Symptomatic myositis–myalgia in hypercholesterolemic statin-treated patients with concurrent vitamin D deficiency leading to statin intolerance may reflect a reversible interaction between vitamin D deficiency and statins on skeletal muscle

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Abstract
Myositis–myalgia is the most common cause of statin intolerance, leading to cessation of statin use, with consequent failure to lower LDL cholesterol to target levels for primary and secondary prevention of cardiovascular disease (CVD). We hypothesize that symptomatic myositis–myalgia in hypercholesterolemic statin-treated patients with concurrent 25 (OH) vitamin D deficiency and statin intolerance may reflect a reversible interaction between vitamin D deficiency and statins on skeletal muscle. In hypercholesterolemic, vitamin D deficient patients, intolerant to statins because of myositis–myalgia, three non-blinded clinical case series have uniformly demonstrated that after supplementation with oral vitamin D2 which normalizes serum 25 (OH) vitamin D levels, statins can be successfully re-instituted in >90% of patients, without recurrent myositis–myalgia, with reduction of LDL cholesterol to target levels. Empirically, in 68 hypercholesterolemic patients, unable to tolerate >1 statin because of myositis–myalgia, selected by low (<32 ng/ml) serum 25 (OH) vitamin D, we have prospectively assessed whether resolution of vitamin D deficiency would result in statin tolerance, free of myositis–myalgia. On no statins, 50,000 units of vitamin D2 was given twice/week for 3 weeks, and was then continued once/week. After 3 weeks on vitamin D supplementation, statins were restarted, and patients were re-assessed after 3 months on statins while continuing vitamin D supplementation. At 3 months follow-up, on vitamin D supplementation and re-instituted statins, 62 of 68 (91%) previously statin-intolerant patients now tolerated statins well and were asymptomatic without myositis–myalgia. In these 68 patients, on vitamin D supplementation and statins, mean ± SD vitamin D rose from 22 ± 7 to 43 ± 13 ng/ml (p < 0.0001), and LDL cholesterol fell from 162 ± 55 to 101 ± 35 mg/dl (p < 0.0001). Despite published and new empirical evidence, the medical establishment has refused to accept the hypothesis, requiring placebo-controlled, double-blind studies, none having been reported to date. A placebo-controlled, double-blind study is needed to document that normalization of serum 25 (OH) vitamin D levels in vitamin D deficient, statin intolerant patients would facilitate re-introduction of statins with concurrent freedom from myositis–myalgia. The ability to reverse myositis–myalgia in vitamin D deficient, statin intolerant, hypercholesterolemic patients by vitamin D supplementation would be extraordinarily valuable, facilitating reinstitution of statins to lower LDL cholesterol to reduce risk of CVD events. We hypothesize that symptomatic myositis–myalgia in hypercholesterolemic statin-treated patients with concurrent vitamin D deficiency producing statin intolerance may reflect a reversible interaction between vitamin D deficiency and statins on skeletal muscle.

Introduction/background
Although statins are usually well tolerated, muscle symptoms, ranging from mild myalgia to rhabdomyolysis are important side effects and a leading cause of statin intolerance [1–8]. There have been three small non-blinded studies which have reported resolution of statin-induced myositis–myalgia by correcting serum 25 (OH) vitamin D deficiency [5,7,9]. Ahmed et al. [7] recently reported resolution of myalgia in 92% of statin intolerant, vitamin D deficient patients after vitamin D supplementation, and hypothesized 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. Duell et al. [10] reported that 64% of statin-taking patients with myalgia had low serum 25 (OH) vitamin D versus 43% of symptom-free patients. To optimally document that correcting serum 25 (OH) vitamin D deficiency in statin-intolerant patients...
with myositis-myalgia would restore statin tolerance, placebo-controlled, double-blind studies are necessary [11,12].

Vitamin D deficiency [13] is very common [14–16] in diverse populations, especially in pigmented subjects [16,17], in diabetics [18], and is present in 9% of the pediatric population [19]. Serum 25 (OH) D tracks (maintains its rank order) over time in a fashion similar to blood pressure and serum lipids [20].

In subjects not receiving statins, low serum 25 (OH) D levels have been associated with myositis [21] and reduced muscle function [22–24]. Vitamin D may improve muscle strength through a highly specific nuclear receptor in muscle tissue [25]. Serum 25 (OH) D is related to physical performance [26,27].

Since myositis-myalgia is the major cause of statin intolerance [8], and the tripartite association of serum 25 (OH) vitamin D deficiency, statins, and myositis-myalgia has physiologic plausibility [21–28], resolution of vitamin D deficiency interacting with statins to produce myositis-myalgia would have significant clinical importance, allowing re-institution of statins to optimize LDL cholesterol and prevent CVD.

The hypothesis

Symptomatic myositis-myalgia in hypercholesterolemic statin-treated patients with concurrent serum 25 (OH) vitamin D deficiency leading to statin intolerance may reflect a reversible interaction between vitamin D deficiency and statins on skeletal muscle, Table 1. Reversible myalgia-myositis-myopathy, associated with prolonged statin half-life in the blood, has been reported in statin-intolerant patients who are hypothyroid [29], take macrolide antibiotics [30], or take cyclosporine [31], Table 1.

Data supporting the hypothesis have come from 3 small, uncontrolled, case series [5,7,9], but current thinking [11,12] has discounted the value of these non-blind studies, citing the requisite gold-standard need for placebo-controlled double-blind trials. However, patients with a history of statin-induced myositis-myalgia causing statin intolerance are very unlikely to consent to a double-blind trial in which half of the patients would get vitamin D supplementation and half a placebo, since the vitamin D deficient patients had previously stopped statins because of myositis-myalgia, despite the medical necessity to optimize LDL cholesterol.

Evaluation of the hypothesis

A double-blind, placebo-controlled study is the gold standard for evaluation of the hypothesis. Patients found to have serum 25 (OH) D levels < 32 ng/ml who had failed to tolerate ≥ 2 different statins because of statin-induced myositis-myalgia would be eligible for the study. Patients will be excluded who were taking corticosteroids or who had co-morbidities that would result in muscle or bone pain (diabetic neuropathy, osteomalacia, fibromyalgia, polymyalgia rheumatica, rheumatoid or other inflammatory arthritis, peripheral vascular disease, sensory neuropathy, hypothyroidism), or who had baseline hypercalcemia, hyperparathyroidism, renal failure, were taking immune suppressant drugs, or had sarcoidosis, multiple myeloma, or cancer.

Sample size and power calculations would be based on our recent study [7] of 38 vitamin D deficient, statin intolerant patients with myositis-myalgia, 35 (92%) of whom successfully resumed statins without myositis-myalgia after supplementation with 50,000 units of vitamin D/week for 3 months. With alpha = 0.05 and power = 0.8, at least 63 vitamin D deficient, statin-using patients with myositis-myalgia would need to be studied to demonstrate that ≥ 80% of patients would become statin tolerant after 3 months on vitamin D supplementation. Assuming that at least 50% of patients would drop out of a double-blind, placebo controlled study because of recurrent myositis-myalgia (predominantly in the placebo group), 126 patients should be selected for the double-blind study. However, development of myositis-myalgia severe enough to cause the patient to stop Crestor is a study endpoint-outcome, so that the sample size of 126 should be more than adequate to test the hypothesis.

Because development of myositis-myalgia might differ by gender (more common in women) and race (more common in African-Americans), stratified double-blind randomization should be used assigning patients to the vitamin D and placebo groups. Half the patients would be randomized to receive vitamin D2 supplementation (50,000 units twice per week for 3 weeks, then 50,000 units once per week thereafter) and half placebo. After 3 weeks, Crestor 20 mg would be started in all patients to remove the variance that might occur with differing statins.

The nature of the muscle symptoms which had led to statin discontinuation would be documented at entry by history, and at each of the monthly outpatient follow-up visits using standardized descriptive categories for clinical muscle problems: myalgia, mild myositis, severe myositis, and rhabdomyolysis [2]. The distinction between myalgia and non-myalgic groups is necessarily imprecise, based entirely on subjective reports [2], and CPK levels, particularly when they are less than 10 times the laboratory upper normal limit, do not regularly facilitate distinction between myositis-myalgia and non myositis-myalgia [7]. To obtain quantitative data on muscle performance, handgrip, elbow and knee isometric and isokinetic strength, knee extensor endurance, and maximal aerobic exercise performance would be determined at study entry and at each monthly visit.

At the initial visit, after an overnight fast, blood would be drawn for serum total 25 (OH) vitamin D levels (D2 + D3), quantitated by two-dimensional liquid chromatography (HPLC) with tandem mass spectrometry detection after protein precipitation [32]. The laboratory lower normal limit for serum total 25 (OH) vitamin D by this method is 32 ng/ml [32]. Additional measures would include complete blood count, fasting plasma cholesterol, triglyceride, HDL cholesterol and LDL cholesterol, calcium, phosphorous, CPK, glucose, insulin, and renal, thyroid, and liver function tests.

At initial and monthly follow-up visits detailed history would be obtained for statin and other prescription drug use, and fasting

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**Table 1**

Causes of reversible myalgia-myositis in patients receiving statins.

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Intervention</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D deficiency</td>
<td>Hypothetical: Interaction with statin on vitamin D deficient skeletal muscle fibers</td>
<td>Vitamin D supplementation normalizes serum vitamin D</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Prolongs statin half-life in blood</td>
<td>Correct hypothyroidism</td>
</tr>
<tr>
<td>Macrolide antibiotics</td>
<td>Prolongs statin half-life in blood</td>
<td>Stop macrolide antibiotics</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Prolongs statin half-life in blood (lovastatin, simvastatin, atorvastatin)</td>
<td>Use statins not cleared through the cytochrome P450 system (Lescol Crestor, or Pravastatin)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Statin tolerance restored</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Statin tolerance usually restored</td>
</tr>
</tbody>
</table>

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Consequences of the hypothesis and discussion

Since statin therapy significantly reduces CVD morbidity and mortality in both primary and secondary prevention trials [33], patients' failure to take statins because of statin-induced myositis-myalgia directly increases their risk for CVD morbidity and mortality. A placebo-controlled, double-blind trial should provide gold-standard [11,12] proof for confirmation of the hypothesis of a reversible interaction of vitamin D-deficiency and statins in the development of myositis-myalgia. However, it would be difficult to recruit patients for a placebo-controlled, double-blind trial, because a requirement for study entry would be myositis-myalgia on >2 previous statin therapies severe enough to cause cessation of the statin. Half of the patients would get a vitamin D placebo, and all would get a statin, with the potential for half of the patients to again experience myositis-myalgia. A simple statin rechallenge after vitamin D supplementation shown to normalize serum 25 (OH) D has already been done by us [7] and others [5,9]. Confirmation of the hypothesis would also be important as a waypost on the journey to understand biochemical-molecular mechanisms of how statins induce myositis-myalgia.

Conflict of interest statement

None of the authors have any financial and personal relationships with other people or organizations which could inappropriately influence their work. This work was funded by the Lipoprotein Research Fund of the Jewish Hospital of Cincinnati. There were no sponsors.

References