible and thus contribute to the deranged Ca2+ homeostasis. Whether oxidative factors are related to the statin-mediated early and selective mitochondrial swelling and fibre necrosis commonly observed in type II fibres (i.e., fast-twitch fibres) is not known.

Drug interactions and 3-hydroxy-3-methylglutaryl CoA-reductase inhibitor therapy

The concomitant administration of HMGRIs with other medications poses a significant risk for the development of myotoxicity. As already discussed, CYP3A4 is the predominant isoform responsible for
HMGRI biotransformation. Current evidence suggests that the muscle damage is precipitated through inhibition of CYP3A4 with secondary elevations in serum HMGRI levels.\textsuperscript{81,120-122} For example, erythromycin,\textsuperscript{121,122} azole antifungals,\textsuperscript{4,56} cyclosporin A (CsA),\textsuperscript{56} mibebradil\textsuperscript{1} and nefazadone\textsuperscript{1} are all oxidized by CYP3A4 and have been associated with myopathy or rhabdomyolysis when taken with lipophilic HMGRIs (Table 2). Indeed, the pharmacokinetics of pravastatin, a hydrophilic HMGRI with non-CYP450-dependent metabolism and fluvastatin, which relies on the CYP2C9 isoform for biotransformation, are only modestly affected by the co-administration of CsA.\textsuperscript{31,123} CsA is unique in that it augments serum statin levels via 2 mechanisms. First, CsA competitively inhibits the CYP3A4 isoyme and increases blood levels of lovastatin, simvastatin and cervistatin. Fluvastatin is less affected by CsA due to alternative metabolism. Notably, HMGRIs tend not to affect the pharmacokinetics of CsA since CsA has a greater affinity for CYP3A4 and since its serum concentrations are approximately 10-fold higher.\textsuperscript{4} Second, CsA is known to induce cholestasis in humans.\textsuperscript{56} Smith and colleagues\textsuperscript{124} demonstrated that the cholestatic effect of CsA increased muscle HMGRI levels (up to 13-fold) and resulted in light microscopic changes including myofibre necrosis, interstitial edema and inflammatory cell infiltration. Interestingly, periodic acid-Schiff staining revealed decreased glycogen content in type IIb fibres, which were most sensitive to the myotoxic effects of HMGRIs. Decreased availability of glycolytic substrate and increased reliance on β-oxidation, in aerobically deficient cells, compounded by the possible statin-mediated impaired ETC function (i.e., decreased ubiquinone synthesis) may suppress myocyte viability. Mevalonate but not coenzyme Q10 supplementation ameliorated the myopathy suggesting that the toxic effect was not due to deficiency of the latter.\textsuperscript{124} Interestingly, HMGRIs in certain experimental situations can induce apoptosis,\textsuperscript{66} and CsA inhibits the mitochondrial permeability transition pore (MPT) by preventing the binding of cyclophilin-D to the adenine nucleotide transporter (a component of the MPT).\textsuperscript{125,126} Therefore, it appears that, in the appropriate physiologic condition(s), the deleterious effects of HMGRIs overwhelm the protective effects CsA. Alternatively, HMGRI-mediated myofibre necrosis may not proceed through an MPT-mediated pathway. Furthermore, CsA independently causes muscle dysfunction, characterized by

\begin{table}[h]
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\begin{tabular}{|c|c|c|c|c|}
\hline
CYP1A2 & CYP2C9 & CYP2C19 & CYP2D6 & CYP3A4 \\
\hline
Acetaminophen & Alpranolol & Fluvastatin & Amritryptiline & Atorvastatin \\
Caffeine & Diclofenac & N-DMDZP & Butarafol & Cervistatin \\
Clozapine & Fluvastatin & Tolbutamid & Codeine & Chloraexylon \\
Phenacetin & (S)-Warfarin & (S)-Warfarin & Debrisoquine & Ethanol \\
Theophylline & N-DMDZP & MethylPB & Desipramine & Halothane \\
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\end{tabular}
\caption{Various drugs metabolized by the human cytochrome P450 mixed oxidase isoenzyme system}
\end{table}

N-DMDZP = N-desmethyldiazepam, MethylPB = methylphenobarbital, CsA = Cyclosporin A, (S- and (R)-Warfarin = enantiomers of warfarin. Note, azole antifungals (itraconazole, fluconazole, ketoconazole and miconazole), the selective serotonin reuptake inhibitors (fluoxetine, fluvoxamine and sertraline) and cimetidine inhibit both the CYP2C and CYP3A4 isoforms. Quinidine, non-dihydropyridine calcium channel blockers and grapefruit inhibit the CYP3A4 isoyyme. Trimethoprim-sulfamethoxazole, omeprazole, and amiodarone impair CYP2C activity. Rifampin and phenobarbital induce CYP2C and CYP3A4. Carbamazepine and phenytoin also induce CYP3A4.

reduced muscle capillary density, mitochondrial respiration and endurance capacity.56

The other major HMGRI drug interaction occurs with hypolipemic agents such as fibric acid derivatives127–129 and niacin.47,128 Although fibrates can impaire hepatic function the interaction appears to be more pharmacodynamic than pharmacokinetic.32 A plausible mechanism may be attributed to dual membrane-cholesterol lowering effects that result in increased sarcolemmal fluidity and subsequent destabilization.130,131

Conclusions and clinical approach

From the current literature there are a few conclusions that can be made regarding the use of statins and myopathy. First, myalgias and cramps are the most frequent muscle-related side effects of statin therapy, while true myopathy is much less common (approximately 0.1%). Second, there are several medications in which the potential for myotoxic interactions with statins is increased (i.e., CsA, erythromycin, fibric acid derivatives, niacin). Third, there are a few pre-existing conditions in which statins should not be used, such as untreated hypothyroidism, muscle coenzyme Q10 deficiency, mitochondrial cytopathies (except with coenzyme Q10 supplementation) and in patients in whom myopathy was documented with a statin (not absolute — see below). Fourth, the exact mechanism of action of the statins causing myopathy is unclear but may involve any or all of the following; coenzyme Q10 depletion, altered excitation-contraction coupling, decreased membrane fluidity, decreased sarcolemmal ionic flux and altered Ca2+ modulation. Currently there is insufficient evidence with which to propose a definitive clinical pathway for the care of patients with muscle symptoms who are taking statins; however, there are some guidelines that may be of benefit to the clinician as outlined below.

In clinical practice, there are several scenarios that may arise in patients treated with statins; asymptomatic hyperCKemia, myalgias with normal CK activity; myalgias with hyperCKemia; and the use of statins in patients with pre-existing neuromuscular disease.

Prior to starting statin therapy it is important to measure baseline CK activity, thyroid-stimulating hormone level and liver enzymes at least once. In the absence of symptoms, there is no evidence to suggest that routine monitoring of plasma CK activity is of benefit. However, this is occasionally done in asymptomatic people and found to be elevated. In such a case, if the CK is less than 3 times the upper limit of normal and the physical examination and routine blood chemistry values are normal (complete blood count, thyroid-stimulating hormone and electrolytes levels), further evaluation is usually not revealing. In the case of myalgias or cramps (or both) associated with normal CK activity the clinician must consider other causes, and a physical examination and some blood tests (above tests plus measurement of plasma magnesium and calcium) may reveal a cause. If no cause is found, then the patient and the clinician must decide whether the symptoms warrant a discontinuation of therapy. Analgesics or anti-inflammatory agents or even a brief trial of coenzyme Q10 (60 mg twice daily for 2 mo) may be considered. In the case of myalgias with hyperCKemia (assuming the baseline CK was normal), it is important to consider that another acquired myopathy may have developed and investigations may include a history, physical examination, blood chemistry measurements (thyroid-stimulating hormone, electrolytes, antinuclear antibody, complete blood count) and electromyography and nerve-conduction studies. Consideration may be given to a neuromuscular disease consult and possible a muscle biopsy, depending on the scenario. If the CK is greater than 10 times the upper limit of normal, screening for rhabdomyolysis and renal function is indicated, including measurement of uric acid, urine myoglobin, potassium, creatinine, bicarbonate and blood urea nitrogen. If renal dysfunction is found, the patient should be admitted to hospital and the nephrology department consulted. If there is no renal dysfunction, the statin therapy should be stopped and the patient should be followed up clinically and biochemically until resolution. At this point, the decision to switch to a hydrophilic statin (pravastatin) or another agent, or to avoid hypocholesterolemic medications requires careful assessment of the risk:benefit ratio of each decision. The role for coenzyme Q10 in treatment and prophylaxis is unclear; however, the case reports mentioned above suggest that at least in a
subgroup of patients, this may be of benefit. In general, the only patients with neuromuscular disorders who should not be given statins are those with untreated hypothyroidism, a rare form of myopathic coenzyme Q10 deficiency (6 cases reported worldwide) and patients with mitochondrial cytopathies (although treatment may be considered if simultaneous coenzyme Q10 is given in the latter group). With the recent interest in the rhabdomyolysis attributed to cerivastatin, it is hoped that further research into statin-induced myotoxicity will ensue and that more definitive clinical guidelines and a deeper understanding of the pathogenesis will emerge.

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Clin Invest Med • Vol 24, no 5, October 2001


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