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Impact of Vitamin D Status on Statin-Induced Myopathy

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ABSTRACT

Introduction: There is a multitude of evidence supporting the benefit of statin use in cardiovascular disease; however, statin-induced myopathy is a major reason for statin discontinuation and non-adherence. Vitamin D deficiency has been independently associated with muscle weakness and severe myopathy, and may be a confounder for statin-induced myopathies. Since there is no consensus on a treatment course of action for statin-induced myopathy, investigation into potential confounders to elucidate the dynamics of statin-induced myopathy is warranted.

Methods: A retrospective chart review was conducted on 105 patients in a cardiometabolic clinic with a vitamin D drawn from December 2006 to April 2008. Patients exposed to statins were divided into two groups: (1) patients with low vitamin D (<32 ng/mL) [n=52] and (2) patients with a sufficient vitamin D level (≥32 ng/mL) [n=32]. Data were compared via t-tests or Fisher's Exact, as appropriate.

Results: There were 41 statin-specific myopathies amongst the 24 statin-intolerant patients. Low vitamin D was significantly associated with statin-induced myopathy (p=0.048). Following prescription vitamin D supplementation, statin tolerance rates were significantly higher in patients with a baseline vitamin D ≤20 ng/mL than those with a baseline vitamin D >20 ng/mL (90% vs 33%; p=0.036).

Conclusion: Vitamin D status may be considered a modifiable risk factor for muscle-related adverse effects of statins, and supplementation of vitamin D (particularly when ≤20 ng/mL) may improve statin tolerance.

Low vitamin D serum concentration is a growing public health concern, even in regions with higher sun exposure.[1,2] Vitamin D serum concentrations can be defined as (1) sufficient or $\geq$ 30 ng/mL, (2) insufficient or 21-29 ng/mL, or (3) deficient or $\leq$ 20 ng/mL.[3] Low vitamin D is associated with a multitude of disease states, including

osteoporosis, muscle weakness, cancer, autoimmune disease, diabetes, schizophrenia, depression, lung dysfunction, and cardiovascular disease (CVD).[4,5] Currently, the role of vitamin D in cardiovascular disease has become an emerging area of research. The Framingham Offspring Study demonstrated a 62% increase in risk of developing a first cardiovascular event in patients with hypertension and vitamin D deficiency.[6] One hypothesis is that inadequate vitamin D status may complicate the adverse effect risk of 3-hydroxy-3- methylglutaryl coenzyme A reductase inhibitors or statins, which are commonly prescribed for cholesterol reduction in patients at risk for CVD.[7]

The adherence rate with statins is quite poor, with reports showing patients may go without medication for as much as 20.4% of the time, even in the absence of typical health-system barriers to adherence (i.e., high co-pays).[8] The reasoning behind this abundant non-adherence is multi-factorial and statin-induced muscle symptoms are a major reason for drug discontinuation and non-adherence. Vitamin D deficiency has been independently associated with muscle weakness and severe myopathy and may, in fact, be a confounder for statin-induced myopathies.[7,9,10] Myopathy is differentiated into 3 categories: (1) myalgia – muscle aches/weakness without CK elevation, (2) myositis – muscle symptoms with CK elevation, and (3) rhabdomyolysis – muscle symptoms associated with marked CK elevations (>10 times the upper limit of normal).[10]

The association between vitamin D status and statin-induced muscle symptoms is tenuous. Three different study designs (prospective, cross-sectional, and case series) have demonstrated a positive correlation between statin-induced myopathy and low vitamin D concentrations.[11-13] Further, two of these evaluations indicated that statin-induced myopathy could be reversible with supplementation of vitamin D.[11,14] Conversely, the results of two separate retrospective reviews have reported no significant relationship between statin-induced myopathy and vitamin D.[15,16] Some expert opinion has been so opposed to the potential association that they refer to it as “far-fetched”.[17] A recent Consensus Panel statement on statin-induced muscle symptoms acknowledged vitamin D deficiency as a concurrent condition associated with statin-induced myopathy, but did not recommend vitamin D supplementation to treat or prevent statin-induced myopathy.[18] Despite this controversy, all of these reports agree that patients requiring statin therapy would benefit if a relationship could be substantiated to support any therapeutic options for managing statin intolerance.

Since the development of statin-induced myopathy, only principles of treatment have been developed. Given there is no consensus on the relationship with vitamin D, further investigation into this complication is necessary.[19,20] We performed a retrospective chart review to evaluate the hypothesis that an association exists between inadequate vitamin D status and statin-induced myopathy.

Methods

This retrospective chart review was conducted at the University of Mississippi Medical Center's ambulatory cardiometabolic clinic from December 2006 to April 2008. This study was approved by the University of Mississippi Medical Center Institutional Review Board. The cardiometabolic clinic is a part of the University Physicians Pavilion, which offers a multitude of services and is staffed by physicians, nurses, pharmacists, and various other health professionals. A report was produced on patients with a vitamin D concentration drawn during the study period. The electronic health records for these patients was reviewed to ascertain pertinent information. Patients exposed to statins were divided into two groups: (1) patients with low vitamin D (25-(OH)D <32 ng/mL) and (2) patients with a sufficient vitamin D (≥32 ng/mL). These serum concentration cutoffs were chosen based on previous studies conducted in this field of study.[11,14] Each group was split into two subgroups: (a) patients with a prior history of statin intolerance due to myopathy and (b) patients currently receiving statins without myopathy. Patients in either group were excluded from analysis if they had never received a statin (n=21). Before data analysis, statin-induced myopathy was defined as specific documented complaints of muscle weakness, soreness, or pain eliciting statin discontinuation. As per standard practice in the cardiometabolic clinic, all patients with vitamin D <30 ng/mL received prescription supplementation (50,000 International Units twice weekly for 3 months). All laboratories and diagnoses are within 6 months of vitamin D reported in Table 1.

Descriptive statistics were used to quantify results. Statin intolerance rates are recorded as statin-specific (allowing for multiple intolerances in one patient) rather than patient-specific which qualifies a patient as statin-intolerant or not, regardless of number of statins discontinued. Group demographics were compared using a two-sided unpaired *t*-test (parametric data) and Fisher's exact test (dichotomous data). Statistics were performed using StatsDirect version 2.5.7.

Results

A retrospective chart review was conducted on 105 patients in a cardiometabolic clinic with a 25-(OH)D level drawn from December 2006 to April 2008. Current or previous statin use in all patients was 80% (n=84). At baseline, there was a larger number of patients with low vitamin D (n=52) than those with sufficient vitamin D (n=32). A comparison of demographic data is reported in Table 1. There were 41 statin-specific myopathy occurrences amongst the 24 statin-intolerant patients. Patients with statin-induced myopathy had significantly lower vitamin D concentrations [24.9 ± 9.7 ng/mL] than those who tolerated statins without myopathy [30.6 ± 14.1 ng/mL] (p=0.037). The majority (79%) of patients with documented statin-induced myopathy had a vitamin D <32 ng/mL. Additionally, documented statin discontinuation due to myopathy was significantly higher in low vitamin D patients (See Figure 1).

In patients with low vitamin D, the percentage of myopathy was similar regardless of statin lipophilicity. However, in patients with sufficient vitamin D status, atorvastatin appears to have the lowest rate of documented myopathy (17%). The statins that were associated with higher rates of myopathy in the setting of low vitamin D concentrations appear to be rosuvastatin (↑ 23%) and atorvastatin (↑ 14%). We did not see this trend in patients with low vitamin D concentrations on pravastatin (0% change) or simvastatin (↓ 7%).

All patients with statin intolerance and vitamin D ≤31 ng/mL (n=19) were re-challenged with a statin. Prescription supplementation of vitamin D was given in 84% of those patients that were re-challenged. Following vitamin D supplementation (n=16), statin tolerance rates were significantly higher (p=0.036) in patients with baseline vitamin D deficiency (≤20 ng/mL) (90%) than those with a baseline vitamin D serum concentration >20 ng/mL (33%). Of patients with low vitamin D and prior statin-induced myopathies, pravastatin (45%) and rosuvastatin (27%) were most tolerated by patients attempting statin re-challenge after vitamin D supplementation. A similar percentage of patients had intolerance to more than one statin in both the low vitamin D (58%) and vitamin D sufficient (60%) groups (p=NS).

Discussion

These results contribute to the existing body of support for an association between vitamin D and statin-induced myopathy. Over half of our patients (62%) have a vitamin D level <32 ng/mL at baseline. This is to be expected given our study is limited to patients with an indication for obtaining a vitamin D level. Conversely, the proportion of patients (28.6%) in this study with vitamin D ≤20 ng/mL is lower than general population estimates.[21] Despite the lower proportion of patients, the prevalence of statin-induced myopathy in the low vitamin D group (36.5%) appears to be higher than general population estimates.[10,22] The improvement demonstrated in statin tolerance rates following vitamin D supplementation in patients with a baseline vitamin D ≤20 ng/mL provides evidence that considering vitamin D ≤20 ng/mL as a risk factor for statin-induced myopathy is reasonable. Our findings also appear consistent with previously published data in regards to statin tolerance following vitamin D supplementation.[11,23]

A previous retrospective chart review performed by Kurnik and colleagues assessed the relationship between vitamin D concentrations and statin-induced myopathy in a similar fashion to our study, comparing patients who were changed from one statin to another versus patients who remained on the same statin throughout therapy.[15] Unlike our study, the authors found no differences in serum vitamin D concentrations among patients who switched from one statin to another, regardless of cause (including muscle pain).[15] Key differences in our design include recruitment from a cardiometabolic clinic and assessment following vitamin D supplementation. Although geographical location differed, two demographic variables were similar between their studies, specifically a higher percentage of females and ~30% rate of diabetes. Kurnik and colleagues contended in their review that differences in these two demographics may account for their conflicting results from previously published literature. Backes and colleagues had a very similar design and methodology to our study, yet found no difference in vitamin D concentrations between groups.[16] The high prevalence of African American patients in our study may account for some degree of variability in findings.

The findings of a recent meta-analysis indicate that a statins' relative hydrophilicity or lipophilicity is related to the type and frequency of adverse reactions.[24] There are 3 general groupings based on the continuum of lipophilicity: (1) highly lipophilic – simvastatin, and lovastatin, (2) modestly lipophilic –atorvastatin and fluvastatin, and (3) lowly lipophilic – rosuvastatin and pravastatin.[25] There may be a relationship between statin lipophilicity and the incidence of statin-induced myopathy or vitamin D concentrations, as our data indicate that lowly

lipophilic statins (pravastatin and rosuvastatin) may be better tolerated when re-challenging a statin in a patient with previous statin-induced myopathy and previously low vitamin D levels.

Each statin may affect vitamin D concentrations differently. Smaller, short-term studies have shown that more lipophilic statins (simvastatin and lovastatin) can cause increases in various metabolites of vitamin D, while less lipophilic statins (pravastatin) provide no improvement in vitamin D.[26-28] Additionally, recent studies suggest atorvastatin and rosuvastatin can increase serum vitamin D concentrations.[29] The mechanisms involved with increasing serum vitamin D concentrations following statin administration are not yet certain, but it has been proposed that statin potency may play a role.[29] Further research is warranted to elucidate the effect of long-term statin administration on vitamin D concentrations.

The mechanism on statin-induced myopathy with vitamin D is uncertain. A synergistic mechanism involving vitamin D deficiency worsening myopathy seems feasible given the pleiotropic effects statins have on skeletal muscle and the role of vitamin D receptors (VDRs) on skeletal muscle protein synthesis..[30] Another hypothesis proposed is through the induction of CYP enzymes by vitamin D, a known inducer of CYP3A4 and CYP2C9.[31] Higher vitamin D concentrations may cause enhanced enzyme activity and metabolism of certain statins leading to less drug bioavailability. Conversely, low vitamin D may decrease CYP activity, thus indirectly increasing toxicity of some statins.

Given the retrospective nature of this review, there are several limitations. Retrospective research is useful in establishing associations, but is unable to identify a causal relationship. Additionally, there is a lack of specifics on sun exposure and supplementation adherence, especially considering its importance to vitamin D concentrations. The small sample size is an important limitation, but is common when considering statin-induced myopathy evaluations. Our sample size was further limited by the need for a vitamin D level, as it is not routine practice to check for deficiencies in patients prescribed statins. Also, women accounted for the majority of our patients which may be related to the higher likelihood of getting vitamin D levels as part of an osteoporosis work up. The statin selected for re-challenge, although often the same statin, was variable in regards to specific statin and dose. There is a certain degree of subjectivity to defining myopathy that is an inherent limitation to this study. The definition of low vitamin D lacks a consensus, but was defined based on previously literature in this field of study. There was no ability to discern the existence of drug-drug interactions as a cause of underlying myopathy.

193

194 **Conclusion**

195 This study provides insight to the potential relationship between vitamin D levels and statin-induced
196 myopathy. We found that patients with documented statin-induced myopathy had significantly lower vitamin D
197 levels and the majority of these myopathies were observed in patients with a vitamin D level <32 ng/mL. In a
198 clinical setting, vitamin D status may be considered a modifiable risk factor for muscle-related adverse effects of
199 statins, and supplementation of vitamin D (particularly when ≤20 ng/mL) may improve statin tolerance. Well-
200 designed, prospective research could be warranted to evaluate this hypothesis.

201

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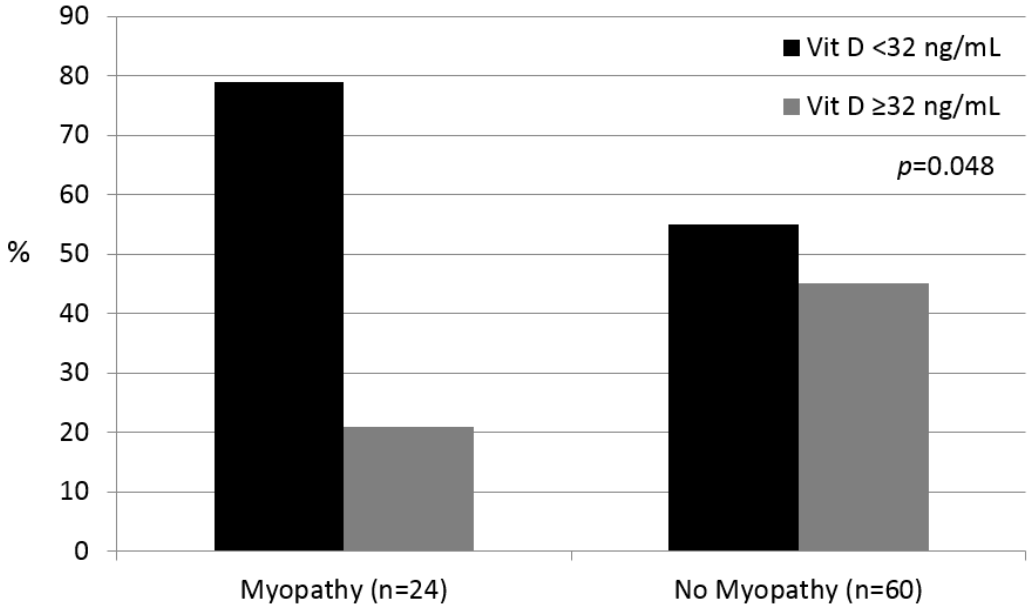
Figure 1. Rate of Statin-induced Myopathy by Vitamin D Status before Vitamin D Supplementation



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272 **Table 1.** Patient Demographics[a]

Characteristic	*n*	Vitamin D <32 ng/mL	*n*	Vitamin D ≥32 ng/mL	*p*-value
Age (years)	52	61.6 ± 11.2	32	61.0 ± 10.9	0.80
Gender					
F	47	90.4%	25	78.1%	0.20
M	5	9.6%	7	21.9%	
Race					
Caucasian	35	67.3%	26	81.3%	0.21
Non-Caucasian [b]	17	32.7%	6	18.8%	
Osteoporosis/Osteopenia	19	36.5%	14	45.2%	0.65
Hypertension	40	76.9%	24	75%	0.99
Diabetes Mellitus	18	34.6%	9	28.1%	0.63
Hypothyroidism	14	26.9%	6	18.8%	0.44
Smoker	7	13.5%	3	9.4%	0.73
Vitamin D (ng/mL)	52	21 ± 6.6	32	42 ± 10.5	<0.0001
CPK (30-170 IU/L)	30	164.9 ± 156.1	15	101.8 ± 69.4	0.10
Body Mass Index (kg/m^2)	49	31.3 ± 5.7	29	29.6 ± 6.0	0.12
Total Cholesterol (mg/dL)	52	216 ± 78.8	32	206 ± 79.8	0.59

273 a. Data reported as means ± standard deviations as appropriate
274 b. 96% of non-Caucasians were African American
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Highlights:

- Vitamin D status plays an important role in the consideration of statin-induced myopathy
- Correction of vitamin D deficiency (≤20 ng/mL) can improve statin tolerance rates