CLINICAL OBSERVATION

Presymptomatic Neuromuscular Disorders Disclosed Following Statin Treatment

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It is well recognized that statins affect muscular tissue adversely and that their use is associated with clinically important myositis, rhabdomyolysis, mild elevation of serum creatine kinase (CK) levels, myalgias, muscle weakness, muscle cramps, and persistent myalgias or serum CK level elevations after statin treatment is discontinued. The association between statins and the disclosure of presymptomatic metabolic myopathy is another underrated phenomenon related to statin therapy that was recently recognized in rare cases. The purpose of this report is to provide additional support for this association and to report other neuromuscular disorders that have also been seen following statin intake. The present case series illustrates that statins may act as unmasking agents in asymptomatic patients with a latent neuromuscular disorder. Thus, it may be postulated that statin intake may be a sufficient insult to precipitate neuromuscular symptoms and substantially increase muscle enzymes in presymptomatic patients with an abnormal neuromuscular substrate. In conclusion, muscular symptoms or increased serum CK levels persisting after statin treatment discontinuation should alert the clinician to pursue further diagnostic evaluations for the detection of potential underlying neuromuscular diseases.

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Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are an efficacious and well-tolerated class of lipid-altering agents for primary and secondary cardiovascular protection. Statins adversely affect muscle tissue, and their use is associated with myositis, rhabdomyolysis, mild elevation of serum creatine kinase (CK) levels, myalgias, muscle weakness, muscle cramps, and persistent myalgias or increased levels of serum CK after the statin treatment has been discontinued.[1,2] Presymptomatic metabolic myopathy is another underrated phenomenon related to statin therapy that has been recently recognized in rare cases.[3-5] Herein, we provide additional support for this association and report other neuromuscular disorders that have been seen following statin intake.

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REPORT OF CASES

CASE 1

A 48-year-old man with a history of hypertension, diabetes mellitus, and surgically treated bilateral cataracts was prescribed pravastatin for hypercholesterolemia. Three months later, he complained of general fatigue, muscular aches, and stiffness; CK concentrations were persistently elevated. Discontinuation of pravastatin treatment resulted in mild symptom improvement and a moderate fall in CK levels (**Table**). Neurologic examination disclosed a mild neck flexor weakness, whereas percussion myotonia was absent. Needle electromyography revealed mild myopathic findings and myotonic discharges in proximal muscles. Analysis of muscle biopsy specimens disclosed numerous internal nuclei, nuclear clumps, and variations in fiber size. Mo-

Table. Baseline Characteristics, Medications, Symptoms, and Biochemical Investigations

Characteristic	Case No. 1	2	3	4
Age, y	48	62	51	58
Sex	Male	Male	Male	Male
History of NM disorders	Negative	Negative	Negative	Negative
Family history of NM symptoms	Negative	Negative	Negative	Negative
Statin	Pravastatin, 20 mg/d	Simvastatin, 20 mg/d	Atorvastatin, 40 mg/d	Pravastatin, 40 mg/d
Concomitant medications	Glibenclamide, 5 mg/d Perindopril, 4 mg/d	Glibenclamide, 5 mg/d Aspirin, 325 mg/d Metoprolol, 25 mg/d	Amiloride hydrochloride, 2.5 mg/d Hydrochlorothiazide, 25 mg/d	Allopurinol, 100 mg/d Aspirin, 100 mg/d Metoprolol, 50 mg/d Ramipril, 2.5 mg/d
Symptoms under statin treatment	Myalgias, muscle stiffness, fatigue	Fatigue	Rhabdomyolysis (myalgias, muscle stiffness, muscle cramps, diffuse muscle weakness, and dark urine)	Muscle twitching, muscle cramps, difficulty in climbing stairs
CK level				
Before statin treatment	Not measured	Normal*	Normal*	Not measured
During statin treatment	1125-1130 U/L	320-4400 U/L	45 100-48 300 U/L	850-1050 U/L
After ending statin treatment	578-730 U/L	825-1160 U/L	635-1030 U/L	435-565 U/L
Thyroid function†	Normal	Normal	Normal	Normal
Serum electrolytes‡	Normal	Normal	Normal	Normal

Abbreviations: CK, creatinine kinase; NM, neuromuscular.
*Normal range, lower than 190 U/L.
†Based on measured T3, T4, and thyrotropin levels.
‡Based on measured magnesium, calcium, and potassium levels.

lecular genetic testing established the diagnosis of myotonic dystrophy (580 CTG repeats in the *DMPK* [myotonic dystrophy protein kinase] gene; normal range, 5-37).

CASE 2

A 62-year-old man with a history of myocardial infarction, diabetes mellitus, and hypercholesterolemia was treated with simvastatin for 3 years. Despite his normal pretreatment CK levels, the patient presented with persistently elevated CK levels for 12 months, and these levels did not normalize after statin discontinuation. He was referred by his treating physician to our outpatient neuromuscular clinic for further evaluation (Table). Although the patient claimed to be otherwise healthy and denied any muscular symptoms, after detailed questioning it emerged that he had been experiencing symptoms of fatigue for the past 2 years, which he attributed to his poor physical condition due to his sedentary lifestyle. Findings from neurologic and neurophysiologic evaluations were unremarkable, whereas the ischemic lactate-ammonia test findings were consistent with glycogenosis (flat lactate response [9% rise] in the presence of a good ammonia response [410% rise]). Muscle biopsy specimens revealed numerous periodic acid-Schiff–positive subsarcolemmal vacuoles, while the findings of histochemical studies (absent stain for enzymatic activity of phosphorylase; normal stain for enzymatic activity of adenylate deaminase and phosphofructokinase) were consistent with McArdle disease (**Figure 1**A-C).

CASE 3

A 51-year-old man with a history of hypertension and hypercholesterolemia (treated with atorvastatin for 18 months) was hospitalized for rhabdomyolysis. Atorvastatin treatment was discontinued, and the systemic complications of rhabdomyolysis were effectively managed. The patient's clinical symptoms improved substantially within 2 months, but the serum CK levels failed to return to the normal pretreatment baseline levels (Table). Three months after discontinuation of statin treatment, he still reported exercise intolerance and muscle fatigue. Findings from the neurologic examination were normal, while prominent elevation of fasting serum lactic acid levels was documented (39.8 mg/dL; normal range, 3-12 mg/dL). The findings from the muscle biopsy (subsarcolemmal mitochondrial [mt] proliferation with ragged red fibers and numerous myofibers [35%] staining negative under cytochrome oxidase stain) (Figure 1D-F) and muscle biochemical analysis (selective reduction in cytochrome oxidase activity) were consistent with the diagnosis of mt myopathy. Molecular analysis of frozen muscle mtDNA did not detect any mtDNA rearrangements (Southern blot analysis) or common mtDNA mutations (A3243G, A8344G, T8993G, or T3271C) (polymerase chain reaction analysis). On follow-up evaluations, the patient still reported exercise intolerance and fatigue. Most recently, he has developed mild proximal lower limb weakness (Medical Research Council grade, 4+/5).

CASE 4

A 58-year-old man with a history of hypertension, hyperuricemia, and coronary artery disease was treated with pravastatin, 20 mg/d, for hypercholesterolemia over a 6-month period. Owing to suboptimal lipid control, the dose was increased to 40 mg/d. Shortly afterwards, he experienced muscle twitching, frequent muscle cramps, and difficulty in climbing stairs; his serum CK level was significantly elevated (Table). Discontinuation of statin therapy was associated with mild clinical and

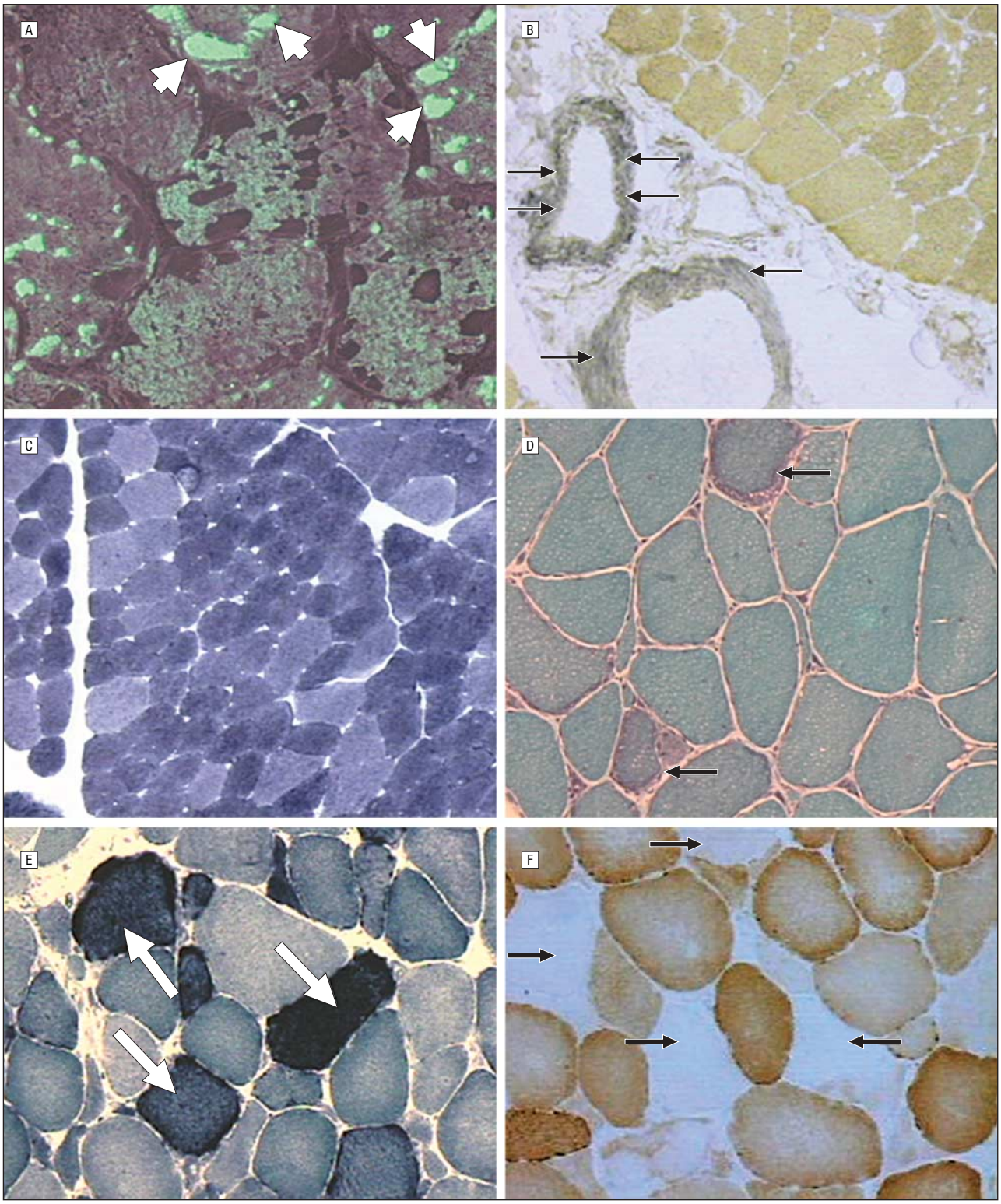

Figure 1. Muscle biopsy specimens and histochemical studies (original magnification for all ×500). A, Periodic acid-Schiff (PAS)-stained frozen section illustrates muscle fibers containing subsarcolemmal vacuoles (arrows) with PAS-positive material in case 2. B, Absent stain for the enzymatic activity of phosphorylase in muscle fibers of case 2; normal stain for the enzymatic activity of phosphorylase in the smooth muscle fibers of the vessel (arrows). C, Normal stain for the enzymatic activity of phosphorylase in muscle fibers of a control patient. D, Gomori trichrome stain demonstrating ragged red fibers (arrows) in case 3; the peripheral rim of red staining in some fibers represents aggregates of mitochondria. E, Succinate dehydrogenase (SDH) stain demonstrating intense activity in some fibers (ragged blue fibers) (arrows); these fibers correspond to the ragged red fibers on Gomori trichrome stain. F, Cytochrome oxidase (COX) stain demonstrating COX-negative fibers (arrows); these fibers correspond to the ragged blue fibers on SDH stain.

biochemical improvement. Four months later, the findings from needle electromyography (positive sharp waves, fibrillation potentials, and polyphasic motor unit potentials with increased duration and amplitude) and muscle biopsy (grouped atrophy, small angular muscle fibers, and target fibers) were consis-

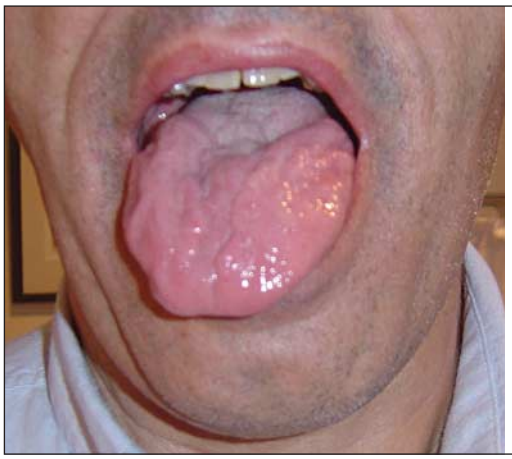

Figure 2. Atrophy of the tongue in case 4. The marked wasting of the large group of glossal muscles on each side has caused them to separate and form a longitudinal midline furrow.

tent with muscle denervation and active reinnervation. Certain of the patient's clinical characteristics (prominent perioral fasciculations and tongue atrophy simulating a longitudinal midline furrow) (**Figure 2**) were suggestive of Kennedy disease, which was substantiated by molecular analysis (52 CAG repeats in the androgen receptor gene; normal range, <40).

COMMENT

The present report illustrates that statins may act as unmasking agents in asymptomatic patients with a latent neuromuscular disorder. Thus, it could be postulated that statin intake may be a sufficient insult to precipitate neuromuscular symptoms and substantially increase levels of muscle enzymes in presymptomatic patients with an abnormal neuromuscular substrate. This is analogous to disclosure of diabetes mellitus in previously asymptomatic patients after beginning treatment with corticosteroids.

The reported disclosure of a metabolic myopathy following statin prescription in case 2 has also been recognized lately in 2 other patients with myophosphorylase deficiency[3,4] and 2 individuals with acid maltase deficiency.[3,5] As in our patient, statin therapy had triggered muscular symptoms and serum CK level elevation that did not resolve after its discontinuation. The treating physicians were alerted, and further diagnostic workup was performed leading to the eventual diagnosis of the underlying disorders. Numerous factors have been involved in the mechanisms of statin-induced myopathy. More specifically, statins reduce the cholesterol content of skeletal muscle membranes, making them unstable.[1] Furthermore, it has been shown that exercise in combination with lovastatin produces greater CK elevations than those produced by exercise alone,[6] suggesting that statins can exacerbate exercise-induced skeletal muscle injury. This concept is supported by in vitro studies indicating that statins inhibit pathways that activate guanosine triphosphate–binding regulatory proteins,[1,7] which in turn have been implicated in skeletal muscle cellular response to exercise stress.[8] Consequently, it has been postulated that statins may affect adversely the muscle's ability to appropriately respond to physical exertion.[1] Because in metabolic myopathies the myofibers are more susceptible to exercise-induced injury, concomitant statin intake may further impair the ability of muscle cells to recover from this damage.

Recent evidence supports mt dysfunction as an underlying mechanism for statin myopathy. The lactate/pyruvate ratio is higher in statin-treated patients, which suggests a shift toward anaerobic metabolism and a possible defect in mt function.[9] It has also been suggested that the statin-induced serum decrease in the level of ubiquinone, a steroid isoprenoid that participates in electron transport during oxidative phosphorylation in mammalian mitochondria, might constitute another pathogenic mechanism of statin myotoxicity.[10] However, it should be acknowledged that in contrast with serum ubiquinone concentrations, intramuscular levels of ubiquinone are not reduced by statin treatment.[11] Interestingly, features of mt dysfunction (ragged red fibers, cytochrome oxidase–negative myofibers, and increased lipid stores) have been demonstrated by biopsy in individuals with muscle complaints under statin treatment. Moreover, symptoms and pathologic abnormalities reversed on discontinuation of statin therapy.[12] There is also a case report of MELAS syndrome (mt encephalopathy, lactic acidosis, and strokelike episodes) induced or unmasked by simvastatin.[13] Likewise, it may be assumed that statin intake in case 3 revealed a preexisting subclinical mt myopathy.

To our knowledge, no case of myotonic disorder occurring on initiation or during statin treatment has been previously reported. However, experimental data had previously suggested that statins modify the electrical properties of muscle membranes and impair their integrity, while simvastatin has been shown to decrease chloride conductance and destabilize membrane electrical potentials, thus increasing susceptibility to myotonic afterdepolarizations.[2,14] In addition, electrical myotonia has been observed following statin treatment in rabbit skeletal muscle.[15] Finally, daily subcutaneous injections of clofibrate have induced myotonia in both normal and chronically denervated rat skeletal muscles.[16] Conversely, it may be argued that the reported temporal relationship between statin administration and the manifestation of myotonic dystrophy in case 1 was merely a chance association.

Statin-induced neuropathy (with improvement or complete resolution occurring after cessation of therapy) has increasingly been described, and nerve-related toxic effects have recently emerged as potential complications of statin treatment.[17,18] Proposed mechanisms include an alteration in cholesterol synthesis that produces a disturbance in cholesterol-rich neuronal membranes or mt dysfunction caused by reduced levels of ubiquinone, which in turn leads to neuronal damage.[17,18] Thus, it is conceiv-

able that statin administration in case 4 may have exacerbated and uncovered an inherited lower motor neuron disorder. This hypothesis is speculative and requires further confirmation because the association between statins and neuropathy is based solely on observational data, and the proposed underlying mechanisms remain to be validated by future studies. On the other hand, the findings of a recent in vivo study in diabetic mice indicate that rosuvastatin, a new 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, has a favorable effect on diabetic neuropathy that is independent of its cholesterol-lowering effect and may be associated with the restoration of the vasa nervorum.[19]

The main limitation of the present report is its retrospective and anecdotal nature. Given the widespread use of statins, it is also possible that the appearance of symptoms in the reported cases was by chance association alone. However, the present 4 cases were identified from a series of 38 patients who were referred to our outpatient neuromuscular clinic because of persistent muscular symptoms or excessive elevation of serum CK levels that developed during statin therapy and did not resolve following statin discontinuation over a 5-year period (January 2000 to January 2005). Although the prevalence of underlying neuromuscular disorders (4/38; 10%) in the former case series is slightly higher than the reported incidence of myotoxic reactions in patients treated with statins (1%-7%),[1,2] it can be argued that the data from this report may involve selection or referral bias because patients referred to a tertiary center are likely to be different from those treated by primary care physicians. Furthermore, it should be acknowledged that the limited number of cases prohibits any statistical analyses that could test the validity of the present clinical observation.

The second limitation of our study is related to the absence of baseline measurements of CK levels prior to the initiation of lipid-lowering treatment in cases 1 and 4. Hence, it may be postulated that CK levels were elevated before statin treatment and that the presenting muscular symptoms (myalgias, muscle stiffness, and muscle cramps) allegedly associated with statins simply revealed the underlying problem. However, it should be noted that in the remaining 2 cases, pretreatment CK levels were within the normal range, while in all the reported cases, no regression of symptoms was noticed several months following statin discontinuation. Moreover, CK values remained above the normal limits at numerous measurements. Interestingly, Hansen et al,[20] after having evaluated the clinical course and outcome in 45 patients with statin-associated myopathy, recently reported that all patients experienced full resolution of muscle pain and other clinical symptoms after cessation of statin therapy (mean period of recovery, 2.3 months; range, 0.25-14 months). These findings when combined with the observations of our group and other investigators[3-5] imply that the resolution of muscular symptoms after statin discontinuation (which may also be followed by substantial reduction of increased CK levels) could assist the clinician to differentiate statin-associated myopathy from a latent neuromuscular disorder that was potentially disclosed by the intake of 3-hydroxy-3-methylglutaryl coenzyme A inhibitors.

It is currently recommended that patients with symptoms of muscle discomfort associated with CK level elevations that persist after discontinuation of statin treatment should be evaluated for other conditions (hypothyroidism, polymyalgia rheumatica, and temporal arteritis) that may have been unmasked by lipid-lowering therapy.[1] We propose that the suspicion of a subclinical neuromuscular disorder should also be raised and that a diagnostic workup of persistent serum CK level elevation should also be performed in this specific patient subgroup. More specifically, the diagnostic approach to such cases should include a precise and accurate clinical history (family history of neuromuscular disorders or increased CK values, history of malignant hyperthermia, use of β-blockers, other lipid-lowering agents, or antipsychotic medications), and a careful and detailed neurologic examination (grading of muscle weakness, documentation of muscle atrophy or hypertrophy, fasciculations, and concomitant cardiac disorders). Ancillary investigations should include evaluations of serum electrolytes, thyroid function, needle electromyography, post-ischemic lactate ammonia, blood lactate, urine amino acid, and organic acid levels. After common causes of increased CK levels are excluded, muscle biopsy and molecular genetic testing are the only tools able to establish the diagnosis of an underlying neuromuscular disorder.[21,22] It should also be kept in mind that measurement of α glucosidase activity in leucocytes or skin fibroblasts may disclose a latent acid maltase deficiency that may become symptomatic during statin treatment.[3,5] Finally, since asymptomatic CK elevations are common, the present clinical observation underscores the importance of the currently recommended pretreatment measurements of CK levels, which might be helpful in the diagnostic evaluation and optimal management of more complex cases with elevated serum CK levels and muscular symptoms.[23]

In conclusion, latent neuromuscular disorders can be disclosed by statin therapy in presymptomatic patients. Muscular symptoms and elevated serum CK levels persisting after statin treatment discontinuation should alert the clinician to pursue further diagnostic evaluations for the detection of potential underlying neuromuscular diseases.

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REFERENCES

1. Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. *JAMA*. 2003;289:1681-1690.
2. Rosenson RS. Current overview of statin-induced myopathy. *Am J Med*. 2004;116:408-416.
3. Livingstone C, Al Riyami S, Wilkins P, Ferns GA. McArdle's disease diagnosed following statin-induced myositis. *Ann Clin Biochem*. 2004;41:338-340.

4. Barth JH, Brownjohn AM, Jamieson DR. The case of stainless statins. *Ann Clin Biochem*. 2003; 40:576-577.
5. Voermans NC, Lammens M, Wevers RA, Hermus AR, van Engelen BG. Statin-disclosed acid maltase deficiency. *J Intern Med*. 2005;258:196-197.
6. Thompson PD, Zmuda JM, Domalik LJ, Zimet RJ, Staggers J, Guyton JR. Lovastatin increases exercise-induced skeletal muscle injury. *Metabolism*. 1997;46:1206-1210.
7. Flint OP, Masters BA, Gregg RE, Durham SK. Inhibition of cholesterol synthesis by squalene synthase inhibitors does not induce myotoxicity in vitro. *Toxicol Appl Pharmacol*. 1997;145:91-98.
8. Riegger G, Abletshauser C, Ludwig M, et al. The effect of fluvastatin on cardiac events in patients with symptomatic coronary artery disease during one year of treatment. *Atherosclerosis*. 1999;144:263-270.
9. De Pinieux G, Chariot P, Ammi-Said M, et al. Lipid-lowering drugs and mitochondrial function: effects of HMG-CoA reductase inhibitors on serum ubiquinone and blood lactate/pyruvate ratio. *Br J Clin Pharmacol*. 1996;42:333-337.
10. Ghirlanda G, Oradei A, Manto A, et al. Evidence of plasma CoQ10-lowering effect by HMG-CoA reductase inhibitors: a double-blind, placebo-controlled study. *J Clin Pharmacol*. 1993;33: 226-229.
11. Laaksonen R, Jokelainen K, Laakso J, et al. The effect of simvastatin treatment on natural antioxidants in low-density lipoproteins and high-energy phosphates and ubiquinone in skeletal muscle. *Am J Cardiol*. 1996;77:851-854.
12. Phillips PS, Haas RH, Bannykh S, et al; Scripps Mercy Clinical Research Center. Statin-associated myopathy with normal creatine kinase levels. *Ann Intern Med*. 2002;137:581-585.
13. Chariot P, Abadia R, Agnus D, Danan C, Charpentier C, Gherardi RK. Simvastatin-induced rhabdomyolysis followed by a MELAS syndrome. *Am J Med*. 1993;94:109-110.
14. Pierno S, De Luca A, Tricarico D, et al. Potential risk of myopathy by HMG-CoA reductase inhibitors: a comparison of pravastatin and simvastatin effects on membrane electrical properties of rat skeletal muscle fibers. *J Pharmacol Exp Ther*. 1995;275:1490-1496.
15. Sonoda Y, Gotow T, Kuriyama M, Nakahara K, Arimura K, Osame M. Electrical myotonia of rabbit skeletal muscles by HMG-CoA reductase inhibitors. *Muscle Nerve*. 1994;17:891-897.
16. Kwiecinski H. Myotonia induced with clofibrate in rats. *J Neurol*. 1978;219:107-116.
17. Backes JM, Howard PA. Association of HMG-CoA reductase inhibitors with neuropathy. *Ann Pharmacother*. 2003;37:274-278.
18. Chong PH, Boskovich A, Stevkovic N, Bartt RE. Statin-associated peripheral neuropathy: review of the literature. *Pharmacotherapy*. 2004;24: 1194-1203.
19. Ii M, Nishimura H, Kusano KF, et al. Neuronal nitric oxide synthase mediates statin-induced restoration of vasa nervorum and reversal of diabetic neuropathy. *Circulation*. 2005;112:93-102.
20. Hansen KE, Hildebrand JP, Ferguson EE, Stein JH. Outcomes in 45 patients with statin-associated myopathy. *Arch Intern Med*. 2005;165:2671-2676.
21. Reijneveld JC, Notermans NC, Linssen WH, Wokke JH. Benign prognosis in idiopathic hyper-CK-emia. *Muscle Nerve*. 2000;23:575-579.
22. Prelle A, Tancredi L, Sciacco M, et al. Retrospective study of a large population of patients with asymptomatic or minimally symptomatic raised serum creatine kinase levels. *J Neurol*. 2002; 249:305-311.
23. Pasternak RC, Smith SC Jr, Bairey-Merz CN, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *Stroke*. 2002;33:2337-2341.