

# A Neuromuscular Approach to Statin-Related Myotoxicity

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**ABSTRACT:** Approximately 95% of statin-treated patients tolerate this form of cholesterol management without any adverse effects. However, given their efficacy in reducing low density lipoproteins and cardiovascular events large numbers of patients are selected for statin therapy. Therefore muscle complications are, in fact, quite common. Limited understanding of the underlying pathophysiology has hampered physicians' ability to identify patients at risk for developing statin myotoxicity. A growing number of published case reports/series have implicated statins in the exacerbation of both acquired and genetic myopathies. A clinical management algorithm is presented which outlines a variety of co-morbidities which can potentiate the adverse effects of statins on muscle. In addition, a rational approach to the selection of those patients most likely to benefit from skeletal muscle biopsy is discussed. Ongoing work will define the extent to which statin-intolerant patients represent carriers of recessive metabolic myopathies or pre-symptomatic acquired myopathies. The expanding importance of pharmacogenomics will undoubtedly be realized in the field of statin myopathy research within the next few years. Such critical information is needed to establish more definitive management and diagnostic strategies.

**RÉSUMÉ:** Approche neuromusculaire de la myotoxicité due aux statines. Près de 95% des patients qui reçoivent une statine tolèrent bien ce traitement hypocholestérolémiant, sans réactions indésirables. Cependant, les complications musculaires sont relativement fréquentes parce qu'un grand nombre de patients reçoivent ce traitement à cause de son efficacité pour abaisser le taux de lipoprotéines de faible densité et pour diminuer l'incidence d'événements cardiovasculaires. Comme on connaît mal leur pathophysiologie, il est difficile d'identifier les patients à risque de développer une myotoxicité sous statine. Il y a de plus en plus de cas ou de séries de cas rapportés qui impliquent les statines dans l'exacerbation de myopathies tant acquises que génétiques. Nous présentons un algorithme concernant la conduite à tenir le cas échéant, qui énumère différentes co-morbidités pouvant potentialiser les effets indésirables des statines sur le muscle. De plus, nous discutons d'une démarche rationnelle pour identifier les patients qui sont les plus susceptibles de bénéficier d'une biopsie musculaire. Les travaux en cours permettront de définir dans quelle mesure les patients qui sont intolérants aux statines sont porteurs de myopathies métaboliques récessives ou de myopathies acquises pré-symptomatiques. L'importance croissante de la pharmacogénomique jouera sans doute un rôle dans le domaine de la recherche sur la myopathie due aux statines dans les prochaines années. Cette information est d'une grande importance pour établir des stratégies de diagnostic et de traitement.

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The statins, as a class, are one of the most widely prescribed medications. An estimated 25 million patients worldwide (13 million Americans) are treated with statins of the 200 million patients worldwide (36 million patients in the United States) being eligible for hypolipemic therapy.<sup>1,2</sup> Numerous randomized controlled trials have demonstrated both their general tolerability and efficacy in reducing cardiovascular end-points.<sup>3-6</sup> In fact myogenic complaints rarely differed between placebo and statin groups. However, continuing post-market surveillance suggests that treatment-limiting myalgias or myopathies occur in approximately 5-7% of patients. Thus 1.75 million (i.e.,  $0.07 \times 25 \times 10^6$ ) hypercholesterolemic patients may be withdrawn from a form of therapy which significantly reduces cardiovascular end-points. This has potentially significant health economic implications as statins reduce cardiovascular end-points by approximately 30%. Therefore, 525,000 (i.e.,  $0.30 \times 1.75 \times 10^6$ ) patients may experience earlier cardiovascular events secondary to the withdrawal of statins. If the average cost of a non-fatal

stroke or myocardial infarction is estimated at \$10,000 CAD, then statin withdrawal secondary to myalgias alone may cost the global healthcare system \$5.25 billion. With the ever increasing profile of statins, spurred by positive landmark trials<sup>6-8</sup> and the growing trend to make them available over-the-counter,<sup>9</sup> the global use of statins will increase, resulting in a proportionate rise in the incidence of clinical statin myotoxicity. Furthermore,

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up to 30% of patients who develop hyperCKemia or symptom-limiting side-effects from the statins do not readily recover after drug discontinuation,<sup>10</sup> making the task of finding preemptive management strategies and effective treatments more germane.

### INTRODUCTION TO STATIN PHARMACOLOGY

At the pharmacodynamic level (i.e., their site of action) all statins function similarly by selectively binding to the active site of hydroxymethylglutaryl co-enzyme A (HMG-CoA) reductase thus inhibiting the enzyme competitively.<sup>11</sup> However, at the pharmacokinetic level (i.e., their absorption, distribution, metabolism, and excretion), they have metabolic differences related to their physiochemical properties, which in turn may translate into differences in their myotoxic potential.

The clinical benefits of statins are thought to arise primarily from their ability to lower serum total cholesterol and low-density lipoprotein cholesterol (LDLc) levels (Table 1). There are currently six statins approved for prescription in North America: lovastatin (Mevacor), simvastatin (Zocor), pravastatin (Pravachol), fluvastatin (Lescol), atorvastatin (Lipitor), and rosuvastatin (Crestor). The portion of the statin structure

attributed to enzyme inhibition is an HMG mimic. First-generation statin drugs, which include lovastatin, simvastatin, and pravastatin, are fungal natural products or semi-synthetic with similar chemical structures containing a substituted decalin ring structure.<sup>12,13</sup> Second-generation statin drugs, which include fluvastatin, atorvastatin, cerivastatin (Baycol), and rosuvastatin, are synthetic and structurally dissimilar compounds containing fluorophenyl groups linked to the HMG-like moiety.<sup>13</sup> Due to these structural differences, statins vary in half-life, systemic exposure, maximum plasma concentration, bioavailability, protein binding, lipophilicity, metabolism, and excretion routes (Table 1).<sup>13</sup> For example, statins with low systemic bioavailability (i.e., lovastatin and simvastatin) exhibit greater increases in serum levels when the activity of cytochrome P450 is slowed or inhibited compared to statins with higher bioavailabilities (i.e., fluvastatin). Pravastatin is not metabolized by the P450 system but rather undergoes cytosolic sulfation.<sup>14</sup> Cytochromes 2C9 and 2C19 contribute minimally to the breakdown of rosuvastatin.<sup>15</sup>

Transmembrane pumps that transport statins represent additional levels of potential pharmacokinetic interactions. Examples of these include the P-glycoprotein system, which

**Table 1: Pharmacokinetic Parameters of HMG-CoA Reductase Inhibitors**

	Lovastatin	Simvastatin	Pravastatin	Fluvastatin	Atorvastatin	Rosuvastatin	Cerivastatin
<b>Efficacy</b>							
LDLc (% decrease)	21-40	14-47	22-34	17-35	26-60	45-63	28
TG (% decrease)	16	18	24	10	29	10-35	13
HDLc (% increase)	9	12	12	8	6	8-14	10
<b>Absorption</b>							
Dose range (mg/d)	10-80	10-80	10-40	10-80	10-80	5-40	0.3
Fraction absorbed (%)	30	60-80	34	98	30	-	98
T <sub>max</sub> (h)	2-4	1.3-2.4	0.9-1.6	0.5-1	2-3	3	2.5
C <sub>max</sub> (ng/mL)	10-20	10-34	45-55	448	27-66	37	2
Bioavailability (%)	5	5	18	19-29	12	20	60
Effect of food	increased	no effect	decreased	decreased	decreased	minimal	no effect
<b>Distribution</b>							
Fraction bound (%)	>95	94-98	43-55	>99	80-90	88	>99
Lipophilicity*	lipophilic	lipophilic	hydrophilic	lipophilic	lipophilic	hydrophilic	lipophilic
<b>Metabolism</b>							
Hepatic extraction (%)	>70	78-87	46-66	>68	>70	-	-
Cytochrome(s) involved (CYP)	3A4	3A4	NS	2C9	3A4	2C9,2C19	3A4,2C8
Effect on P-glycoprotein <sup>165</sup>	inhibitor	inhibitor	no significant inhibition	no significant inhibition	inhibitor	no significant interaction	-
<b>Excretion</b>							
t <sub>1/2</sub> (h)	2.9	2-3	1.3-2.8	0.5-2.3	15-30	20	2.1-3.1
Urinary excretion (% of dose)	10	13	20	6	2	10	30
Fecal excretion (% of dose)	83	58	71	90	70	90	70

T<sub>max</sub>, time to peak concentration; C<sub>max</sub>, maximum concentration; T<sub>1/2</sub>, elimination half-life; LDLc, low-density lipoprotein-cholesterol; TG, triglyceride; HDLc, high-density lipoprotein-cholesterol; -, unknown; NS, not significant. Modified from Corsini et al,<sup>13</sup> Sabia et al,<sup>12</sup> and Bellosta et al<sup>166</sup>

\*Lipophilicity: simvastatin=cervastatin>lovastatin=fluvastatin=atorvastatin>pravastatin=rosuvastatin. Potency: rosuvastatin>atorvastatin>cervastatin>simvastatin>fluvastatin>pravastatin.

serves as an efflux pump for toxic compounds (Table 1), and the human organic anion transporter polypeptides (OATPs), which deliver the statins across the hepatic and sarcolemmal membranes. Cyclosporine inhibits P-glycoprotein,<sup>16</sup> as well as cytochrome 3A4<sup>17</sup> and the hepatic statin transporter, OATP2,<sup>18</sup> thereby decreasing transport. Various other mechanisms, however may also explain the interaction between cyclosporine and statins. For example, the hydrophilic statins, pravastatin and rosuvastatin, likely interact with cyclosporine via hepatic uptake as they are not substrates or inhibitors of P-glycoprotein or cytochrome 3A4 although they are transported by OATP2.<sup>19,20</sup> Despite growing evidence of numerous potential modes of drug-drug interactions, the exact mechanisms that determine statin myotoxicity remain enigmatic. However, since the risk of myopathy appears dose-dependent,<sup>21</sup> understanding the factors governing intramuscular statin concentration are of prime importance.

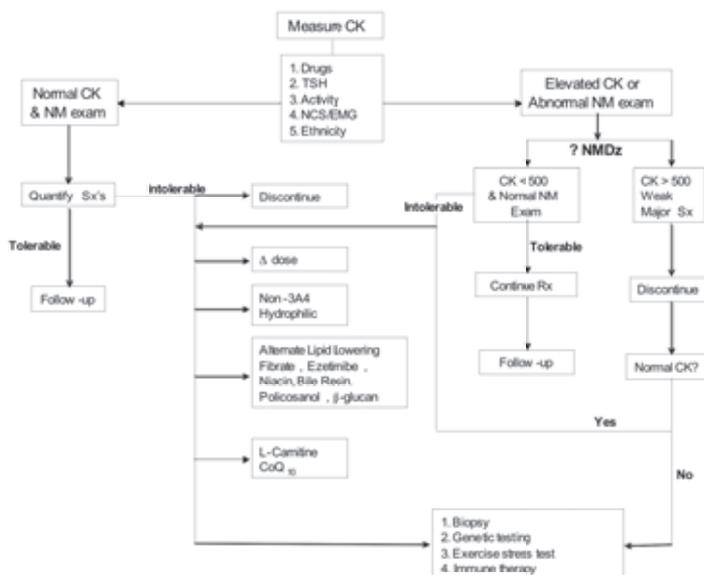
### CLINICAL MANAGEMENT OF STATIN RELATED MYOTOXICITY

The statins have attracted widespread notoriety with respect to potential musculoskeletal side-effects. While the pathophysiology of statin myopathy is unknown, there are accepted muscle-related side-effects which include myalgia, cramps, myopathy, myositis, and rhabdomyolysis. A lack of general consensus regarding these definitions has complicated clinical management. For example, myalgia, defined as simply muscle aches or flu-like symptoms, may or may not occur in the context of an underlying myopathy. The latter diagnosis implies pathology and should be supported by findings on a muscle biopsy. Myositis and rhabdomyolysis are arbitrarily defined as serum creatine kinase (CK) levels of less than or greater than ten times the upper limit of normal, respectively. Low-grade hyperCKemia can be caused by disorders that are not primarily myogenic which renders a diagnosis of statin-myositis based only on a CK levels challenging. The diverse pathophysiology of statin-related muscle side-effects poses further challenges. For example, a patient with myalgia may have biopsy-proven myopathy, myositis, or neither whereas another patient may have asymptomatic rhabdomyolysis. Thus there is a clear need for a rational clinical algorithm to assist in the management of these patients.

Given the high degree of public awareness regarding the possible muscle effects of statins, patients may inappropriately ascribe myalgias to the statin. Therefore, a complete neuromusculoskeletal exam should be performed to exclude common conditions such as muscle strain, bursitis, tendonitis, osteoarthritis, radiculopathy, and myofascial pain. Physical findings will dictate the need for subsequent investigations such as x-ray, ultrasound, computerized tomography, magnetic resonance imaging (MRI), or electromyography (EMG). In cases where statins appear culpable in the production of muscle side-effects, with or without CK elevation, there are five immediate issues that require consideration (Figure).

#### (1) Drug-Drug Interactions

Myalgias may be attributed to drug-drug interactions. Lipid-soluble statins (i.e., atorvastatin, lovastatin, simvastatin) have been detected at elevated levels in serum when co-administered with other cytochrome P450 3A4-dependent drugs.<sup>22</sup> For



**Figure:** Management algorithm for statin-induced muscle disease. CK, creatine kinase; CoQ<sub>10</sub>, co-enzyme Q<sub>10</sub>; NCS, nerve conduction studies; NM, neuromuscular; NMDz, neuromuscular disease; Rx, therapy; Sx, symptoms.

example, we recently reported a case of colchicine (3A4-dependent) triggered fulminant rhabdomyolysis in a long-term simvastatin-exposed patient.<sup>23</sup> By contrast, there is limited risk for drug-drug interactions with the hydrophilic (i.e., rosuvastatin and pravastatin). Simple pharmacokinetics, however, cannot explain the entirety of statin myotoxicity. Indeed, a recent correlational study did not find any relationship between CYP450 polymorphisms and the expression of muscular side effects in 100 statin-treated patients—half of whom were asymptomatic.<sup>24</sup> Additionally, the highest incidence of drug interaction associated statin rhabdomyolysis occurs when other lipid lowering agents, particularly fibrates, are added to statin therapy.<sup>25,26</sup>

A final issue regarding drug interactions is that of co-administered drugs with independent myotoxic potential. While gemfibrozil raises statin activity,<sup>27,28</sup> fenofibrate does not.<sup>28,29</sup> Yet fenofibrate carries a risk for drug interaction-induced statin rhabdomyolysis.<sup>30-32</sup> This argues for an effect of combined therapy independent of statin levels (i.e., pharmacodynamic interaction). Melli et al,<sup>33</sup> found that the antipsychotics, as a class, were responsible for more cases of rhabdomyolysis than were the statins in a review of hospitalized toxic myopathy patients. Therefore, systematically excluding multiple myotoxic medications represents a logical approach to discerning the responsible drug.

#### (2) Hypothyroidism

Hypothyroidism is a cause of secondary hypercholesterolemia and is known to increase the risk for statin myopathy.<sup>34,35</sup> Thyroid hormone regulates HMG-CoA reductase messenger

RNA.<sup>36</sup> Thus a combination of statin treatment and pre-existing hypothyroidism may compound the reduction in enzyme activity. Both overt and sub-clinical hypothyroid myopathy may also be independently associated with CK elevations<sup>37</sup> and further predispose a patient to statin myotoxicity. Conversely, simvastatin has been associated with thyroid stimulating hormone (TSH) elevations in L-thyroxine-treated patients, possibly via accelerated T4 metabolism through CYP450 3A4.<sup>38</sup>

Statins have been implicated in carnitine dyshomeostasis. Sinclair et al,<sup>39</sup> documented a significant inverse correlation between serum TSH and muscle carnitine levels. Gamma-butyrobetaine hydroxylase is the terminal rate-limiting enzyme in carnitine synthesis and its reduced activity in hypothyroidism<sup>40</sup> may explain reductions in tissue carnitine levels. This therefore suggests another level of interaction in hypothyroid patients. Treating sub-clinical hypothyroidism or increasing L-thyroxine levels in patients with existing hypothyroidism may mitigate symptoms; however, evidence to justify such an approach is required.

**Table 2: Non-iatrogenic causes of asymptomatic hyperCKemia**

Disorder	Reference
<i>Inflammatory Myopathy</i>	
Polymyositis	53
Macrophagic myositis	53
Inclusion body myositis	53
Non-specific myositis	53
<i>Muscular Dystrophy</i>	
Dystrophinopathy (including carrier status)	53,136,167
$\alpha$ -glucosidase deficiency	53
Sarcoglycanopathy	167
FKRP deficiency	53
Caveolinopathy	53,168
Calpainopathy	53
Dysferlinopathy	53
Distal myopathy (pre-symptomatic)	169
Myofibrillar myopathy	53
Myotonic Dystrophy type 2	170
<i>Metabolic Myopathy</i>	
McArdle disease	53,167
Mitochondriopathy	53,54
Alcoholism	54,171
Malignant hyperthermia	172-174
Central core disease	167
Myoadenylate deaminase deficiency	56,175
Partial phosphorylase B kinase deficiency	56
Partial carnitine palmitoyl transferase deficiency	56
<i>Endocrine/Nutritional Myopathy</i>	
Hypothyroidism	171
Hypoparathyroidism	176
Alcoholism	177
<i>Non-specific Myopathy</i>	
Desminopathy	178
Myopathy with tubular aggregates	167

FKRP - Fukutin-related protein

### (3) Physical Activity

Identifying activity patterns prior to CK measurement is exceedingly important, particularly because statins are associated with exaggerated exercise-induced CK elevations. For example, Thompson et al,<sup>41</sup> found that five weeks of lovastatin treatment (40 mg/d) increased CK elevations 24 hours after 45 minutes of downhill (-15% grade) walking by a mean of 191 U/L compared to 103 U/L for placebo (P<0.05). Similarly, elite athletes with familial hyperlipidemia are generally intolerant to statin therapy as a result of their rigorous training.<sup>42</sup> Eccentric (i.e., muscle lengthening) contractions are particularly damaging to myofibers. Eccentric upper extremity activity (2 sets of 25 reverse biceps curls) raised CK to a mean of > 7000 U/L in 203 healthy subjects by day four post-exercise (range: 55 – 80550 U/L). In 51 subjects the CK was > 10000 U/L on day four.<sup>43</sup> This highlights the extreme inter-individual variability that must be considered when interpreting CK values. Another factor influencing post-exercise CK is the patient's (task-specific) fitness. Unaccustomed muscular work causes far greater elevations in CK compared to work for which an individual is trained.<sup>44,45</sup> However, even in highly trained endurance athletes prolonged submaximal running can produce extreme exertional hyperCKemia. For example, the mean CK of 39 ultramarathoners (mean age 41) upon completion of a 246 km continuous race averaged 43,763  $\pm$  6,764 U/L.<sup>46</sup> By contrast, a single day 230 km mountainous road cycling race produced trivial excursions in CK in 38 males (mean age 35) from a pre-race value of 63 U/L to a 24-hr post-race value of only 234 U/L.<sup>47</sup>

These divergent CK responses to exercise support the well-known observation that myocellular damage can be induced by eccentric activity<sup>48</sup> and highlight the importance of clarifying any muscular activity that occurred prior to CK measurement. To obtain an unbiased measurement, patients should abstain from exercise for  $\geq$  72 hours prior to the blood draw. Even with this precaution physicians must recognize that CK levels can remain elevated for over a week after eccentric exercise.<sup>49</sup>

### (4) Radiculopathic and Neuropathic HyperCKemia

Clues to presence of lumbosacral radiculopathy or motor neuropathy should be sought. Indeed, denervation is known to cause mild creatine kinase elevations.<sup>50,51</sup> Whether statins potentiate denervation-related CK elevation is not known. Equally unclear is whether statin-treated patients with motor neuropathy or radiculopathy experience higher resting CK levels or greater post-exercise CK elevations compared to individuals without these conditions. In this context the value of thorough neuromuscular and electrodiagnostic examinations cannot be overstated.

### (5) Ethnicity & Idiopathic HyperCKemia

Asian populations may be particularly susceptible to statin related muscle adverse effects possibly due to higher serum drug concentrations.<sup>52</sup> A recent attempt to ascribe such ethnic idiosyncrasy to polymorphisms in the human organic anion transporting polypeptide 1B1 (which contributes to hepatic uptake of the statins) failed to correlate genotypes with pharmacokinetic parameters.<sup>52</sup> Therefore, it appears that other

factors may underlie the observed ethnic variability in serum statin levels.

African-Americans may have elevated baseline CK levels with certain healthy individuals harboring values persistently exceeding four times the upper limit of normal (i.e., 800-1000 U/L). The cryptogenic factors which give rise to this benign hyperCKemia may also contribute to the modest CK elevations evident in these individuals when treated with statins. Idiopathic hyperCKemia (IH) is found across all ethnic groups and is more common amongst men than women. A normal clinical and family history, neuromuscular exam, and electrodiagnostic study tends to exclude the need to perform comprehensive investigations although extensive work-up may disclose pathology in up to 55% of cases.<sup>53-56</sup> In 46% of cases IH may occur in a familial form.<sup>57</sup> Idiopathic hyperCKemia is genetically heterogeneous exhibiting autosomal dominance in 60% of kindreds, with increased penetrance in males.<sup>57</sup> These patients manifest persisting hyperCKemia despite statin withdrawal. Muscle biopsies appear normal or display minor nonspecific changes (i.e., variability in fiber-type proportion or size).<sup>57</sup> Statin therapy for asymptomatic patients whose CK level does not normalize after withdrawal should be reinstated for cardiovascular protection. Judicious clinical follow-up and intermittent CK monitoring should be performed to ensure patient tolerance.

#### NORMAL VS. ELEVATED CREATINE KINASE

After the above five determinants of statin-intolerance have been considered, it is necessary to assess the CK levels. An important caveat is that a subclinical myopathy may exist even when the CK is normal.<sup>58,59</sup> The histological changes may include mild lipidosis, cytochrome oxidase-negative fibers, and ragged red fibers. Creatine kinase levels cannot be used as an absolute biomarker of muscle damage. However, a normal level tends to exclude myositis.

Various myopathic reactions to statins are documented (Table 3). While skeletal muscle may undergo pathologic alterations in response to statins, muscle experts agree that a biopsy need not be performed in every symptomatic patient.<sup>60</sup>

Baseline CK levels are clinically useful. Individuals with pre-statin elevations warrant serial CK monitoring. Currently, there is a lack of consensus on the definition of an acceptable rise in CK after statin introduction. For example, a 30% rise in creatinine within the first two months of angiotensin-converting enzyme inhibitor therapy is considered acceptable.<sup>61</sup> Similar information should be available to physicians prescribing statins. However, the variability of serum CK values and their fluctuations in response to physical activity make such a numbers-driven approach less tenable. This emphasizes the importance of clinical acumen in the management of statin-treated patients.

#### NORMAL CK LEVELS

If the CK is normal (i.e., left-side of algorithm), it is important to confirm that the pain stems from the muscle. Tendinopathies,<sup>62</sup> arthropathies,<sup>63,64</sup> lupus-like syndromes,<sup>64,65-67</sup> and neuropathies<sup>68-70</sup> have been attributed to statins. Chance association might account for these observations which require additional support in the literature. Muscle-derived symptoms, if

**Table 3: Clinical spectrum of myotoxic reactions to statin drugs**

1. Myalgias ± cramping ± stiffness
2. Myopathy<sup>§</sup> ± weakness
  - a. with elevated serum CK
    - i. CK ≤ 500 U/L
    - ii. CK ≥ 500 U/L
  - b. without elevated CK (muscle biopsy required)
3. Rhabdomyolysis
  - with renal failure
  - without renal failure
4. Asymptomatic hyperCKemia

§ The definition of clinical myopathy implies the presence of weakness; however, histological changes can occur without weakness or CK elevation. Therefore, clinical and histological myopathy should be differentiated when possible.

tolerable, should be closely followed and the statin continued. If the symptoms are intolerable the statin must either be discontinued or replaced with another lipid-lowering drug. Alternatively, if cholesterol targets are achieved, a down-titration may be considered although the latest Canadian cholesterol management guidelines make this option less likely for patients receiving secondary prevention therapy (i.e., 2006: LDL ≤ 2.0 mmol/L<sup>71</sup> vs. 2003: LDL ≤ 2.5 mmol/L<sup>72</sup>). When a drug-drug interaction is thought to be responsible for the emergence of symptoms, converting to a non-cytochrome P450-dependent or hydrophilic statin (i.e., pravastatin or rosuvastatin) may be considered. Golomb et al<sup>73,74</sup> reported that statin-intolerant patients have a 55% chance of symptom recurrence if a subsequent lower potency statin is prescribed compared to 95% chance if an equipotent statin dose is used, independent of lipophilicity.

#### ALTERNATE LIPID-LOWERING THERAPIES

Alternatively, agents such as ezetimibe, fibrates, or niacin can be prescribed. Ezetimibe is a novel lipid-lowering agent that binds to the Niemann-Pick C1 Like 1 transporter,<sup>75</sup> which critically regulates intestinal cholesterol absorption at the brush-border surface<sup>76</sup> and whole-body cholesterol homeostasis.<sup>77</sup> Ezetimibe has not been systematically evaluated in statin-myopathy patients and numerous reports implicate it in muscle adverse effects.<sup>78-80</sup> Phillips et al,<sup>80</sup> reported that the majority of statin-intolerant patients also exhibit intolerance to ezetimibe secondary to recurrent myotoxicity. Ezetimibe may also exhibit pharmacogenomic myotoxicity, given the report of rhabdomyolysis being triggered in a patient with McArdle's disease.<sup>81</sup> A recent retrospective review<sup>82</sup> of administrative claims data reported similar relative risk estimates for myopathy requiring hospitalization for gemfibrozil (0.84), ezetimibe (0.98), atorvastatin (1.0), simvastatin (1.24), pravastatin (1.25), and rosuvastatin (1.36). Niacin, fenofibrate, cerivastatin, and

concomitant use of CYP3A4 inhibitors were associated with 2.5, 4.3-, 6.7- and 6.0-fold higher reporting rates for myopathy compared to atorvastatin, respectively. Close monitoring for muscle side-effects is required in any statin-intolerant patient testing alternative lipid lowering therapies.

Bile acid resin monotherapy has not been associated with rhabdomyolysis. In four patients, pre-existing myopathy lead to exaggerated myopathic symptoms upon exposure to statins, fibrates, or niacin. By contrast, cholestyramine was well tolerated.<sup>83</sup> This finding was recently extended by Phillips and colleagues,<sup>84</sup> who reported on the clinical efficacy and safety of colsevelam in statin myopathy patients. Finally, policosanols, a mixture of long-chain primary aliphatic saturated alcohols derived from the waxes of such plants as sugar cane (*Saccharum officinarum*) and yams (*Dioscorea opposita*), as well as  $\beta$ -glucan, a soluble fiber derived from oatmeal and oat bran, have been used as nutraceutical options to lower LDL. While preliminary small trials<sup>20,21,85-88</sup> provided promising results for policosanols, two recent randomized controlled trials<sup>89,90</sup> failed to establish a cholesterol-lowering effect. Dietary oat bran (56 g/day) supplementation for six weeks produced a 16% reduction in LDL.<sup>91</sup> A meta-analysis concluded that 3.0 g soluble fiber from oats (3 servings of oatmeal, 28 g each) can decrease total and LDL cholesterol by approximately 0.13 mmol/L.<sup>92</sup> There are no reports on the LDL-lowering effects of combining cholestyramine with policosanols or  $\beta$ -glucan. For patients with multi-agent lipid-lowering myopathy, these nutraceutical options require increased consideration.

#### MYOPROTECTIVE SUPPLEMENTS

The clinical utility of co-enzyme Q<sub>10</sub> is unproven. Numerous studies suggest that blood levels of co-enzyme Q<sub>10</sub> are reduced by statin treatment.<sup>93-110</sup> This effect is most likely a function of lipoprotein reduction as these proteins serve as carriers for co-enzyme Q<sub>10</sub>.<sup>100,105</sup> There are conflicting data regarding the effect of statins on myocellular levels of co-enzyme Q<sub>10</sub>. Several studies have reported an increase by 9.0 to 46.6% after one to six months of simvastatin therapy (20 mg/day).<sup>93,100</sup> Päivä et al<sup>111</sup> documented a 33.5% reduction after eight weeks of simvastatin (80 mg/day) but not atorvastatin (40 mg/day) treatment. Additionally, the mitochondrial volume marker, citrate synthase, was reduced to 55% of baseline activity suggesting that statins may impair mitochondrial biogenesis. Vladutiu et al<sup>10</sup> found reduced skeletal muscle co-enzyme Q<sub>10</sub> levels in 47% of 41 biopsy specimens from statin-intolerant patients with varying CK levels. By contrast, Lamperti et al found similar mean muscle co-enzyme Q<sub>10</sub> levels between controls and statin myositis patients.<sup>107</sup> Three of 18 patients with statin myositis had muscle levels greater than two standard deviations below the control mean. However, no mitochondrial abnormalities or TUNEL (terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick-end labeling) positive nuclei were noted in these patients.

Conflicting reports of muscle co-enzyme Q<sub>10</sub> levels underscore the uncertain utility of this compound in the treatment of statin myopathy. Preliminary evidence from a randomized blinded trial demonstrated improved myalgias in 18 of 21 patients who received 100 mg/d of co-enzyme Q<sub>10</sub> for four weeks as opposed to 3 of 20 who received 400 IU of vitamin E

( $P < 0.001$ ).<sup>112</sup> Additional randomized-controlled double-blinded trial evidence is needed to address this issue in order to establish more definitive evidence-informed management guidelines.

#### ELEVATED CK LEVELS

In cases where CK levels are elevated (i.e., right-side of algorithm), whether symptomatic or not, a complete neuromuscular exam should be performed to assess for evidence of muscle weakness. In oligo-/asymptomatic patients, if the neurological examination is normal and CK levels are not above 500 U/L, the statin can be continued in agreeable patients. Patients requesting statin discontinuation should be prescribed alternate lipid lowering therapies. Patients should be advised about the potential for vigorous or unaccustomed exercise to cause hyperCKemia and the theoretical potential of rhabdomyolysis particularly with dehydration.<sup>113,114</sup> In certain individuals it may still be informative to discontinue the statin for approximately one month in order to document a decline in serum CK. Some patients with modest CK excursions (i.e., 250–400 U/L) may be found to harbour muscle pathology, however there is a need to establish minimum biopsy criteria in order to select patients with abnormal histopathology. Patients manifesting muscle weakness or CK values above 500 U/L warrant statin discontinuation and serial CK monitoring to determine if the values normalize. If the CK returns to pre-statin levels then the “normal CK” arm of the algorithm can be worked through.

In the context of either a persistently elevated CK or an abnormal neurologic exam consideration should be given to a growing list of neuromuscular disorders attributed to statin therapy.<sup>58,94,115-129</sup> Included in this list are the idiopathic inflammatory myopathies [i.e., overlap myositis (personal observation), polymyositis,<sup>125</sup> dermatomyositis,<sup>123,126-128</sup> and inclusion body myositis<sup>124</sup>], myasthenia gravis,<sup>117,118</sup> mitochondrial myopathy,<sup>58,94,130</sup> McArdle disease,<sup>121,122,130</sup> acid maltase deficiency,<sup>129</sup> carnitine-palmitoyl transferase deficiency,<sup>120</sup> rippling muscle disease (RMD),<sup>115</sup> malignant hyperthermia (MH),<sup>116,119</sup> myotonic dystrophy type 1 (DM1),<sup>130</sup> Kennedy disease,<sup>130</sup> and amyotrophic lateral sclerosis.<sup>131</sup> For genetically-based muscle disorders statins are believed to trigger myogenic symptoms more readily than in normal muscle. It seems likely that the diverse neuromuscular phenotypes associated with statin use reflect multiple mechanisms acting either singly or synergistically.

Patients with significant stereotypic hyperCKemia in response to multiple statins, a single exuberant episode of hyperCKemia (including rhabdomyolysis), weakness, or treatment-limiting myopathic symptoms should be biopsied to determine if the pathology is more typical of a known neuromuscular disorder or statin-induced damage as has been previously reported in rodent and human statin myopathy (Tables 4 & 5). Enzymology (i.e., mitochondrial respiratory chain, CPT, myophosphorylase), muscle co-enzyme Q<sub>10</sub> and L-carnitine quantification, and genetic analyses of the three commonest triggerable metabolic myopathies (i.e., *AMPD1*, MIM 102770; *PYGM*, MIM 232600; and *CPT2*, MIM 255110) are additional considerations. Recently, statin myopathy patients were found to be 20-fold and 13-fold more likely to be carriers of McArdle disease and CPT2 deficiency, respectively, compared to the

**Table 4: Histomorphologic changes in skeletal muscle after pharmacologic doses of lovastatin (1 mg/g body weight for 30 days)**

Microscopy	Pathologic Observations
Light	Increased variability in fiber diameter Myofiber splitting Increased nuclear internalization Perimysial fibrosis Coarsening of intermyofibrillar membranous network Clumping of intermyofibrillar membranous material Diffuse decrease in NADH dehydrogenase staining in non-necrotic myofibers Myofiber necrosis with macrophage invasion Hypercontacted fibers Relative sparing of slow-twitch oxidative fibers with earlier involvement of fast-twitch glycolytic fibers
Electron	Two types of mitochondrial alterations: (1) fragmented inner mitochondrial membrane (IMM) or absent or effaced cristae; replacement of cristae with fine granular material; outer MM (OMM) intact (2) spared IMM and matrix; redundant and thickened OMM ± circular loops formed by OMM material Dilated cisterns of the sarcoplasmic reticulum Normal T-tubules Myeloid figures in degenerating mitochondrial membranes Vacuolization Intermyofibrillar and subsarcolemmal accumulations of abnormal mitochondria Z-band streaming

Adapted from Waclawik, A.J., Lindal, S., Engel A.G. Experimental lovastatin myopathy. *J Neuropathology and Experimental Neurology* 1993, 52: 542-9 (with permission). Biopsies were taken from Lewis rat superficial (white/glycolytic) and deep (red/oxidative) regions of the gastrocnemius and soleus (red/oxidative) 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 myopathologic changes.

general population.<sup>10</sup> This preliminary data offers compelling evidence that latent partial deficiencies of metabolic pathways when further “stressed” by pharmacologic toxicity will produce symptomatic muscle disease. Conceptually, this is similar to a statin accelerating symptom onset in patients with a sub-clinical inflammatory myopathy. Indeed, when such pathology is found treatment with routine agents is warranted (i.e., prednisone, azathioprine, methotrexate, cyclosporine, cyclophosphamide, intravenous immunoglobulin, mycophenolate mofetil, plasma exchange, or rituximab; for excellent reviews see references).<sup>132-135</sup>

#### STATINS AND NEUROMUSCULAR DISEASES: PATHOPHYSIOLOGIC CONSIDERATIONS

##### *Idiopathic Inflammatory Myopathies and Myasthenia Gravis*

There are a variety of mechanisms that may account for triggering or aggravating muscular disorders upon statin treatment. For example, given the autoimmune pathogenesis of idiopathic inflammatory myopathies and myasthenia gravis, it is possible that statin use could induce a dysimmune process.<sup>118,123</sup> With inflammatory myopathies this may well occur as a result of low grade myotoxicity exposing muscle antigens thereby facilitating loss of tolerance in susceptible individuals.<sup>136</sup> Alternatively, statins are immunomodulatory insofar as they increase production of Th2 cytokines (i.e., IL-4, 5, & 10).<sup>137</sup> The documentation of patients requiring long-term immuno-

**Table 5: Pathological abnormalities reported from patients manifesting statin-related adverse muscle effects**

Cytochrome oxidase negative fibers Electron-dense membranous debris Fiber atrophy Glycogen storage Increased oxidative enzyme staining Inflammatory infiltrate Lipid-filled vacuoles Necrosis Paracrystalline inclusions (mitochondrial) Ragged-blue fibers (Succinate dehydrogenase stain) Ragged-red fibers (Gomori trichrome stain) Vacuolization
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suppression for an acquired inflammatory myopathy that developed shortly (i.e., one - three months) after statin treatment supports the triggering potential of these drugs in chronic myopathy. It is, however, possible that these patients were destined to develop the myopathy and the statin served as an accelerant. However, chance associations cannot be dismissed and thus further observation is warranted.

Presynaptic statin-induced coenzyme Q<sub>10</sub> depletion/mitochondrial dysfunction may also contribute to inefficient neuromuscular transmission in myasthenia gravis. Interestingly, the mitochondrial disorder, chronic progressive external ophthalmoparesis, is associated with jitter on single-fiber electromyography.<sup>138</sup> This supports the importance of mitochondrial function in neuromuscular transmission. Another hypothesis for the triggering effect of statins in myasthenia gravis is the dependency of nicotinic acetylcholine receptor clustering on the actin<sup>139</sup> and microtubule<sup>140</sup> cytoskeleton, both of which may be vulnerable to the effects of HMG-CoA reductase inhibition.<sup>141</sup>

##### *Metabolic Myopathies*

The metabolic disorders (i.e., mitochondrial myopathy, McArdle disease, and carnitine palmitoyl transferase deficiency) may be precipitated by statin-triggered metabolic dysregulation. For example, inhibition of HMG CoA-reductase depletes cellular farnesyl levels which are required for the synthesis of the ten isoprene unit tail of ubiquinone. Farnesylation of the redox active quinoid nucleus functionalizes co-enzyme Q<sub>10</sub> by conferring lipophilicity and thus mobility within the inner mitochondrial membrane. Co-enzyme Q<sub>10</sub> shuttles reducing equivalents from complexes I and II to complex III in the electron transport chain. Reductions in muscle co-enzyme Q<sub>10</sub> levels are variable amongst statin-intolerant patients with hyperCKemia.<sup>107</sup> Only a minority of patients manifest levels below control values which argues against the primary pathogenicity of co-enzyme Q<sub>10</sub> depletion in statin myopathy. However, in patients with mitochondrial disorders any subtle deterioration of electron transport chain function must be

avoided even if speculative. The triggering of a MELAS syndrome in two patients treated with statins supports the contention that mitochondrial fidelity may be sensitive to HMG-CoA reductase inhibitors.<sup>94,142</sup> Indeed the Michaelis-Menton constant ( $K_m$ ) of NADH cytochrome c reductase for co-enzyme  $Q_{10}$  ( $2.4 \pm 1.7$  nmol/mg protein) is within the physiologic range for intra-mitochondrial co-enzyme  $Q_{10}$  (1-4 nmol/mg protein).<sup>143</sup> Statin-induced decrements in co-enzyme  $Q_{10}$  may therefore impair complex I-III activity and unmask myopathic symptoms in patients harboring mutations in mitochondrial genes encoded by either nuclear or mitochondrial DNA. Regarding the latter, subthreshold myopathy may exist due to replicative tissue segregation (i.e., heteroplasmy). Drug-induced triggering of genetic defects is referred to as pharmacogenomic synergism.

A role for genetics as a potential determinant was recently demonstrated in subjects who developed myopathy on statin monotherapy.<sup>144</sup> Single nucleotide polymorphisms (SNP) in the CoQ2 gene encoding para-hydroxybenzoate-polyprenyl transferase—the second enzyme in the CoQ<sub>10</sub> biosynthetic pathway—was significantly associated with inter-individual variation in statin tolerability (odds ratios: SNP1, 2.42; SNP2, 2.33; 2-SNP haplotype, 2.58).<sup>144</sup> These preliminary pharmacogenetic results suggest that statin-induced muscle intolerance is associated with genomic variation in CoQ2 and thus perhaps with the CoQ<sub>10</sub> biosynthetic pathway.

Preliminary evidence in animal models suggests that statins may impair fatty acid oxidation by reducing tissue carnitine levels<sup>145</sup> or enzymes of  $\beta$ -oxidation.<sup>146</sup> For example, serum acylcarnitines increased while tissue carnitine levels decreased in rabbits fed lovastatin (30 mg/d x 16 weeks). *In vitro*, the lipophilic statins exhibited mitochondrial toxicity through various mechanisms involving electron transport and  $\beta$ -oxidation. This was associated with dissipation of membrane potential, cytochrome c release, and apoptosis.<sup>146</sup> These results suggest that individuals with partial metabolic deficiencies upstream of or involving oxidative phosphorylation may be more susceptible to statin-induced downregulation of critical enzymes or substrates necessary for intermediary metabolism.

### ***Malignant Hyperthermia (MH) and Rippling Muscle Disease (RMD)***

Simvastatin has been shown to produce mitochondrial  $Ca^{2+}$  efflux *in vitro* through both the permeability transition pore and the  $Na^+$ - $Ca^{2+}$  exchanger prior to larger secondary sarcoplasmic reticulum-mediated  $Ca^{2+}$  release.<sup>147</sup> These perturbations may be particularly relevant to the deranged calcium release in MH. *In vitro* contracture tests were positive in seven of nine patients with statin-associated hyperCKemia.<sup>148</sup> Two exhibited both halothane- and caffeine-induced contracture confirming MH susceptibility whereas five were positive for a single test. The authors did not specify whether patients were taking the statin at the time of the biopsy.

Another disorder with presumed calcium dysregulation is RMD. The unusual manifestations of muscle hyperexcitability (i.e., percussion-induced rapid contractions, myoedema, and rippling) in this condition may be due to calcium transients that ostensibly arise from silent action potentials within the T-tubular system.<sup>149</sup> We recently reported a case of immune-mediated RMD which was unmasked by simvastatin exposure.<sup>115</sup> After

publication this patient was treated with ezetimibe which also produced clinical worsening of his rippling. Interestingly, hereditary RMD is due to caveolin-3 mutations<sup>150</sup> and caveolin trafficking from the Golgi to the plasma membrane is exquisitely dependent on the cholesterol microenvironment of the cell.<sup>151</sup> Therefore, despite the fact that statins deplete membrane expression of caveolins,<sup>152</sup> it may be alterations in cellular cholesterol that determines symptomatic aggravation in RMD patients treated with lipid lowering therapy.

In these and other scenarios, a single disruption of two pathways or a double disruption of one pathway appears necessary to manifest disease in a subset of patients. Statins may thus unmask muscle pain, weakness, or serum CK elevations in an asymptomatic carrier (recessive condition) or pre-/oligosymptomatic patient (dominant or acquired condition). Further support of this can be found in the report of combined partial deficiencies of carnitine palmitoyl transferase II and mitochondrial complex I presenting with hyperCKemia.<sup>153</sup> Similarly, the combination of a heterozygous R50X nonsense mutation in the myophosphorylase gene and 7444 G>A transition in cytochrome oxidase subunit I gene produced proximal myopathy, high CK and lactate, and exercise intolerance.<sup>154</sup> The multiple pathway synergy model is an attractive explanation for the numerous potential neuromuscular manifestations of statin therapy and may account for a wide range of clinical manifestations (i.e., drug-drug, drug-gene, and gene-gene).<sup>155</sup>

### **CONCLUSIONS**

A Pubmed search, limited to the last ten years and review articles, using the key words “statin myopathy” revealed 166 items. The literature is indeed replete with numerous views and opinions on statin safety. A clear management algorithm for statin myotoxicity, which addresses the growing list of associated neuromuscular disorders, has thus far been lacking. Many patients with moderate to severe myotoxic reactions to statins will be referred for specialist evaluation. The current algorithm offers a logical approach to triage and manage these patients in primary and tertiary care settings. Additionally, awareness of the growing spectrum of neuromuscular disorders attributed to statin treatment will enable the specialist to provide optimal management strategies for patients intolerant to statins. Determining the clinical utility of myoprotective supplementation strategies is another important area of research given that the number of statin “myopathy” patients rivals other diagnostic categories in neuromuscular disease.

The fact that some individuals can tolerate statins while others cannot, attests to an underlying cryptogenic predisposition. Indeed, suprapharmacologic doses of any statin will cause myopathy, although the toxic dose will vary between individuals. Similar idiosyncratic tolerances or thresholds are an accepted phenomenon in the epilepsy literature and are largely attributed to genetic variability in ion channels.<sup>156</sup> Subclinical metabolic defects in potentially numerous proteins may expose vulnerable muscle to statin toxicity. Ongoing work, employing metabolomics and gene arrays, into the permissive genetic defects associated with statin myotoxicity will hopefully provide a deeper understanding into the pleiotropy of this class of drugs in susceptible individuals.

**APPENDIX: APPLICATION OF MANAGEMENT ALGORITHM****Case 1**

A 52-year-old Caucasian female, with a history of non Q-wave myocardial infarction, hypercholesterolemia, and 30-pack-years of smoking, was found to have hyperCKemia (570 U/L) upon routine surveillance approximately one year after starting atorvastatin. She reported mild weakness, cramping, and myalgias in her upper arms and legs. Ezetimibe monotherapy perpetuated her myalgias and was discontinued. The CK remained elevated. Neurological examination revealed grade 4 MRC (medical research council) strength proximally in the arms and legs.

Nerve conduction studies were normal. Electromyography demonstrated spontaneous activity (i.e., positive sharp waves or fibrillations) in the right deltoid and vastus medialis.

Chest plain films were unremarkable. Cervical spine MRI demonstrated moderate diffuse disc bulging at C5-C6 and C6-C7 with mild flattening of the spinal cord. Scattered inflammatory infiltrates around both vessels and myofibers, macrophage invasion, variable fiber morphology, and type II atrophy were noted on muscle biopsy. Allele specific amplification using polymerase chain reaction failed to detect mutations in *PYGM* (R49X, G204S), *CPT2* (P50H, S113L, Q413fs, G549D), and *AMPD1* (Q12X, P48L) genes.

Bloodwork revealed an elevated anti-phospholipid antibody titre at 39 GPL Unit (normal < 15) and a non-specific inhibitor. These tests remained positive six months later.

Prednisone (20 mg daily) normalized her strength and CK level. Methotrexate (20 mg weekly) was added and the prednisone was tapered slowly (1 mg q 2 weeks). Low dose rosuvastatin (5 mg daily) was initiated without symptom aggravation.

This case highlights the importance of underlying muscle disorders which can masquerade as statin-myopathy. Anti-phospholipid antibody syndrome with myositis has been previously reported.<sup>157</sup> It is impossible to determine if the statin was an accelerant or a trigger for the myositis. It is important to note that pre-existing myopathies likely renders muscle more vulnerable to the myotoxic effects of statins. For example, when the above patient was treated for her myositis she tolerated statin re-introduction.

**Case 2**

A 38-year-old Caucasian male heavy machine operator reported stiffness, proximal weakness, myalgias, and fatigue within approximately six months of starting atorvastatin. Both simvastatin and rosuvastatin caused bilateral calf tightness particularly in the morning. His CK was elevated (956 U/L) but dropped by approximately 50% after statin discontinuation.

Neuromuscular examination revealed temporalis wasting, subtle bilateral ptosis, and oral tenting. Cataracts were not observed on indirect ophthalmoscopy. Motor examination demonstrated reduced distal bulk. Strength testing revealed both proximal and distal weakness. Forceful eyelid and hand closure produced mild slowness of reopening. Thenar percussion brought the thumb into abduction/opposition for a few seconds prior to relaxation. Muscle stretch reflexes were present but diffusely hypoactive. Sensory testing was normal.

Sensory and motor nerve conduction studies were normal. Needle EMG demonstrated 1+ to 2+ myotonia proximally and distally in the arms and legs.

Genetic testing of the *DMPK* gene revealed a pathologic allele possessing 150 CTG repeats. A diagnosis of myotonic dystrophy type 1 (E0 = 50-200 repeats) was confirmed. An electrocardiogram revealed a normal PR interval of 182 ms. His hemoglobin A1C was 5.5% and testosterone levels were normal.

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. Statins produce electrophysiologic myotonia by impairing membrane chloride conductance.<sup>158</sup> In experiments employing both rats<sup>159,160</sup> and rabbits<sup>158,161</sup> pravastatin exerted little to no effect on electromyographic activity and membrane chloride conductance whereas simvastatin caused dose-dependent reductions in the latter. Despite pravastatin's reduced potential to cause myotonia in experimental models, a 37-year-old man with sarcoidosis experienced severe myotonia after receiving pravastatin.<sup>162</sup> Patients with myotonic disorders may be at risk for symptomatic aggravation in response to statins and their use should be guarded. The absence of reported myotonic side-effects from ezetimibe, niacin, and bile acid resins suggests that these agents are preferable to manage hyperlipidemia in this unique patient group.

**Case 3**

A 62-year-old male with hypertension, hypercholesterolemia, bilateral calcified pleural plaques from asbestos exposure, and biclonal gammopathy of undetermined significance developed shoulder girdle pain and weakness two months after starting Lipitor (20 mg/day). His CK was elevated at 855 U/L. After discontinuation the myalgias subsided but the hyperCKemia persisted (range: 523 to 725 U/L). He reported ongoing weakness in overhead activities that had not been present prior to the statin exposure.

He had neck flexion, scapulohumeral, and hip flexion weakness. Muscle stretch reflexes and sensory testing were normal.

Electrophysiologic studies revealed normal sensory and motor amplitudes and conduction velocities. Fibrillations and positive sharp waves were noted in the right deltoid (2+), biceps (2+), and brachioradialis (1+) on needle EMG. The motor unit action potentials displayed an admixture of normal and early, brief, polyphasic morphologies.

Bloodwork revealed a mildly positive antinuclear antibody titer at 1:80 in a speckled pattern. Pulmonary single positron emission computerized tomography (SPECT) revealed no increased uptake of fluoro-2-deoxy-D-glucose tracer in the lung fields nor elsewhere.

Skeletal muscle biopsy revealed multifocal inflammatory infiltrate consisting of lymphocytes and histiocytes. Immunohistochemistry for UCHL1 was highly reactive confirming a T-cell predominance. The B-cell marker L26 was immunonegative. Passive T-cell invasion of non-necrotic muscle cells was noted.

The patient was started on prednisone (20 mg/day), bisphosphonate, and vitamin D. His strength normalized to 5/5 in

the upper extremities and his CK dropped from 465 to 159 U/L over two months.

This case represents a statin-triggered polymyositis. Asbestosis has been associated with myositis, however the negative SPECT tends to rule this diagnosis out. Similar cases have been reported previously (see above). A chance occurrence of symptom onset after statin initiation cannot be excluded. Similarly it is unknown whether statins act as an accelerant for existing sub-clinical acquired muscle disease or whether they truly cause the inflammation. Campbell has recently hypothesized that statins may favour a pro-inflammatory state through reduction of endogenous steroid synthesis or possibly through enhanced apoptosis thereby inciting immune cells against apoptotic remnants.<sup>163</sup> Indeed statins do cause increased apoptosis in numerous cell types<sup>164</sup> although such findings are not universal.

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