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Underappreciated Statin-Induced Myopathic Weakness Causes Disability

Bruce H. Dobkin
From the University of California Los Angeles, Reed Neurologic Research Center

Abstract

Introduction—*Myopathic syndromes induced by 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) include muscle complaints, myalgia, myositis, and rhabdomyolysis. No prospective study of statins, however, included tests of strength, so the incidence of weakness, with or without muscle symptoms and elevated enzymes, is unknown, and perhaps overlooked.*

Methods—*From a convenience sample of patients referred to an outpatient neurorehabilitation clinic over the course of 1 year, 8 patients with hemiparetic stroke and 10 patients with other presumed neurologic diseases presented with new difficulty walking by 3 to 12 months after starting one of 3 statins. They reported no myalgias, exercise-induced aches, or weakness. Examination revealed proximal paresis graded 4/5 on the unaffected side in the hemiparetic patients and symmetrical bilateral proximal limb and neck flexor weakness graded 4/5 in the others. They stood up with difficulty and walked with bilateral hip drop and imbalance on turns.*

Results—*Laboratory tests did not reveal myositis or other causes for paresis. No improvement in strength or mobility was found 6 weeks after initiating resistance exercises. The statin agent was stopped. By 3 months off statin, all recovered 5/5 proximal strength. Walking improved, and they arose from a chair without pushing off with their arms.*

Discussion—*Serial manual muscle testing after initiating a statin may detect a reversible cause of disability. A genetic predisposition to statin-induced myopathic proximal weakness with normal creatine kinase is consistent with a continuum of previously reported symptoms and signs but may be underappreciated.*

Keywords

Statin; myopathy; stroke; disability

Few contraindications to the use of the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) for primary or secondary prevention of coronary artery disease and atherothrombotic stroke have been found, even in the elderly.[1] Four statin-induced myopathic syndromes were described by a clinical advisory on drug use and safety: any muscle-related complaints, myalgia without raised creatine phosphokinase (CK),

Address correspondence to Bruce H. Dobkin, MD, Professor of Neurology, University of California Los Angeles, Reed Neurologic Research Center, 710 Westwood Plaza, Los Angeles, CA 90095. bdobkin@mednet.ucla.edu.

myositis with raised CK (less than 10 times normal), and rhabdomyolysis.[1] Myopathy, defined as a CK level greater than 10 times the upper limit of normal, is estimated to occur in 0.5% of patients treated with statins during clinical trials. Rhabdomyolysis was estimated in hospitalized patients at 0.45 for atorvastatin, pravastatin, or simvastatin, compared to 5.3 per 10,000 person-years for cerivastatin.[2] No prospective studies have included routine testing of muscle strength or muscle enzymes, however,[3,4] so the incidence of weakness, the sine qua non of a myopathy, may be underappreciated.

Methods

The investigator prospectively assessed patients for proximal muscle weakness who were taking a statin after finding several patients he had managed during inpatient stroke rehabilitation to have developed proximal weakness with a decline in walking that was reversed by discontinuing the statin. The patients were referred to his outpatient neurologic rehabilitation clinic over 12 months between 2003 and 2004. Eighteen subjects were identified. This highly selected convenience sample of patients referred for evaluation and management of disability in walking represented approximately 15% of those who took a statin.

All patients had laboratory tests that included a CK, aldolase, thyroid-stimulating hormone, hepatic transaminases, antinuclear antibody, and Westergren sedimentation rate. After a period of observation and with the approval of their primary care physicians, the patients discontinued their statin and were reexamined monthly for 3 months with manual muscle testing using the British Medical Council scale.

Results

Subjects

Table 1 lists the characteristics of this group. Until specifically asked about gradual changes in routine activities, the patients had paid little notice to a decline in distances walked, difficulty arising from a toilet or car seat, and mild fatigue during shopping or climbing stairs. Unsteadiness in walking, especially on uneven surfaces or on changing direction, was the most common complaint. They usually could not pinpoint the onset, but their history of daily activities suggested functional changes by 6 months after the 1st use of a statin. The patients and their physicians did not suspect muscle weakness. They attributed symptoms to complications of chronic or recent neurological disorders (last column, Table 1). Indeed, none of these patients acknowledged any loss of strength until the neurological examination demonstrated this. All but 2 routinely exercised. No patient complained of generalized arthralgias, myalgias, or muscle fatigability with repetitive use. Several reported mild aches after an unusual amount of exercise. Six of the patients had an atherothrombotic stroke with hemiparesis and had been evaluated by the investigator during inpatient and after 6 weeks of outpatient rehabilitation. They started a statin during the inpatient stay. No paresis of the unaffected limbs had been found. They returned because of greater difficulty walking from 6 to 12 months after starting the statin.

Evaluations

Strength in the 6 patients with prior stroke and who had been previously examined revealed new paresis of the affected hip flexors and gluteal muscle groups, along with new proximal weakness on the unaffected side. This weakness was similar to that of all the other subjects, graded 4/5 in the deltoids, supraspinatus, biceps, and triceps, and 4/5 in the neck flexors, iliopsoas tested with the patient supine, and gluteal hip extensors and hamstrings knee flexors tested with the patient prone. Distal groups were 5/5. Sensation to pinprick and proprioception and deep tendon reflexes were normal, except for the subjects with stroke or a myelopathy, who had expected hyperreflexia. Most subjects stood from a chair by pushing off with their arms, bending forward and straightening slowly from the hips and knees. Twelve had a mild to moderate waddle from bilateral hip drop when walking. Electromyography revealed a modest number of myopathic units and no insertional irritability or sharps waves in the 4 tested.

Laboratory tests obtained at the 1st visit were in the normal range, with the exception of 1 subject who had a raised CK (50% above the laboratory's norm). In retrospect, the elevation had been present for all 4 years of statin use. His physician believed this was of no consequence. Only 1 subject took a drug that shares its metabolism with the cytochrome P-450 system (warfarin), which has been associated with myositis or rhabdomyolysis in combination with statin use.[5]

Examination 4 to 6 weeks after discontinuing a statin revealed modest or no clear change in strength or function. By 8 to 16 weeks, the examiner could no longer overcome the resistance of patients' neck flexors and proximal limb groups, except for the hemiparetic side in those with stroke, although strength here did improve. Handheld digital dynamometry (Lafayette Inc, Lafayette, IN) of the neck flexors, deltoid, and knee and hip flexors revealed a 20% to 40% increase in voluntary force between baseline and 3 months after discontinuation in 8 subjects so tested. Waddling or shuffling gait with short stride length was eliminated in all. Six patients with stroke and 1 who also had a subdural hematoma after repeated falls had walked especially slow, 50 feet in 17 to 40 seconds. When their strength recovered, they walked that distance in 13 to 19 seconds.

Four recovered subjects returned for a reevaluation having restarted a different statin, but they did not inform the investigator until he found a recurrence of proximal weakness. This decline in strength occurred by 2 to 6 weeks after restarting their statin and recovered by 4 weeks off the drug. Two subjects with coronary artery disease restarted a low dose of the same statin 3 days a week, which kept their total cholesterol level below 180 mg/dL. They developed mild gluteal weakness after a few weeks and then a recurrence of a more disabling proximal myopathy by 3 months. This resolved again upon stopping their statin. Other patients were placed on ezetimibe without inducing paresis. Five subjects did not meet clear criteria for needing a statin agent and remained off the drug.

Discussion

Over the course of assessing patients in a weekly outpatient neurologic rehabilitation clinic, then reexamining those subjects suspected of having a statin-associated myopathy, a likely

causal relationship between disabling myopathy and the use of statins was found. Although a single-subject, double-blinded statin versus placebo test-retest design would make this association more concrete, it is of interest that recurrences were detected at times when the investigator was unaware that some of the subjects had been restarted on a statin by their primary physicians.

The 50,000 participants in 6 large randomized clinical trials of statins were monitored prospectively for musculoskeletal symptoms, but not for muscle weakness.[6] A statin-induced myopathy may go unrecognized by clinicians who do not test muscle strength. Patients often do not have insight into slowly progressive walking and balance related functional decline, especially when already being treated for a medical problem that can affect gait. Changes in mobility may be discounted as part of normal aging, rather than due to weakness.

All of the statins have myotoxic potential, which has been most notable when combined with certain other medications, but the mechanism is uncertain. For example, the risk for rhabdomyolysis increases from 0.45 to 6.0 for combined therapy with atorvastatin, pravastatin, or simvastatin and a fibrate.[2] Older age and a high dose of statin compared to body mass may contribute to an elevation of the CK and myalgias.[1] The latter seems unlikely in the 18 subjects reported, because body weight was in the normal range for height.

Mechanisms for a myopathy or frank myositis induced by statins have been proposed. This class may alter small GTP (guanosine triphosphate) regulatory binding proteins necessary for myocyte function.[5] The negative effect of statins on selenoprotein synthesis was postulated to account for the myopathy and perhaps the 4 per 10,000 incidence of polyneuropathy.[7] Mitochondrial dysfunction has been suspected, but neither mitochondrial injury nor a decrease in muscle ubiquinone levels was confirmed in a study of statin-induced myositis in rats.[8] In another case series, 4 patients developed weakness and myalgias with normal CK after initiating a statin.[9] Muscle biopsies revealed the accumulation of lipid in type I fibers, and 1 had ragged red fibers that are typical of a mitochondrial myopathy. Symptoms and pathology resolved by 3 months after stopping the statin.

A wide variation in interindividual responses to statin therapy has been found. People who are heterozygous for a variant of the HMG-CoA reductase gene may have a significantly smaller benefit in lowering their cholesterol than homozygous patients.[10] Minor decrements in cognitive functions have been found over 6 months in some patients, which may suggest another genetic predisposition.[11] Differences in gene expression, activity, or drug binding may be the consequence of a polymorphism. Biochemical transformations along the many pathways that proceed beyond HMG-CoA to mevalonate could have an exceptional effect on a noncholesterol product that affects muscle. The spectrum of symptoms and signs of statin-induced myopathy suggest a continuum from myalgias to weakness to myositis to profound muscle injury that could be explained by a genetic predisposition.

Electromyography, muscle biopsy, and genetic studies are important for longitudinal and mechanistic evaluations, but these tests are not necessary for clinical diagnosis. Reliance on

a raised CK for diagnosis is not sufficient. It is, of course, not unusual for a myopathy to be present in the absence of a muscle enzyme leak in endocrine-opathies, critical illness myopathy, and in inclusion body and mitochondrial diseases, for example. Simply discontinuing the statin and reassessing strength and mobility for 2 to 4 months will allow attribution of weakness to the drug after a neuromedical evaluation determines the absence of other causes.

Clinical Implications

The Food and Drug Administration has approved at least a half-dozen statins for people who are at high risk for coronary events because of ongoing coronary heart disease, diabetes, peripheral vascular disease, and history of stroke. Statins have become a routine prescription for secondary prevention in patients after transient ischemic attack and stroke for their effects on lipids and possible antithrombogenic effects.[12] In this regard, statins even show experimental promise for neuroprotection and neural repair.[13] Simvastatin has been considered for over-the-counter use in Great Britain. As the use of statins grows, pre- and postmarketing surveillance for a myopathy that can only be diagnosed by manual muscle testing seems unlikely, given the time and expertise that is usually not available to physicians in family practice, internal medicine, and cardiology.

Neurologists, physiatrists, and physical therapists are in a unique position to detect bilateral myopathic weakness, if they perform diligent manual muscle testing during stroke rehabilitation and diagnostic evaluations for gait disturbances. Any decline in function of patients on statins should raise the possibility of statin-induced weakness, especially if symmetrical proximal paresis is found, even in the absence of elevated CK or myalgias. The best long-term approach to the management of myopathic proximal weakness versus the benefits of statins remains an individualized one.

Greater attention to this possibly underappreciated cause of disability is needed to determine the incidence, prevalence, mechanisms, potential for pharmacogenetic phenotyping of patients, and development of rescue agents.

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Table 1

Characteristics of a Convenience Sample of Subjects with Reversible Signs of a Stain-Induced Myopathy

Age/Sex	Statin, mg	Months on Drug	Symptoms; Duration	Associated Diseases
79/m	Atorvastatin, 20	12	Imbalance, shortened stride length; 8 months	Brainstem stroke, 1 year
74/m	Lovastatin, 40	18	Progressive gait instability and difficulty arising; 8 months	Prior vertebral artery occlusion, 18 months
70/m	Atorvastatin, 40	40	Retropulsion on arising and unsteady gait with falls; at least 2 years	Possible Parkinson's; stroke with mild hemiparesis; recent subdural hematoma
73/m	Atorvastatin, 40	16	Falls with unsteady gait especially on turns; 8 months	Prior hemiparetic stroke, 16 months
74/f	Pravastatin, 40	9	Decline in walking speed and balance; 3 months	Hemiparetic stroke, 9 months
75/f	Pravastatin, 20	16	Decline in walking speed and balance; 2 months	Hemiparetic stroke, 7 months
80/f	Pravastatin, 20	8	Falls, decline in walk, 4 months	Hemiparetic stroke, 8 months
67/f	Simvastatin, 40	48	Unable to walk safely after heart surgery; 1 year	Coronary bypass complicated by mild hemiparetic stroke, 1 year
64/m	Pravastatin, 20	18	Progressive gait instability and short stride length, 8–12 months	Chronic cervical myelopathy
52/m	Simvastatin, 20	14	Decline in balance and stride length, 6 months	Chronic central cervical spinal cord injury
73/f	Lovastatin, 40	20	Unsteady on golf course, 1 year	Polyneuropathy
74/m	Fluvastatin, 40	30	Falls, short stride length, 12 months	Treated without success for Parkinson's
80/m	Atorvastatin, 20	24	Shuffling gait with short stride length, 12 months	Sensory neuropathy
72/f	Pravastatin, 20	36	Imbalance	Diabetic neuropathy
61	Lovastatin, 20	50	Imbalance on turns and rising; 12 months	Cervical and lumbar fusions
56/m	Atorvastatin, 20	18	Imbalance and low back pain; 6– 12 months	Lumbar stenosis
61/f	Atorvastatin, 10	6	Imbalance; 3 months	Evaluation
58/f	Pravastatin, 20	18	Decline in stair climbing; 6 months	Evaluation