Low serum 25 (OH) vitamin D levels (<32 ng/mL) are associated with reversible myositis-myalgia in statin-treated patients

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Our specific aims were to determine whether low serum 25 (OH) vitamin D (D2 + D3) (<32 ng/mL) was associated with myalgia in statin-treated patients and whether the myalgia could be reversed by vitamin D supplementation while continuing statins. After excluding subjects who took corticosteroids or supplemental vitamin D, serum 25 (OH) D was measured in 621 statin-treated patients, which consisted of 128 patients with myalgia at entry and 493 asymptomatic patients. The 128 myalgic patients had lower mean ± standard deviation (SD) serum vitamin D than the 493 asymptomatic patients (28.6 ± 13.2 vs 34.2 ± 13.8 ng/mL, P < 0.0001), but they did not differ (p > 0.05) by age, body mass index (BMI), type 2 diabetes, or creatine kinase levels. By analysis of variance, which was adjusted for race, sex, and age, the least square mean (± standard error [SE]) serum vitamin D was lower in the 128 patients with myalgia than in the 493 asymptomatic patients (28.7 ± 1.2 vs 34.3 ± 0.6 ng/mL, P < 0.0001). Serum 25 (OH) D was low in 82 of 128 (64%) patients with myalgia versus 214 of 493 (43%) asymptomatic patients (χ² = 17.4, P < 0.0001). Of the 82 vitamin-D–deficient, myalgic patients, while continuing statins, 38 were given vitamin D (50,000 units/week for 12 weeks), with a resultant increase in serum vitamin D from 20.4 ± 7.3 to 48.2 ± 17.9 ng/mL (P < 0.0001) and resolution of myalgia in 35 (92%).

We speculate that symptomatic myalgia in statin-treated patients with concurrent vitamin D deficiency may reflect a reversible interaction between vitamin D deficiency and statins on skeletal muscle. (Translational Research 2009;153:11–16)

Abbreviations: BMI = body mass index; CK = creatine kinase

Vitamin D deficiency or insufficiency is becoming more widespread in diverse clinical populations in variegated settings and environments. Low serum 25 (OH) vitamin D levels have been associated with myositis. Erkal et al reported a strong correlation between low serum 25 (OH) D levels and higher rates and longer duration of generalized bone pain and/or muscle aches and pains (often diagnosed as fibromyalgia). Bischoff-Ferrari al have reported that vitamin D may improve muscle strength through a highly specific nuclear receptor in muscle tissue. Lips reported that muscle cells contain vitamin D receptors and noted that serum 25 (OH) D is related to physical performance. Hypovitaminosis D is highly prevalent in adults with type 2 diabetes.

Mild clinical muscle problems (myositis-myalgia) are common in subjects treated with statins. In a retrospective analysis of members of a health maintenance organization, which included 10,247 patients with diabetes and 21,978 patients without diabetes, Nichols and Koro employed National Heart, Lung, and Blood Institute categories for clinical muscle problems: myalgia, mild myositis, severe myositis, and rhabdomyolysis. A
Risk significantly associated with statin monotherapy (relative risk 10 times the laboratory upper normal limit, is significantly associated with myalgia with creatine kinase (CK) more than 5.5 times the laboratory normal limit). Although uncommon, severe myositis, which is also called myopathy with CK elevation, is also associated with statin monotherapy. Low serum vitamin D levels are associated with myalgia in statin-treated patients; while continuing statins, this myalgia can largely be reversed by vitamin D supplementation that normalizes serum vitamin D levels. We speculate that vitamin D deficiency reversibly augments statin-induced myalgias.

MATERIALS AND METHODS

Study design: patients. The study conformed to the ethical guidelines of the Jewish Hospital Institutional Review Board for human research. From May 2007 to May 2008, in the temporal order of their referral to our outpatient Cholesterol Center for diagnosis and therapy of hyperlipidemia, serum 25 (OH) vitamin D (D2 + D3) (≤32 ng/mL) was measured in 687 statin-treated patients, 140 of whom had myositis-myalgia at study entry and 547 patients were asymptomatic. After excluding subjects who were taking corticosteroids or supplemental vitamin D, or who had comorbidities that would result in muscle or bone pain (fibromyalgia, arthritis, peripheral vascular disease, and sensory neuropathy), we studied 621 statin-treated patients, of whom 128 had symptomatic myositis-myalgia and 493 were asymptomatic at study entry.

At the initial visit, after an overnight fast, blood was drawn for a total of 25 (OH) vitamin D levels (D2 + D3), quantitated by 2-dimensional liquid chromatography with tandem mass spectrometry detection after protein precipitation. The laboratory lower normal limit for total 25 (OH) vitamin D was 32 ng/mL. Additional measures included plasma cholesterol, triglyceride, and high-density lipoprotein cholesterol, along with CK, glucose, and insulin testing, as well as renal, thyroid, and liver function tests.

At the initial and follow-up visits, a detailed history was obtained for statin, prescription drug, and supplemental vitamin use. Patients were instructed not to take supplemental vitamins, and, where initial serum vitamin D was low, and when myalgia was present, were given a prescription to take 50,000 units of vitamin D (ergocalciferol) once per week for 12 weeks. Most patients were continued during follow-up on the same statins that they had been taking at study entry.

At the initial visit and at every follow-up visit, patients were interviewed by the principal investigators, who employed National Heart, Lung, and Blood Institute categories for clinical muscle problems: myalgia, mild myositis, severe myositis, and rhabdomyolysis. The distinction between myalgia and nonmyalgic groups is necessarily imprecise; it is based entirely on subjective reports. In the current study, at entry, we characterized the most severe myositis-myalgias as those that had caused patients to discontinue more than 3 different statins.

In all, 38 statin-treated patients with myalgia and low serum vitamin D at study entry had follow-up visits for 3 months on statins plus vitamin D (50,000 units/week for 12 weeks). We prospectively assessed changes in their myositis-myalgia symptoms and serum vitamin D levels. Adherence to the weekly vitamin D (50,000 units/week) was reviewed by the investigators at each follow-up visit (1 and 3 months after study entry).

Statistical analyses. All statistical analyses were performed using SAS (version 9.1; SAS Institute, Inc., Cary, NC). Sample size calculations were based on population studies of serum vitamin D and assessments of optimal serum vitamin D levels, using an estimate of mean ± standard deviation (SD) serum vitamin D of 28 ± 10 ng/mL for statin-using patients with myositis-myalgia, and 35 ± 10 ng/mL for asymptomatic statin-using patients. With alpha = 0.05 and power = 0.8, 34 statin-using patients with myositis-myalgia and 34 asymptomatic statin-using patients would be required to detect differences in serum 25 (OH) vitamin D levels.
Comparisons of categorical variables were performed by $X^2$ tests, the Fisher exact tests, or Mantel-Haenszel $X^2$ tests. Comparisons of numerical variables were done using nonparametric Wilcoxon tests. An analysis of variance was used to compare least square mean serum vitamin D in patients with and without entry myositis-myalgia, after covariance adjusting for age, sex, and race. Changes in serum vitamin D after 3 months of supplementation with vitamin D (50,000 units/week) in 38 symptomatic statin users with low serum vitamin D at entry were compared using nonparametric-paired Wilcoxon tests.

**RESULTS**

We studied 621 statin-treated patients, which consisted of 128 patients with myalgia at study entry and 493 asymptomatic patients. These patients were categorized by low serum 25 OH D ($<$32 ng/mL), and subsequent treatment with vitamin D supplementation in 38 myalgic, vitamin-D–deficient patients while continuing statin therapy (Figs 1 and 2, Tables I–III). All 621 patients had normal thyroid-stimulating hormone and thyroxine.14

The 128 symptomatic and 493 asymptomatic statin-taking patients did not differ ($P > 0.1$) at study entry by age, body mass index (BMI), type 2 diabetes mellitus, or high CK, but more nonwhites (12% vs 5%, $P = .012$) and women (59% vs 44%, $P = 0.0025$) were present in the symptomatic than in the asymptomatic group (Table I). Of the 128 symptomatic statin-taking patients, 3 had developed myositis-myalgia that caused discontinuation of more than 3 statins prior to referral to our center.

At study entry, the distribution of serum vitamin D was shifted to lower levels in the 128 patients with myalgia versus the 493 asymptomatic patients (Fig 2). The mean serum vitamin D was lower in the 128 patients with myalgia than in the 493 asymptomatic patients (28.6 ± 13.2 vs 34.2 ± 13.8 ng/mL, $P < 0.0001$; Fig 1, Table II). By analysis of variance, which was adjusted for race, sex, and age, the least square mean ± standard error (SE) serum vitamin D was lower in the myalgia group than in the asymptomatic group (28.7 ± 1.2 vs...
34.3 ± 0.6 ng/mL; \( P < 0.0001 \); Table II). When the serum vitamin D distribution was examined categorically, the myalgia group was overrepresented in the lower end of the distribution, and the asymptomatic group was overrepresented in the upper end of the distribution (Mantel-Haenszel \( \chi^2 = 16.9, P < 0.0001 \); Table II). In all, 64% of the 128 patients with myalgia had low vitamin D versus 43% of the 493 asymptomatic patients (\( \chi^2 = 17.4; P < 0.0001 \); Table I).

Vitamin D supplementation was given only to patients who had myalgia symptoms and vitamin D levels less than 32 ng/mL, and it was not given to the 46 symptomatic patients who had normal entry serum vitamin D levels (Fig 1). Of the 82 myalgic, vitamin-D–deficient patients, 38 received 50,000 units vitamin D per week for 12 weeks, 8 had just started vitamin D therapy, 22 had only 1 visit without follow-up, and 14 were currently untreated (Fig 1). The 38 patients did not differ (\( P > 0.05 \)) from the 44 patients by entry vitamin D levels (20.4 ± 7.3 vs 21.1 ± 7.0 ng/mL), by age (60 ± 12 vs 58 ± 12 years), by CK (165 ± 153 vs 125 ± 98 IU/L), or by BMI (31.1 ± 5.8 vs 31.1 ± 10.6 kg/m\(^2\)). The 38- and 44-patient groups also did not differ by sex (45% male vs 41% male), but they did differ by race, with more nonwhite patients in vitamin D treatment group (29% vs 5%, \( P = 0.0026 \)).

After 3 months follow-up on vitamin D in the 38 myalgic, vitamin-D–deficient, statin-treated patients, mean ± SD serum vitamin D increased from 20.4 ± 7.3 to 48.2 ± 17.9 ng/mL (\( P < 0.0001 \)), and 35 patients (92%) had become free of myalgia (Table III).

In the 38 symptomatic statin-treated patients with low entry vitamin D who subsequently received vitamin D supplementation, the most frequently used statins were rosvastatin at entry and continued (n = 10), atorvastatin at entry then switched to rosvastatin (n = 7), atorvastatin at entry and then continued (n = 4), and pravastatin at entry and then continued (n = 2).

By investigator interview, adherence to the weekly regimen of 50,000 units of vitamin D per week was excellent, with no patients recording missed doses. No side effects attributable to the vitamin D therapy were reported.

**DISCUSSION**

The current report revealed that patients with statin-induced myalgias had lower serum vitamin D levels than statin-treated patients without myalgias. Low serum 25 (OH) vitamin D (D2 + D3) is associated with myalgia in statin-treated patients and, while continuing statins, this myalgia can largely be reversed by vitamin D supplementation which normalizes serum vitamin D levels. We speculate that vitamin D deficiency reversibly augments statin-induced myalgias.
In the current study, the symptomatic (myositis-myalgia) and asymptomatic groups did not differ in variables that can affect serum 25 (OH) vitamin D levels, which include age, BMI, type 2 diabetes, and by selection, exogenous vitamin D, or corticosteroid use. More women (59% vs 44%) and more nonwhites (12% vs 5%) were in the myalgia group than in the asymptomatic group. Statin-treated females seem to have more myopathy than males. This result perhaps is related to lower female exposure to sun, which results in more common vitamin D deficiency. African Americans are much more likely than Caucasians to have vitamin D deficiency, which is related to decreased efficacy of vitamin D production by darker pigmented skin. Low serum vitamin D levels are very common; in this study, lower levels are found in 43% of 493 asymptomatic patients. This result provides a broad base for potential interactions with commonly used statins to facilitate development of myositis-myalgia.

In the current report, vitamin D supplementation that normalized serum vitamin D levels was concurrently associated with resolution of myalgias in 35 of 38 (92%) statin-treated patients with myalgia and low pretreatment serum vitamin D levels. We speculate that statins and vitamin D deficiency interact additively or synergistically on the muscle to produce myalgia that is reversible by vitamin D supplementation, while continuing statin therapy.

Low 25 (OH) vitamin D levels have been associated with myositis-myalgia and reduced muscle function. A case report of reversible muscle weakness in a patient with vitamin D deficiency has been published. The association of vitamin D deficiency, statin use, and myopathy has been commented on in a case report. Vitamin D may improve muscle strength through a highly specific nuclear receptor in muscle tissue. In healthy elderly subjects, 25 (OH) vitamin D levels are related to physical performance.

The pathoetiology of statin-induced myalgia-myopathy is not well understood, but common polymorphic variants within $SLCO1B1$ on chromosome 12 are strongly associated with an increased risk of statin-induced myopathy, perhaps by increasing statin blood levels. Although 95% of statin-associated clinical events involve myalgia or mild myositis, myalgic symptoms are often enough to cause the patients to stop statin therapy. We speculate that symptomatic myositis-myalgia in statin-treated patients may reflect a potentially reversible interaction in muscle between 25 (OH) vitamin D deficiency and statins, which individually are commonly associated with mild myositis-myalgia.

A limitation of our and other studies of myositis-myalgia lies in reliance on patients’ subjective reports of muscle symptoms. Our study was also limited by not having a matched, blinded, vitamin-D-deficient

| Table II. Distribution of serum vitamin D levels in 621 hypercholesterolemic patients taking statins: 128 patients with symptomatic myalgias-myositis and 493 asymptomatic patients at study entry |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Serum Vitamin D (ng/mL) | Mean ± SD | Adjusted Mean ± SE | Adjusted* | p-Value | Wilcoxon test | ANOVA | p-Value | Mantel-Haenszel X² | p-Value |
| Myalgia (n = 128) | 28.6 ± 13.2 | 34.2 ± 13.8 | 28.2 ± 1.2 | 34.2 ± 0.6 | ANOVA | p < 0.0001 | 0.0025 | 5.15, p = 0.0241 |
| Asymptomatic (n = 493) | 34.2 ± 13.8 | 34.2 ± 13.8 | 34.2 ± 0.6 | 34.2 ± 0.6 | ANOVA | p < 0.0001 | 0.0025 | 5.15, p = 0.0241 |

*Adjusted for race, gender, and age.
control group with previous myositis-myalgia on statins, continuing statins, given a vitamin D placebo, and by the absence of a second matched, blinded, vitamin-D–deficient control group with previous myositis-myalgia on statins, given a statin placebo, and vitamin D treatment. The lack of blinding in the current study is an important issue, especially in the context of subjective reports of symptomatic myositis-myalgia. Future double blind, placebo-controlled studies of statin-taking patients with low serum vitamin D and symptomatic myositis-myalgia will be needed to confirm our current observations, which suggest that in vitamin-D–deficient, statin-taking patients with myalgia, vitamin D supplementation that normalizes serum vitamin D is associated with resolution of myalgia in 92% of patients.

**Speculations.** Symptomatic myositis-myalgia in statin-treated patients may reflect a potentially reversible additive or synergistic interaction in muscle between 25 (OH) vitamin D deficiency and statins, which individually are commonly associated with mild myositis-myalgia. Normalization of low serum 25 (OH) D by oral vitamin D largely reverses myositis-myalgia, which otherwise might cause statin intolerance.

### REFERENCES

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