

## Neuromuscular Symptoms and Elevated Creatine Kinase after Statin Withdrawal

**TO THE EDITOR:** The main reported adverse effects of statins are various forms of myotoxicity, ranging from myalgias to rhabdomyolysis.<sup>1,2</sup> The occurrence of neuromuscular symptoms and elevated levels of creatine kinase that persist after the withdrawal of statin therapy is frequent, and there are no guidelines to help physicians determine whether such effects are the result of statin-related myotoxicity or an underlying neuromuscular disorder.<sup>3-5</sup>

Fifty-two consecutive patients (75% male, with a mean age of 54 years) with muscle weakness, myalgia, or both, along with elevated creatine kinase levels (mean, 1000 U per liter; normal, <200 U per liter) that had persisted for more than 3 months (mean duration, 6.5 months) after discontinuation of statin therapy were enrolled from a single center in this 5-year prospective study (see Table A in the Supplementary Appendix, available with the full text of this letter at NEJM.org). Cre-

atine kinase levels before the initiation of statin therapy were unknown in all patients.

In 47 of 52 patients (90%), clinical examination, results on electromyography, and findings on muscle biopsy were normal, and possible statin-induced myotoxicity was diagnosed, with a good clinical and biologic prognosis at the 6-month follow-up in the majority of patients (Table 1). Five patients (10%) presented with abnormalities on electromyography and pathological analysis and received the diagnoses of paraneoplastic polymyositis, amyotrophic lateral sclerosis, Kennedy's disease, muscle phosphorylase *b* kinase deficiency, and necrotic myopathy of uncertain cause (Table B in the Supplementary Appendix).

After adjustment for variables such as sex, the mean interval between statin withdrawal and neuromuscular evaluation, the type of statin, and the mean duration and dose of statin therapy, there was no significant difference between the two

**Table 1. Characteristics of the Patients after Withdrawal of Statin Therapy.\***

Variable	Patients with Possible Statin-Induced Myotoxicity (N=47)	Patients with an Underlying Neuromuscular Disorder (N=5)
Mean age (range) — yr	53 (22–86)	67 (60–82)
Male sex — no. (%)	34 (72)	5 (100)
Neuromuscular symptoms — no. (%)		
Myalgia	47 (100)	3 (60) †
Weakness	0	2 (40) †
Creatine kinase level >1000 U/liter — no. (%)	9 (19)	3 (60)
Mean interval between statin withdrawal and muscle biopsy — mo	6.8	5.5
Mean duration of statin therapy — mo	31	24
Findings on initial clinical examination — no. (%)		
Abnormal electromyogram	0	5 (100) †
Abnormal muscle biopsy	0	5 (100) †
Findings at 6-mo follow-up ‡		
No. of patients	36	4
Myalgia — no. (%)	11 (31)	
Creatine kinase level >200 U/liter — no. (%)	6 (17)	

\* Creatine kinase levels were compared with the use of a rank-sum test, and proportions were compared with the use of a z-test. The normal level for creatine kinase is under 200 U per liter.

† P<0.001.

‡ Among the five patients with an underlying neuromuscular disorder at 6 months, one was lost to follow-up, two had unchanged symptoms, one was undergoing treatment for cancer, and one had died.

groups of patients. In contrast, muscle weakness and abnormal electromyographic findings were associated with an increased risk of an underlying neuromuscular disease (muscle weakness: 0 of 47 patients vs. 2 of 5 patients,  $P < 0.001$ ; abnormal electromyographic findings: 0 of 47 patients vs. 5 of 5 patients,  $P < 0.001$ ). Patients with a neuromuscular disorder were older ( $>60$  years) and had a higher creatine kinase level ( $>1000$  U per liter) than those without such a disorder, although the differences between the two groups were not significant (Table 1).

Patients with neuromuscular symptoms and elevated creatine kinase levels that persist after statin withdrawal should be systematically evaluated for an underlying neuromuscular disease that may require appropriate treatment, especially if they present with muscle weakness, are older than 60 years of age, and have a creatine kinase level of more than 1000 U per liter. In our study, electromyography was an excellent screening test for whether a muscle biopsy was needed. In several patients, the measurement of creatine kinase before the initiation of statin therapy might have been helpful in making an earlier diagnosis of a neuromuscular disease.

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Contact the American Neurogastroenterology and Motility Society, 45685 Harmony Lane, Belleville, MI 48111; or see <http://www.motilitysociety.org>.

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