Commentary

Severe Vitamin D Deficiency, Myopathy, and Rhabdomyolysis

Charles J Glueck, Brandon Conrad

Cholesterol Center, Jewish Hospital of Cincinnati, Cincinnati, Ohio, USA

Address for correspondence: Dr. Charles J Glueck, Cholesterol Center, Jewish Hospital, 2135 Dana Ave, Suite 430, Cincinnati 45207, USA.
E-mail: cjglueck@health-partners.org

In the report by Rasheed *et al*.,[1] a 33-year-old female developed proximal myopathy and rhabdomyolysis associated with very low serum 25 (OH) vitamin D (4 ng/mL, laboratory lower normal limit 31 ng/mL). Rasheed *et al*.,[1] noted that serum 25 (OH) vitamin D levels <20 ng/mL can cause increased body sway, while <10 can lead to inability to rise from a chair, or ascend stairs, coupled with muscle pain.

We have recently assessed exercise-induced severe rhabdomyolysis in a thin, athletic, dark-skinned (Meztizo), highly conditioned, nondiabetic young man, occurring in the setting of a 5 K race. He was subsequently found to have severe 25 (OH) vitamin D deficiency (6 ng/mL). Rhabdomyolysis, myoglobinemia, and even mild renal failure can occur as sequelae of marathon races, military recruit training, strength training, and endurance athletics.[2] Often this muscle damage resolves without incident or treatment and may be detected only upon laboratory testing.[2] We speculate that subjects with preexisting low serum 25 (OH) vitamin D are selected out for exertional rhabdomyolysis during strenuous activities. In subjects not receiving statins, low serum 25 (OH) D levels have been associated with myositi[3] and reduced muscle function.[4] Vitamin D may improve muscle strength through a highly specific nuclear receptor in muscle tissue.[5] Serum 25 (OH) D is related to physical performance.[6]

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Since myositis-myalgia is the major cause of statin intolerance,[7] and the tripartite association of serum 25 (OH) vitamin D deficiency, statins, and myositis-myalgia has physiologic plausibility,[3,4,6,8,9] resolution of vitamin D deficiency interacting with statins to produce myositis-myalgia would have significant clinical importance, allowing reinstitution of statins to optimize low-density lipoprotein (LDL) cholesterol and prevent cardiovascular disease (CVD). Recently, we prospectively studied 150 hypercholesterolemic patients, unable to tolerate ≥1 statin because of myositis-myalgia, selected by low (<32 ng/mL) serum 25 (OH) vitamin D.[10] On no statins, 50,000 units of vitamin D was given twice a week for 3 weeks and then continued once a week. After 3 weeks on vitamin D, statins were restarted. On vitamin D supplementation plus reinstituted statins for a median of 8.1 months, 131 of 150 patients (87%) were free of myositis-myalgia and tolerated reinstituted statins well. Serum 25 (OH) vitamin D increased from median 21 to 40 ng/mL ($P < 0.001$), and normalized (≥32 ng/mL) in 117 (78%) of 150 previously vitamin D deficient, statin-intolerant patients. Median LDL cholesterol decreased from 146 to 95 mg/dL, $P < 0.001$. We concluded[10] that symptomatic myositis-myalgia in hypercholesterolemic statin-treated patients with concurrent serum 25 (OH) vitamin D deficiency may reflect a reversible interaction between vitamin D deficiency and statins on skeletal muscle causing myalgia.

We believe vitamin D deficiency places subjects at higher risk for rhabdomyolysis, which develops during severe exertion. We suggest that when exercise-induced rhabdomyolysis develops, after full recovery and back at normal nutrition, serum 25OH vitamin D be measured. We suggest that when very low vitamin D is documented, it be normalized before major prolonged exertion. We hypothesize that normalization of vitamin D before heavy exertion could perhaps prevent severe

muscle damage events and sequelae, which may occur in previously asymptomatic athletes.

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