

Vitamin D Supplementation to Rechallenge Statin Therapy in Patients with Statin-Induced Myalgia

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The 3-hydroxy-3-methylglutaryl-coenzyme (HMG-CoA) reductase inhibitors, commonly referred to as statins are cholesterol lowering drugs that are used to reduce the risk for developing coronary heart disease (CHD), major coronary events such as myocardial infarction and stroke, and death related to CHD. Statins have demonstrated benefit in reducing these risks in four patient populations including those with a history of Atherosclerotic Cardiovascular Disease (ASCVD), low-density lipoprotein (LDL) cholesterol greater than 190 mg/dL, diabetes, and a 10-year risk for developing ASCVD greater than 7.5%.¹ An estimated 38.6 million Americans are on statin therapy with prevalence of cholesterol-lowering medication use increasing with age, from 17% of adults aged 40-59 to 48% of adults aged 75 and older.² A barrier to effective cardiovascular risk reduction presents with noncompliance and the discontinuation of statin therapy due to adverse events including myalgia, myositis, and in some cases, severe rhabdomyolysis.

A number of risk factors have been associated with adverse effects in statin users including higher doses, older age, female gender, decreased renal and hepatic function, hypothyroidism, medications that inhibit statin metabolism, and conditions that increase muscle susceptibility to injury.³ The prevalence of statin-induced myopathies varies between trials. In the Prediction of Muscular Risk in Observational conditions (PRIMO) survey, muscular symptoms were reported in 10.5% of statin users overall.⁴

Some of the more common strategies for dealing with statin intolerance include changing statins, using intermittent dosing, intensifying lifestyle modifications, or using alternative LDL cholesterol lowering agents such as ezetimibe and bile acid sequestrants. Several studies have found an association between low

serum vitamin D levels and increased risk for statin-induced muscle weakness, aching, cramps, or other symptoms. The purpose of this review is to summarize and evaluate the evidence supporting the restart of statin-therapy after supplementation in vitamin D deficient patients with statin-induced myalgia.

PRESENTATION OF SYMPTOMS

Myalgia typically presents as symmetrical proximal muscle pain that is often described as heaviness, stiffness, cramping, or weakness which can be persistent, intermittent, or appearing only upon exertion. These muscular symptoms present without elevation of creatine kinase (CK). Myositis is further differentiated by the presence of muscle symptoms and CK elevations between 5 and 10 times the ULN (upper limit of normal), occurring far less frequently at a rate less than 0.01% of statin users. Rhabdomyolysis is a severe and life-threatening form of myopathy associated with muscle symptoms and CK elevations greater than 10 times the ULN. Rhabdomyolysis is a very rare, occurring in only 0.002% of statin users, but can lead to serious consequences including hepatic damage, renal failure, and death.³

PATHOPHYSIOLOGY OF SYMPTOMS

Reduced activity of liver influx membrane transporters (i.e. OATP1B1) and of liver and muscle efflux transporters (i.e. MDR1, BCRP) can lead to a buildup of statin concentrations in the myocyte. Individuals may be predisposed to statin-induced myopathy as a result of mitochondrial damage resulting in decreased production of ATP, increase of reactive oxygen species, and leaking of cytochrome c and calcium. These effects may provide for apoptosis, proteolysis, and the remodeling of muscle which produces fatigue, muscle cramps, myalgia, and elevations in CK. Several strategies for preventing these complications include avoiding drug-drug interactions, abstaining from alcohol, correcting low thyroid levels, slow dose titration of statins, and high dose supplementation of vitamin D in patients with low serum levels.⁵

Certain medications that inhibit or induce CYP enzymes may affect the incidence of statin-induced myopathies. An additional factor that can affect the incidence of statin-induced myotoxicity is the lipophilicity of the chosen statins. The PRIMO study demonstrated that hydrophilic statins such as pravastatin and fluvastatin were least likely to cause myalgia, whereas the lipophilic statins including atorvastatin and simvastatin were more likely associated with muscular adverse effects.⁴ Simvastatin has the highest incidence of statin-induced myopathy (18.2%) which can be attributed to its lipophilicity and metabolism by CYP3A4 enzymes. Atorvastatin, another lipophilic statin metabolized by CYP3A4 has a slightly lower incidence of myopathies (14.9%). The hydrophilic statins had lesser incidences of myalgia with 10.9% in pravastatin and 5.1% in fluvastatin XL.

Table 1 summarizes the pharmacology of available statins



IN THIS ISSUE

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Table 1 | Pharmacology of Statins and Myalgia Incidence^{4,6,7}

Statin	Metabolism ^a	Lipophilicity	Incidence of SIM (PRIMO) ⁴	ACC/AHA Intensity Classification ^b
Simvastatin	CYP3A4	Lipophilic	18.2%	Moderate, Low
Atorvastatin	CYP3A4	Lipophilic	14.9%	High, Moderate
Pravastatin	Sulphation, biliary excretion, urinary excretion	Hydrophilic	10.9%	Moderate, Low
Rosuvastatin	CYP2C19, biliary excretion	Hydrophilic	-	High, Moderate
Lovastatin	CYP3A4	Lipophilic	-	Moderate, Low
Fluvastatin	CYP2C9	Lipophilic	5.1% (XL)	Moderate, Low
Pitavastatin	CYP2C8, CYP2C9, lactonization, biliary excretion	Lipophilic	-	Moderate, Low

ACC = (American College of Cardiology); AHA = American Heart Association; CYP = Cytochrome P450; SIM = Statin Induced Myopathy

a. Listed as primary metabolic pathway

b. ACC/AHA intensity is defined by % decrease in LDL: Low <30%, Medium 30-49%, High >50%

and the incidence of statin-induced myopathy (SIM) of those statins evaluated in the PRIMO study.

PROPOSED BENEFIT

Skeletal muscle cells contain vitamin D receptors that modulate transcription factors in muscle cells that are responsible for mediating cell proliferation and differentiation into mature type II muscle fibers. In order for muscular contraction of the sarcomeres to take place, vitamin D is necessary for transport of calcium into the sarcoplasmic reticulum, also playing a role in muscle contractility and myogenesis.⁸ The Endocrine Society has defined adequate vitamin D levels to be a 25-hydroxyl vitamin D level of 30 ng/mL.⁹ Low levels of vitamin D have been associated with proximal muscle weakness, reduced muscle tone, delayed time to peak muscle contraction and relaxation, and generalized pain of the muscles and joints. As a result of vitamin D supplementation, more calcium may be available during the cross-bridging cycle, enhancing skeletal muscle function and reducing the incidence of statin-induced myopathy. Vitamin D deficiency has been suggested to trigger preferential shunting of cytochrome P-450 (CYP) 3A4 for vitamin D hydroxylation, subsequently decreasing the amount of CYP3A4 available for metabolism, which may lead to increased toxicity in certain statins. Vitamin D is further proposed to reduce statin-induced myotoxicity by increasing the metabolism of certain statins through induction of CYP3A4 and CYP2C9 enzymes.⁸

CLINICAL TRIALS

Clinical trials evaluating the effectiveness of vitamin D supplementation to restart therapy in vitamin D deficient patients presenting with statin-induced myalgias are summarized in **Table 2**.

Ahmed et al. conducted a single-institution prospective study in 2009 looking at the potential associations between low serum vitamin D levels and statin induced myopathies.¹⁰ Patients were recruited from the Jewish Hospital of Cincinnati and referred to the Cholesterol Center for hyperlipidemia management. Of the original 621 statin treated patients, only 38 were followed over

three months. Patients were excluded who were taking corticosteroids or supplemental vitamin D and who had comorbid conditions associated with muscle or bone pain such as fibromyalgia, arthritis, peripheral vascular disease, and sensory neuropathy. This study showed that serum vitamin D levels were lower in patients with statin-induced myalgias than in statin-treated patients without myalgias. These two groups did not differ ($p > 0.05$) in variables that can affect serum vitamin D levels including age, BMI, type 2 diabetes, exogenous vitamin D, or corticosteroid use. Vitamin D deficient patients with concomitant myalgias were given a prescription for ergocalciferol (D2) 50,000 units once per week for 12 weeks. No patients reported any missed doses or side effects as a result of vitamin D supplementation. Serum vitamin D levels in patients more than doubled to 48.2 ± 17.9 ng/mL ($p < 0.0001$). The most frequently prescribed statin therapies included rosuvastatin (10 patients), atorvastatin (4), pravastatin (2) and those on atorvastatin at study entry then switched to rosuvastatin (7). Resolution of myalgias was experienced by 35 patients (92%) after 12 weeks of vitamin D supplementation, (table 2). The authors of the study concluded that normalizing low serum vitamin D largely reverses myositis-myalgia that would alternatively cause statin intolerance.

Linde et al. performed a retrospective cohort study in 2010 to investigate the effects of vitamin D repletion in deficient patients and the ability to tolerate restarted statin therapy.¹¹ This study also sought to examine whether or not vitamin D status influences the effect of the SLCO1B1*5 genotype on the risks for developing statin-induced myalgia. This gene polymorphism decreases coding for an organic anion transporter which regulates statin uptake in the liver, thereby increasing the risk of myopathies from statins. The 21 patients with intolerable myalgias and concomitant vitamin D deficiency received varying doses of vitamin D according to the severity of their deficiency. These doses ranged from 1,000 IU daily of D3 to 50,000 IU once weekly of D2. After 2-3 months of vitamin D supplementation, all patients achieved serum vitamin D concentrations ≥ 30 ng/mL. Of the 15 patients willing and able to reinstate statin therapy after vitamin D repletion, 14 remained free of myalgia (93%) while one patient had mild but tolerable symptoms that allowed for a continuation of statin therapy ($p = 0.01$, table 2). Of note, 7 patients (47%) had developed myalgia in

the past on at least two statins and 6 patients (40%) were able to tolerate the same statin that was previously failed after vitamin D supplementation. Fluvastatin (5 patients) and pravastatin (5) were the most frequently reinitiated statins, with patients also receiving rosuvastatin (2), lovastatin (1), simvastatin (1), and atorvastatin (1). The authors of the study concluded that vitamin D deficiency by itself did not lead to myalgias in statin users, however repletion in deficient patients with concomitant myalgias permitted symptom-free reinitiation of statin therapy. The authors further determined that a SLCO1B1*5 genotype comprising of at least one “C” allele was correlated with a three-fold increased risk for myalgias ($p = 0.07$).

Glueck et al. performed a prospective cohort study in 2015 to examine if normalizing vitamin D levels would permit successful restart of statin therapy.¹² This study included 74 men and 72 women (age 59 ± 14 years) who were vitamin D deficient (<32 ng/mL) and had previously failed at least two statins due to myalgias. Patients were excluded from the study who had experienced rhabdomyolysis upon previous statin therapy, were taking corticosteroids, or had comorbid conditions associated with muscle or bone pain including diabetic sensory neuropathy, fibromyalgia, polymyalgia rheumatic, arthritis, peripheral vascular disease, sensory neuropathy, and hypothyroidism. Patients received 50,000 - 100,000 units of vitamin D2 per week and following 3 weeks of vitamin D supplementation, statin therapy was reinitiated. The vitamin D dose was then adjusted to keep serum vitamin between 50-80 ng/mL. The most frequently restarted statin was rosuvastatin at a dose of 10-20 mg/day, however other statins were given based on the insurance coverage of patients. Vitamin D levels normalized between 86% in patients followed up at 12 months and 91% in patients that were followed up for the full 24 months. At the 6-month follow-up visit 88% of patients remained free of muscle symptoms while 12% dropped out due to myalgia-myositis, and median LDL-C fell from 167 to 90 mg/dL ($p < 0.001$). At 12-month’s follow-up 91% of patients remained free of myalgia-myositis and median LDL-C fell to 91 mg/dL ($p < 0.0001$). At the 24-month follow-up visit 95% of patients remained symptom free (table 2) and median LDL-C dropped to 84 mg/dL ($p < 0.0001$, table 2). The strengths of this study included a larger number of patients compared to previous studies completed as well as the extended follow-up time. The authors of this study concluded that myopathies associated with low serum vitamin D can be safely resolved upon high dose vitamin D supplementation in the majority of cases.

Kang, et al. performed a single-institution, retrospective cohort study in 2017 that looked at the effect of vitamin D supplementation on statin-induced myopathy.¹³ This study was conduct-

ed at a pharmacist-run ambulatory care clinic at the VA Medical Center. Patients were included who were 18 years or older with serum vitamin D levels less than 30 ng/mL, had a history of statin-induced myalgia, and were reluctant to reinitiate statin therapy without an intervention aiming to correct their statin intolerance. Of the 27 patients studied the majority were white (81.5%) males (96.3%) with a mean age and standard deviation of 64.8 ± 8.9 years. Patients were excluded who were not vitamin D deficient, had received vitamin D supplementation, hepatitis treatment, corticosteroids or chemotherapy at the time of study entry, had uncontrolled hypothyroidism, acute liver disease, under hospice care, or pregnant. Patients had started and failed an average of 2.9 ± 1.2 statins prior to the study, with the most frequently failed statins being simvastatin (88.9%), rosuvastatin (59.3%) and pravastatin (51.9%). Patients received loading doses of ergocalciferol (D2) 50,000 units per week for 8 to 12 weeks, and were then given maintenance doses of cholecalciferol (D3) 800 to 1000 units daily to keep vitamin D levels above 30 ng/mL. Statins were restarted around 6 months after vitamin D supplementation was initiated, regardless of serum vitamin D concentrations. The most commonly reinitiated statin was atorvastatin (15), a statin linked to higher prevalence of myalgia, followed by pravastatin (6), and rosuvastatin (3). All 27 patients were able to achieve the primary outcome of maintaining their statin therapy without muscle complaints at 12 months after restarting statin therapy (table 2) however, intermittent dosing strategies of once, twice, three times weekly, or every other day were utilized in 11 (40.7%) patients. Eleven patients (40.7%) were able to tolerate the statin they had most recently failed with six of these patients returning to previously failed dose, enabling them to tolerate the appropriate statin intensity level determined by the ACC/AHA 2013 guidelines. After 12 months of reinitiating statin therapy, there was a significant improvement ($p < 0.05$) in lipid panels with total cholesterol (-59.7 mg/dL), LDL (-44.0 mg/dL), and non-HDL cholesterol (-60.7 mg/dL) decreased from baseline. The authors of this study concluded that replenishing low vitamin D levels with high dose vitamin D supplementation seems to effectively allow for continued statin therapy and subsequent prevention of cardiovascular events and death.

STUDY LIMITATIONS

All of the previously mentioned studies had similar limitations that constrain the generalizability and utility of the results. These studies were limited by relying on subjective reports of muscle symptoms and lack of blinding or control groups. Most of the studies reinitiated patients on different statins than what they

Table 2 | Summary of Clinical Trials¹⁰⁻¹³

Trial	Study Type	Myalgia free after statin restart	Number of Patients	Vitamin D Supplementation	Duration of Supplementation
Ahmed et al. (2009)	Prospective Cohort	92%	38	50,000 units/week (D2)	12 weeks
Linde et al. (2010)	Retrospective Cohort	93%	21	1,000 units daily (D3) -or- 50,000 units/week (D2)	2-3 months
Glueck et al. (2015)	Prospective Cohort	86-91%	146	50,000—100,000 units/week (D2)	-
Kang et al. (2017)	Retrospective Cohort	100%	27	50,000 units/week	8-12 weeks*

*Followed by maintenance doses

could previously tolerate, at a lower dose of their previously failed statin, or on a different statin with a lower incidence of statin-induced myalgia. Possible confounding variables such as non-pharmacological interventions and over-the-counter medications or herbal supplements may not have been accounted for. Additional factors including physical activity, weight loss, and smoking cessation may have significantly impacted the outcomes of the studies. Future double-blinded, placebo-controlled studies reinitiating patients on the same statin and dosage are necessary to confirm the results of these studies.

SAFETY OF VITAMIN D SUPPLEMENTATION

None of the studies mentioned previously have reported any adverse effects associated with vitamin D supplementation. A prospective cohort study performed by Glueck et al. in 2016 examined the safety of 50,000-100,000 units of cholecalciferol (D3) in vitamin D deficient patients with high cholesterol and reversible statin intolerance.¹⁴ At 6 and 12-month follow ups this study found therapy with vitamin D3 to be safe and effective as serum concentrations of vitamin D only exceeded 100 ng/mL in 1 patient (0.9%) without reaching toxic levels (>150 ng/mL), and no patients experienced significant elevation in serum calcium or eGFR.

SUMMARY

Current guidelines recommend statin drugs as first line therapy in the reduction of LDL cholesterol and the prevention of cardiovascular events and death. Patients may develop intolerance to these medications due to muscle pain and weakness. Clinical trials have demonstrated an association between low serum vitamin D levels and statin-induced myopathy. Supplementation of 50,000- 100,000 units of cholecalciferol (D3) weekly in patients with serum vitamin D levels less than 30 ng/mL and statin-induced myalgia may be effective to help tolerability of therapy when reinitiating statin therapy in a majority of patients.

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