Statin-Induced Myotoxicity:
Is Vitamin D Deficiency the Cause for this Pain in the Muscle?

Amber Gossett, Pharm.D.

PGY1 Pharmacy Resident
South Texas Veterans Health Care System, San Antonio, Texas
Division of Pharmacotherapy, The University of Texas at Austin College of Pharmacy
Pharmacotherapy Education and Research Center
The University of Texas Health Science Center at San Antonio

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Learning Objectives:

1. Describe the epidemiology and pathophysiology associated high cholesterol and vitamin D deficiency
2. Discuss the diagnostic criteria and risk factors associated with statin-induced myotoxicity and vitamin D deficiency
3. Evaluate current strategies to overcome statin-induced myotoxicity
4. Formulate a recommendation regarding vitamin D supplementation for the prevention of statin-induced myotoxicity

BACKGROUND

I. Introduction [1]
   A. Epidemiology
      a) Heart disease
         i. Number one cause of death in the United States (US)
         ii. Approximately 735,000 people per year suffer from a heart attack, 120,000 of which die
      b) Stroke
         i. Second leading cause of death globally, behind heart disease, accounting for 11.3% of deaths worldwide
         ii. Leading cause of preventable disability
      c) Sudden cardiac arrest
         i. Out of hospital: 326,000 people; 10.6% survived
         ii. Witnessed out of hospital: 19,300 people; 31.4% survived
         iii. In hospital: 209,000 people

   B. Pathophysiology [2-4]
      a) High cholesterol is a major controllable risk factor for coronary events, both primary and secondary
      b) When left untreated, low density lipoproteins (LDL) are left to circulate in the blood and are then able to build up on the inner walls of the arteries
      c) Plaque then forms and leads to narrowing of the arteries and less flexibility, known as atherosclerosis
      d) Plaque rupture creates the formation of clots, which travel through the blood stream and can lead to a heart attack or stroke

   C. Mechanism of LDL reduction with statin therapy [2]
      a) 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors
         i. HMG-CoA reductase catalyzes the rate-limiting step, HMG-CoA to mevalonic acid
         ii. Inhibition results in a decrease in cholesterol biosynthesis
      b) Increased LDL receptors
         i. Reduction of intracellular cholesterol leads to the slicing of sterol regulatory element binding proteins (SREBPs) from the endoplasmic reticulum
         ii. SREBPs translocate to the nucleus and lead to increased gene expression for LDL receptors on the hepatocyte causing increased LDL uptake
      c) LDL cholesterol is then significantly reduced via decreased cholesterol biosynthesis (HMG-CoA) and increased uptake (increased LDL receptors) leading to a decrease in circulating LDL

II. Statin Therapy
   A. Benefits [5]
      a) Statin therapy reduced:
         i. Major coronary events by 27%
         ii. Stroke by 18%
         iii. All-cause mortality by 15%
         iv. Coronary events were reduced by 23% in pravastatin trials and 29% in five trials using other statins

   B. Statin therapy is indicated for primary and secondary prevention of atherosclerotic cardiovascular disease (ASCVD), 2013 American College of Cardiology/American Heart Association (ACC/AHA) treatment recommendations are based on four categories [3]
      a) Patients with clinical ASCVD
      b) Patients with elevations of LDL ≥190 mg/dL
      c) Patients with Type 2 diabetes who are between 40 and 75 years of age with LDL 70-189 mg/dL
      d) Patients without clinical ASCVD or diabetes between 40-75 years of age with LDL 70-189 mg/dL and an estimated 10-year ASCVD risk of 7.5% or higher

Table 1. Statin intensity [6]

Low intensity <30% LDL reduction	Moderate intensity 30 to <50% LDL reduction	High intensity ≥50% LDL reduction
Simvastatin 10 mg	Simvastatin 20-40 mg	Atorvastatin 40-80 mg
Pravastatin 10-20 mg	Atorvastatin 10-20 mg	Rosuvastatin 20-40 mg
Lovastatin 20 mg	Pravastatin 40-80 mg	
Fluvastatin 20-40 mg	Rosuvastatin 5-10 mg	
Pitavastatin 1 mg	Lovastatin 40 mg	
	Fluvastatin XL 80 mg, Fluvastatin 40 mg twice daily	
	Pitavastatin 2-4 mg	

C. Adverse Effects of Statin Therapy [3-4]
   a) Neurological side effects
   b) Increased blood sugar
   c) Rash or flushing
   d) Digestive issues
   e) Liver damage
      i. Cholestatic hepatitis
      ii. Transaminases three times the upper limit of normal (ULN)
         - Incidence: 1%
   f) Muscle pain and damage
      i. Myalgia, myopathy and rhabdomyolysis
      ii. Incidence is both statin and dose dependent effect

III. Myotoxicity [8-10]

Table 2. Spectrum of statin-induced myotoxicity [7]

Clinical term	ACC/AHA/NHLBI	2014 NLA Statin Muscle Safety Expert Panel	NLA	FDA
Myalgia	Muscle ache/ weakness in absence of CK increase	Unexplained muscle discomfort with normal CK	Not defined	Not defined
Myopathy	Any disease of the muscle	Muscle weakness with or without CK elevation	Myalgia, weakness or cramps, and CK >10 times ULN	CK ≥10 times ULN
Myositis	Muscle symptoms with elevated CK	Muscle inflammation	Not defined	Not defined
Myonecrosis	Not defined	Muscle enzyme elevations or hyperCKemia*, may be associated with myoglobinuria	Not defined	Not defined
Rhabdomyolysis	Muscle symptoms with CK elevation (>10 times ULN), creatinine elevation , and urine myoglobin	Not defined	CK >10,000 IU/L or CK >10 times ULN or medical intervention with IV hydration	CK >50 times ULN and evidence of organ damage

ACC, American College of Cardiology; AHA, American Heart Association; CK, creatine kinase; FDA, US Food and Drug Administration; NHLBI, National Heart, Lung, and Blood Institute; NLA, National Lipid Association; ULN, upper limit of normal *mild= >3-fold CK increase from baseline, moderate= ≥10 fold CK increase from baseline, severe= ≥50-fold CK increase

A. Incidence of statin-induced myotoxicity(SIM) [8-11]
   a) Statins are commonly associated with myalgia, less commonly with myositis, and rarely with rhabdomyolysis
      i. Myalgia:
         - Most common
         - Randomized controlled trials demonstrate an incidence of 1.5% to 3%
         - In clinical practice, approximately 10% of patients report muscle pain
      ii. Myopathy:
         - Five to eleven per 100,000 patient years
      iii. Rhabdomyolysis:
         - 0.7 to 1.6 per 100,000 patient years

Table 3. Incidence of myalgia in hydrophilic statins [12]

Hydrophilic statins					
	Metabolism	**Disorder of the Muscle**	**Myalgia**	**Musculoskeletal pain**	**Increased CK**
Pravastatin	Sulfation	< 0.1%	1% to 2.9%	3.9% to 24.9%	1.3% to 5.2%
Rosuvastatin	CYP 2C9, 2C19	< 1%	1.9% to 12.7%		2.6%
Fluvastatin	CYP 2C9		3.8% to 5%		

Table 4. Incidence of myalgia in lipophilic statins [12]

Lipophilic statins					
	Metabolism	**Disorder of the Muscle**	**Myalgia**	**Musculoskeletal pain**	**Rhabdo**
Simvastatin	CYP 3A4	0.02% to 0.9%*	3.7%		4%*
Atorvastatin	CYP 3A4		8.4%	5.2%	
Lovastatin	CYP 3A4		3%		
Pitavastatin	CYP 2C9, 2C8		1.9 to 3.1%		

*dose dependent

B. Presentation of SIM [7]
   a) Myalgia, weakness, low back, proximal muscle pain, generalized aching, tendon pain, and nocturnal cramping of muscles
   b) Rhabdomyolysis is a fulminant and acute, necrotizing myopathy with a presentation of severe pain, muscle swelling, weakness, fatigue, and myoglobinuria

C. Risk Factors [3]

Table 5. Risk factors for SIM

Increasing plasma concentrations	Factors predisposing to muscle injury
Age > 70 years	Additive drug adverse effects
Drug-drug interactions	Alcohol abuse
Female	Substance abuse
High-dose therapy	Untreated hypothyroidism
Low body mass	
Untreated hypothyroidism	

IV. Approaches to management of SIM

A. Prior to re-trial of statin therapy, a "drug free holiday" is recommended which is typically defined in clinical practice as a six week period free of statin therapy [13]
B. Statin re-trial with alternative statin
    a) A study of 45 patients with confirmed SIM
    b) Thirty-seven patients were rechallenged [14]
        i. Twenty-one patients (57%) reported recurrent muscle pain
        ii. Sixteen (43%) tolerated the new statin without reporting symptoms
    c) Statin with reduced drug-drug interaction potential [15]
        i. Pravastatin , rosuvastatin, and pitavastatin are not markedly metabolized by CYP enzymes and, therefore, are not susceptible to drug interactions which may lead to increased statin levels
        ii. Fluvastatin is metabolized by CYP2C9 which can also eliminate some drug interactions
    d) Hydrophilic statin [16]
        i. Least likely to cause myopathy
        ii. Hydrophilic statins include pravastatin, rosuvastatin, and fluvastatin
C. Lower dose of a more potent statin [17]
    a) Study including 61 participants with a history of statin intolerance due to myalgia treated with rosuvastatin 5 mg and 10 mg per day
        i. One individual receiving the 10 mg dose discontinued rosuvastatin treatment due to unilateral muscular pain after 4 weeks
        ii. LDL was lowered with the rosuvastatin 5 mg and 10 mg of 42% and 39%, respectively
        iii. No significant aminotransferase or CK elevation noted and of the 61 patients, one patient receiving the 10 mg/day dose discontinued rosuvastatin due to unilateral muscular pain
D. Alternate-day dosing
    a) Atorvastatin and rosuvastatin should be utilized for this dosing scheme due to their long half-life of 14 hours and 19 hours, respectively
    b) Forty-one participants initially treated with 10 mg of atorvastatin daily switched to every other day dosing once LDL goal of <100 mg/dL in 33 people, per ATP III guidelines, was attained [18]
        i. No observed elevations in liver enzymes
        ii. No observed elevations in CK during the alternate-day dosing period
    c) Fifty-four patients were randomized to atorvastatin 10 mg daily, 10 mg every other day, and 20mg every other day for six weeks of treatment [19]
        i. All groups demonstrated a significant reduction in LDL from baseline
        ii. All regimens were well tolerated with no elevations in CK during the course of the study
E. Twice weekly dosing [20]
    a) Individuals with a history of SIM treated with rosuvastatin 5mg or 10mg twice weekly
        i. Well tolerated by 80% of patients
        ii. Significant 26% reduction of LDL from baseline
F. Once weekly dosing [21]
    a) Fifty patients with a previous statin adverse event treated with rosuvastatin once per week
        i. Tolerated 74% study participants
        ii. Doses ranging from 2.5 mg to 20 mg a week with a mean of 10 mg
        iii. Significant 23% reduction in LDL
G. Evaluation of every other day, once weekly, and twice weekly dosing
    a) Lower LDL-C reduction (up to 10%–15% less) compared to the everyday regimen
    b) Alternative dosing regimens have not been proven to reduce cardiovascular events

V. Mechanism of SIM

A. Exact mechanism of myotoxicity associated with statin use has not yet been defined, however, several mechanisms have been proposed

a) Reduced coenzyme Q10 (CoQ10) [22]

i. The exact mechanism is not known

ii. Thought to be due to statin therapy decreasing production of CoQ10 via blocking an intermediate product, farnesyl phosphate, in CoQ10 synthesis

iii. Decrease CoQ10 levels lead to mitochondrial dysfunction and decreased mitochondrial energy production, which is thought to play a role in SIM

iv. Decreased ubiquinone levels have been demonstrated in cardiac muscle and the liver in animal models with concurrent statin therapy

- Decreased levels have not been found in skeletal muscles

v. Randomized clinical trials have not demonstrated a significant reduction of statin myopathy in in CoQ10 supplementation

b) Reduced cholesterol levels [8]

i. Cholesterol is a key component in maintaining the structure and function of cell membranes

ii. Decreased levels of cholesterol in cell membranes impact membrane fluidity and ion channels, which may modify muscle membrane excitability

iii. Leads to the alterations in the myocyte membrane which may lead to myotoxicity

c) Depletion of isoprenoids [8]

i. Isoprenoids are linked to proteins by farnesylation or geranylation

ii. Other end products of the mevalonate pathway include farnesyl pyrophosphate and geranylgeranyl pyrophosphate

iii. These two end products promote cell maintenance and cell growth and decrease cell apoptosis

iv. Statins have been associated with cell apoptosis which has led to the association of apoptosis and SIM

d) Impaired calcium signaling [8]

i. Statin therapy, particularly simvastatin, has demonstrated mitochondrial depolarization and calcium efflux

e) Vitamin D deficiency [8]

i. Vitamin D deficiency, alone, has been associated with myalgia symptoms

VITAMIN D

I. Background
   A. Measured via 25–hydroxyvitamin (OH) D (25(OH)D)concentrations [23]
   B. Optimal levels remain controversial [23]
   C. Screening recommendation for vitamin D deficiency in individuals at risk for deficiency [24]
      a) Vitamin D screening in the general population is not recommended

Table 6. Categories of vitamin D levels [25-26]

	Endocrine Society	Food and Nutrition Board	Testing Laboratories
Deficient	<20 ng/mL	<12 ng/mL	<31 ng/mL
Insufficient	21-29 ng/mL	12-20 ng/mL	
Sufficient	30-100 ng/mL	>20 ng/mL	32-100 ng/mL
Toxic	>150 ng/mL		

Table 7. Food and nutrition board vitamin D level and health status [27]

Vitamin D statin-induced	Health status
<12 ng/mL	Associated with vitamin D deficiency (rickets in infants and children and osteomalacia in adults)
12–20 ng/mL	Inadequate for bone and overall health in individuals
≥20 ng/mL	Adequate for bone and overall health in individuals
>50 ng/mL	Potential adverse effects to high levels (>60 ng/mL)

   D. Prevalence data from the National Health and Nutrition Examination Survey (NHANES) 2005 to 2006 [28]
      a) Variations exist depending on the definition of vitamin D deficiency utilized
      b) Overall rate of vitamin D deficiency, defined as <20 ng/mL, was 41.6%
      c) Highest prevalence in African Americans and Hispanics at 82.1% and 69.2%, respectively

   E. Vitamin D forms [29]
      a) Vitamin D_2 (ergocalciferol)
      b) Obtained from
         i. Dietary sources
            - Mushrooms
            - Soy milk
            - Egg yolk
         ii. Oral supplements
      c) Vitamin D_3 (cholecalciferol)
      d) Obtained from
         i. Skin exposure to ultraviolet B (UVB) radiation in sunlight
         ii. Foods rich in vitamin D
            - Oily fish, milk, juices, margarines, yogurts, cereals, and soy
         iii. Oral supplements
      e) Calcidiol and calcitriol are also treatment options recommended for patients with kidney or liver dysfunction
         i. Calcidiol is recommended with liver dysfunction
         ii. Calcitriol is recommended with kidney dysfunction
      f) Vitamin D content of most foods is between 50 and 200 IU per serving

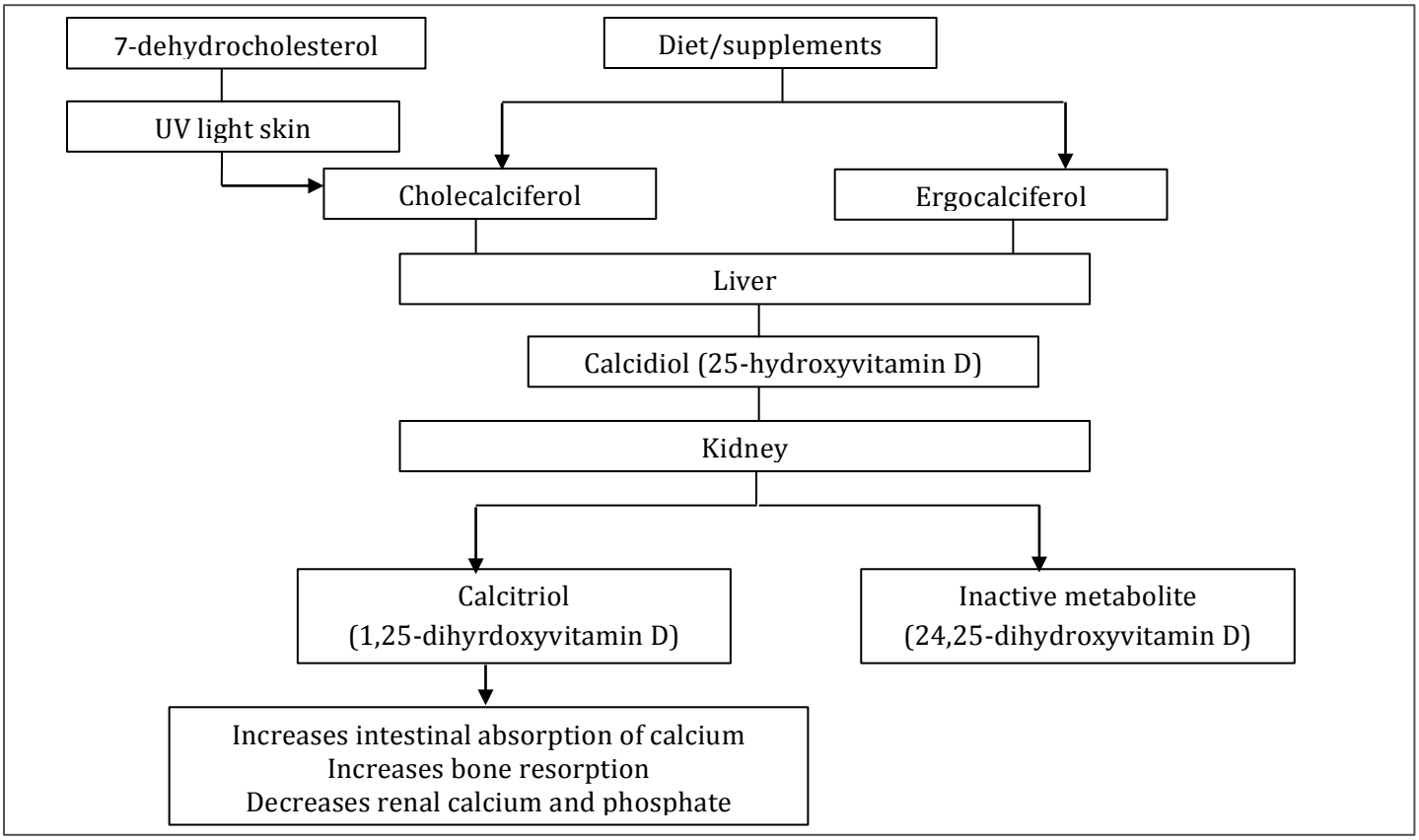

Figure 1. Vitamin D Metabolism

F. Risk factors for vitamin D deficiency [31]
   a) Premature birth
   b) Pigmented skin
   c) Low sunshine exposure
   d) Obesity
   e) Malabsorption
   f) Advanced age

G. Causes of Vitamin D deficiency

Table 8. Causes of Vitamin D deficiency [30]

Cause of Vitamin D Deficiency	Underlying Source
Deficient intake or absorption	Dietary Inadequate sunlight exposure Malabsorption Gastrectomy
Defective 25-hydroxylation	Cirrhosis
Increased catabolism of vitamin D to inactive metabolites	Anticonvulsants
Loss of vitamin D binding protein	Nephrotic syndrome
Defective 1-alpha 25-hydroxylation	Hypoparathyroidism Renal failure 1-alpha hydroxylase deficiency (vitamin D-dependent rickets, type 1)
Defective target organ response to calcitriol	Hereditary vitamin D-resistant rickets (vitamin D-dependent rickets, type 2)

II. Treatment of vitamin D deficiency [31]
   A. Vitamin D2 and D3 are available as dietary supplements
   B. Debate regarding which form of vitamin D should be used for supplementation
      a) In a meta-analysis of seven studies, cholecalciferol compared to ergocalciferol was more effective
      b) This effect was lost when daily dosing of cholecalciferol and ergocalciferol were compared
      c) Guidelines suggest either agent for prevention and treatment of vitamin D deficiency
   C. Severity of deficiency determines oral dosing of vitamin D [31-33]
      a) For every 100 units of added D3, 25(OH)D concentrations increase by approximately 0.7 to 1.0 ng/mL
      b) Larger increases are demonstrated in patients with lower baseline 25(OH)D levels
      c) Increase declines as the 25(OH)D concentration increases above 40 ng/mL
   D. Adults who are vitamin D deficient, <30 ng/mL per the Endocrine Society, should be treated with vitamin D supplementation
      a) Loading dose of 50,000 IU of vitamin D orally once weekly for six to eight weeks [34]
      b) Maintenance/prevention daily dose of 800 to 2000 IU or more will be needed to avoid recurrent deficiency [34-36]

III. Vitamin D Toxicity
   A. Rare and generally occurs only after ingestion of large doses of vitamin D (>10,000 IU/day) for prolonged periods in patients with normal gut absorption concomitantly ingesting high amounts of calcium [37]
   B. Renal stones and hypercalcemia have been noted with levels of 25(OH)D greater than 150 ng/mL [38]
      a) Levels greater than 100 ng/mL should generally be avoided

VITAMIN D DEFICIENCY AND MYOPATHY

I. Mechanism of vitamin D deficiency and myopathy
   A. Specific receptors for 1-25 (OH) vitamin D are found on voluntary skeletal muscles [28]
      a) Proposed through the correction of vitamin D action on the receptor, muscle strength and physical performance should improve
      b) Myalgia should resolve
   B. Muscle function was optimal with a 25(OH)D level higher than 24 ng/mL [30]

II. Mechanism of vitamin D deficiency and SIM
   A. Statins most commonly associated with myalgia are those which exhibit CYP3A4 inhibition [24]
   B. CYP3A4 displays 25-hydroxylase and in vitamin D deficient states, vitamin D is preferentially shunted for hydroxylation to occur [38]
   C. Preferential shunting of vitamin D leads to decreased statin metabolism and increased statin concentrations in the body [38]
   D. Induction of CYP3A4 has also been demonstrated with oral vitamin D supplementation leading to increased clearance of atorvastatin [2]

III. Meta-analysis

Table 9. Data on vitamin D deficient induced myalgia in statin treated patients [39]

Study	Population	Vitamin D levels (ng/mL)	Study type	LDL therapy	Results
Duell et al (2008)	N= 99 Mean age 58.7 yrs	SIM: 20.5 AS: 30.1	Cross-sectional	All types	Vitamin D < 20 ng/mL • 62.1% SIM Vitamin D ≥ 30 ng/mL • 17.6% SIM One third of patients reported lower SIMs after unblinded treatment with high dose ergocalciferol • Most subjects also changed to a different statin
Ahmed et al. (2009)	N=621 Mean age 59 yrs	SIM: 28.6 AS: 34.2	Cross-sectional	Statin therapy: rosuva, atorva, prava	Eighty-two vitamin D deficient, myalgic patients, while continuing statins • Thirty-eight patients were given vitamin D, 50,000 units/week for 12 weeks • Resolution of myalgia in 35 patients (92%)
Linde et al. (2010)	N=64 Mean age 59.4 yrs	SIM: 28.2 AS: 24.3	Retrospective cohort	Statin therapy: All types Other therapy*	Twenty-one statin-treated vitamin D deficient participants with myalgia development • Given 1,000 IU to 50,000 IU once weekly • Fifteen patients rechallenged on statin therapy after vitamin D resolution • Fourteen remained asymptomatic
Backes et al. (2011)	N= 129 Mean age 60.4 yrs	SIM: 21.4 AS: 21.8	Retrospective cohort	Statin therapy: All types	Fifty-seven musculoskeletal complaints resulted in a dose reduction or discontinuation statin therapy • Subsequent resolution of symptoms • Vitamin D levels did not differ among patients with • History of SIM, those currently myalgia free, and those receiving statin therapy
Riphagen et al. (2012)	N= 75 Mean age 65 yrs	SIM: 18 AS: 15.2	Prospective observational	Statin therapy: simva, rosuva, atorva, prava	• Twenty-eight, 20, and five patients reported myopathy, myalgia, and myositis, respectively • No reports of rhabdomyolysis • No differences in prevalence of muscle complaints among different statins or doses of statins utilized
Eisen et al. (2014)	N= 272 Mean age 67.8 yrs	SIM: 19.1 AS: 20.2	Retrospective cohort	Statin therapy: All types	No difference in plasma vitamin D levels in regards to • Myalgia with and without CK elevation and muscle-related adverse events No relationship between plasma vitamin D level and risk of MAEs in statin users
Shantha et al. (2014)	N= 1,160 Mean age 55.9 yrs	SIM: 22.3 AS: 33.8	Retrospective cohort	Statin therapy: All types	SIM for quartiles 1 to 4 of vitamin D were 32.3, 21.5, 18.3 and 14.6%, respectively • Lowest quartile of vitamin D was independently associated with 1.21 times the hazard of the fourth quartile for developing SIM

SIM, statin-induced myopathy; AS, asymptomatic; yrs, years; *Nine patients: Niacin, fenofibrate, diltiazem or verapamil

Khayznikov M, Hemachranda K, Pandit, R et al. Statin intolerance because of myalgia, myositis, myopathy, or myonecrosis can in most cases be safely resolved by vitamin d supplementation. *N Am J Med Sci*. 2015;7(3):86-93. [40]		
Purpose	To examine whether vitamin D supplementation to normalize serum vitamin D levels would allow successful rechallenge of statin therapy.	
Design	Prospective cohort study	
Population	Inclusion criteria: • Hypercholesterolemic patients • Previous statin intolerance (≥2 statins) • Myalgia, myositis, myopathy, and/or myonecrosis • Serum vitamin D <32 ng/mL	Exclusion criteria: • Previous rhabdomyolysis • Corticosteroid use at study entry • Comorbidities associated with bone or muscle pain
Outcome	Incidence of SIM upon re-trial of statin therapy in patients treated with vitamin D supplementation	

Methods	• 146 patients included in the current analysis cohort
	  • At study entry, 85 people were given 50,000 units/week and 61 people were given 100,000 units/week
	  • Vitamin D levels were maintained between 50-80 ng/mL
	• Statin therapy was initiated three weeks after initiation of vitamin D supplementation
	  • Rosuvastatin 10 and 20 mg doses
	  • Adjustments to therapy based on ATP III
	• Data collection occurred at six, 12, and 24 month follow-up visits
	• Muscle symptom definitions were defined per the 2014 National Lipid Association's Statin Muscle Safety Expert Panel and the National Heart, Lung, and Blood Institute
	• Adherence to statin and vitamin D supplementation were reviewed by investigators at each follow-up visit
	• To demonstrate an 80% power, with a significance alpha= 0.05, 75 patients were needed
	• Nonparametric paired Wilcoxon tests were utilized to evaluate significance of the changes on vitamin D supplementation
	• Stepwise logistic regression
	  • Dependent variable: response on vitamin D supplementation and statin therapy
	  • Explanatory variable: Age, race, sex, entry serum 25(OH)D, levels at the last follow-up, change in CPK and vitamin D, and duration of vitamin D supplementation
	  • Significant level entering (SLE= 0.15) and significant level staying (SLS)=0.05	

Results	• Study cohort: 146 people
	  • Seventy-four men and 72 women, mean age of 59
	• Number of people who had follow-up visits at the six, 12 and 24 month times were 134, 103, and 82, respectively
	• Only 64 patients had all three follow-up visits
	• Mean vitamin D supplementation at all follow-up visits was 50,000 units/week
	  • Vitamin D supplementation was between 50-70,000 units/week at months six, 12, and 24 in 43%, 41%, and 38% of people, respectively
	  • Vitamin D supplementation was between 70-100,000 units/week at months six, 12, and 24 in 39%, 36%, and 37% of people, respectively	

Table 10. Mean vitamin D levels and myalgia-myositis rates based on follow-up month

n	Mo	Vit D study entry	Vit D follow-up	Vit D normalization	M-M-free on follow-up	Discontinuation of therapy+
134	6	22ng/mL	53ng/mL*	120 (90%)	118 (88%)	16 (12%)
103	12	23ng/mL	53ng/mL*	89 (86%)	94 (91%)	9 (9%)
82	24	23ng/mL	55ng/mL*	75 (91%)	78 (95%)	4 (5%)

Vit D, Vitamin D; M-M-free, Myositis-myalgia-free; mo,month; *P <0.0001 by paired Wilcoxon test; +due to myalgia-myositis

Table 11. Mean vitamin D levels of 64 patients at all follow-up visits

	Study entry	6-mo follow-up	12-mo follow-up	24-mo follow-up
Vit D	22ng/mL	54ng/mL*	55ng/mL*	56ng/mL*
VitD normalization	0	58 (91%)	58 (91%)	59 (92%)
M-M-free	0	55 (86%)	59 (94%)	57 (95%)

Vit D, Vitamin D; M-M, Myositis-myalgia-free; mo, month, *P <0.0001 by paired Wilcoxon test

- No patients had a CK >10X the ULN and only 3% of patients had a CK > 3X ULN
- Step wise selection
  - Each one-unit increase in serum vitamin D had an odds ratio of 0.96 with a 95% confidence interval (0.933-0.996)
  - The area under the curve (AUC) was 0.719
  - No participants developed hypercalcemia or nephrolithiasis and no consistent abnormal alterations in serum calcium, renal, glucose, or liver function tests throughout the duration of the study

Author's Conclusion

The only significant predictor for muscle symptoms at the last follow-up was serum vitamin D level at that time, consistent with our hypothesis that statin intolerance because of myalgia, myositis, myopathy, and/or myonecrosis was associated with low serum vitamin D and could largely be resolved by vitamin D supplementation.

Critique

Strengths:
- Prospective study

Weaknesses:
- Subjective measurement of myopathy
- Unblinded
- Goal vitamin D levels
- Lack of baseline characteristics
- Small population included in all three follow-up visits
- Rosuvastatin was the most common statin utilized

Take home

Individuals with vitamin D deficiency and history of intolerance to ≥ 2 statins may tolerate statin rechallenge with vitamin D supplementation

Morioka TY, Lee AJ, Bertisch S, et al. Vitamin d status modifies the association between statin use and musculoskeletal pain: a population based study. *Athero*. 2015; 238:77-82. [41]		
Purpose	To evaluate if vitamin D status modifies the association between statin use and prevalent musculoskeletal pain.	
Design	Cross-sectional study	
Population	Inclusion criteria: • ≥40 years old • Participated in the National Health and Nutrition Examination Survey (NHANES) from 2001 to 2004 • Measured serum 25(OH)D	Exclusion criteria: • Individuals with missing covariates of interest
Outcomes	Incidence of musculoskeletal pain reported in response to initial questioning	

Methods	• Data analyzed in 5907 individuals ≥ 40 years old with a mean 25(OH)D of 23.6 ng/mL from the National Health and Nutrition Examination Survey (NHANES) from 2001 to 2004
	• Preplanned analysis
	  • Stratified by 25(OH)D <15 ng/mL and ≥15 ng/mL
	• Exploratory analysis to assess thresholds of serum 25(OH)D
	  • <15 ng/mL, 15-30 ng/mL, and ≥30 ng/mL
	• Stratified multivariable-adjusted logistic regression models
	• Confounders: multivariable models: age, sex, race, smoking , average alcohol consumption in the past year, physical activity during the past 30 days, self-reported health status, coronary heart disease, stroke, congestive heart failure, diabetes, lung disease, arthritis, osteoporosis, body mass index (BMI), serum albumin, serum iron, opioid use in the past 30 days, and prescription nonsteroidal anti-inflammatory drug (NSAID) use in the past 30 days
	• Musculoskeletal pain was self-reported and defined as report of pain in any of the following areas: lower extremities, upper extremities, buttocks, back, and neck.
	Statin users with a 25(OH)D of <15 ng/mL tended to be more likely to have a diagnosis of coronary heart disease, stroke, congestive heart failure, diabetes, use NSAIDs and have higher BMI.	

Results	• Study population: 5907 people; 981 statin users
	  • 52.2% female, mainly non-Hispanic white (78.6%), mean age 56 years
	• Prior to stratification, musculoskeletal pain among statin users was 30%
	• Stratification
	  • 25(OH)D <15 ng/mL with musculoskeletal pain
	  • Statin users: 43.8% (95% CI, 33.5-54.6)
	  • Non-statin users: 27.0% (95% CI, 21.9-31.8)
	  • 25(OH)D ≥15 ng/mL
	  • Statin users: 28% (95% CI, 23.4-33.2)
	  • Non-statin users: 26.3% (95% CI, 24.4-28.3)
	• Multivariable analysis
	  • 25(OH)D <15 ng/mL compared to ≥15 ng/mL was not an independent risk factor for musculoskeletal pain in statin users (OR 1.04, 95% CI, .78-1.39)
	  • Additional factors contributing to musculoskeletal:
	  • <15 ng/mL group were:
	  • Poorer health status, use of opioids, higher alcohol consumption
	  • ≥15 ng/mL:
	  • Younger age, poorer health, opioid use, arthritis, opioid use, prescription NSAID use, current smoking, non-Hispanic white	

	• Exploratory analysis:
	  • <15 ng/mL: 1.90 (95% CI, 1.18 to 3.05)
	  • 15-30 ng/mL: 0.96 (95% CI, 0.72 to 1.26)
	  • ≥30 ng/mL: , 0.68 (95% CI, 0.34 to 1.34)	

Author's Conclusion	Use of a statin was associated with nearly two times greater odds of reporting musculoskeletal pain compared to non-statin users. However, among individuals with vitamin D levels ≥15 ng/mL, no association between statin use and musculoskeletal pain was observed. Our findings support the hypothesis that vitamin D deficiency modifies the risk of musculoskeletal symptoms experienced with statin use.	
Critique	Strengths: • Corrected for confounders • External validity • Sample size	Weaknesses: • Cross-sectional study • Self-reported data • No baseline characteristics • Rosuvastatin as main therapy • Unable to assess which statin and what dose • Limited data to evaluate possible effects of vitamin D at levels >30ng/mL
Take Home	Vitamin D levels <15 ng/mL may be associated with increased incidence of musculoskeletal pain in individuals 40 years and older. However, it was determined that vitamin D levels were not an independent risk factor for musculoskeletal pain between the two groups.	

Glueck CJ, Budhani SB, Masineni SS, et al. Vitamin D deficiency, myositis-myalgia, and reversible statin intolerance. *Curr Med Res*. 2011; 27(9):1683-1690. [42]		
Purpose	To assess whether vitamin D supplementation in vitamin D deficient patients would result in statin tolerance, free of myositis-myalgia.	
Design	Prospective, single center	
Population	Inclusion criteria: • Vitamin D deficient (<32 ng/mL) • Statin intolerant patients	Exclusion criteria: • Corticosteroid use at study entry • Supplemental vitamin D • Patients who refused vitamin D supplementation • Statin intolerant patients previously treated with vitamin D • Comorbid conditions that result in bone or muscle pain

Methods	• 150 participants categorized according to follow-up length
	  • Groups were mutually exclusive
	  • < 3 months, 3 to <5 months, 5 to <8 months, 8 to <14 months, 14 to <20 months, 20 to <25 months, ≥25months
	  • Vitamin D, CPK, LDL, renal and liver function, and blood glucose at each follow-up
	• Population treated with 50,000 units of vitamin D twice a week for three weeks, then once weekly.
	• After the initial first three weeks, participants restarted statin therapy
	  • Predominantly rosuvastatin 10 mg, governed by insurance reimbursement
	  • Statin dosing adjusted based on LDL and ATP III guidelines
	• Muscle symptoms were evaluated based on
	  • Definitions from the National Heart, Lung, and Blood Institute
	Patients at study entry were noted to have a history of severe myositis-myalgia if discontinued on ≥3 statins	

Statistical analysis

- 63 participants needed for 80% power
- alpha=0.05
- Wilcoxon tests for evaluation of treatment length group
- Mantel-Haenszel chi-square test to assess association of normalization of vitamin D, or relief of myositis with duration of therapy
- Fischer's exact test on univariate association of serum 25(OH)D and CPK with myalgia-myositis on re-instituted statins
- Stepwise logistic regression
    - Dependent variable: response: myalgia, no myalgia on statin and vitamin D supplementation
    - Explanatory variables:
        - Age, race, sex, BMI, entry 25(OH)D, and levels at last follow-up, change in CPK, and supplementation treatment duration

Results

Table 12. Statin used prior to and during the study

Statin use prior to and during the study				
Prior to Study Entry*				
Statin Type	Rosuvastatin	Atorvastatin	Simvastatin	Lovastatin, Pravastatin, Fluvastatin
Average dose (mg)	20	40	40	Not stated
Individuals (%)	57 (38)	79 (53)	35 (23)	38 (25)
During Study*				
Statin Type	Rosuvastatin	Atorvastatin	Fluvastatin	Simvastatin, Lovastatin, Pravastatin, Pitavastatin
Average dose (mg)	10	20	80	Not stated
Individuals (%)	97 (65)	31 (21)	7 (5)	15 (10)

*5% and 20% of patients took fibric acid in addition to statin therapy prior to and during study duration, respectively

Table 13. Vitamin D Levels and M-M on follow-up

Vitamin D level at follow-up on vitamin D supplementation and statin re-initiation*			
	n	Vitamin D Level ≥32 ng/mL	Vitamin D Level <32 ng/mL
M-M free on follow-up (%)	131	105 (80)	26 (20)
M-M on follow-up (%)	19	12 (63)	7 (37)

* p= 0.13, M-M, Myositis-myalgia-free

- The association of myalgia-myositis and vitamin D levels was not significant
    - Vitamin D normalized in 78% (p=0.68) of patients and myalgia resolved in 87% (p=0.69)
- Baseline elevations of CPK in 88% of patients remained elevated throughout the study duration
- CPK did not facilitate a distinction between patients with and without myalgia-myositis

Author's Conclusion

Participants treated with vitamin D deficiency who developed previous myositis-myalgias on statin therapy may have success on a retrial of statin therapy with vitamin D supplementation.

Critique	Strengths: • Prospective • Statin utilization	Weaknesses: • Subjective measures for muscle symptoms • Unblinded • Lack of control group • Some patients were also taking fibric acid during the duration of the study
Take Home	Normalization of vitamin D levels is not associated with the resolution of myalgia-myositis in patients able to tolerate reinitiating statin therapy.	

SUMMARY

I. Vitamin D screening
   A. Not recommended in the general population
   B. Screening of individuals at risk of vitamin D deficiency
II. Myopathy symptoms from meta-analysis seem to start around 30 ng/mL
III. Benefit and evidence for continuing statin therapy
   A. Demonstrated in several clinical trials
   B. Determining strategies to continue therapy is clinically necessary in patients who meet criteria for statin therapy
IV. While alternative dosing regimens for statin therapy have been utilized to overcome SIM, none have shown the clinical benefit compared to standard statin dosing

CONCLUSIONS

I. For patients currently on statin therapy who develop SIM, initiate a six week statin holiday and assess reason for possible increase in statin levels [13]
   A. Statin metabolism
      a) Choosing a statin metabolized by a different enzymatic system may improve tolerability
         i. Lovastatin, simvastatin and atorvastatin are metabolized by the CYP450 3A4 system in the liver
         ii. Pravastatin, rosuvastatin, fluvastatin, and pitivastatin are metabolized by alternate pathways
   B. Lipophilicity
      a) Hydrophilic statins such as pravastatin, rosuvastatin, and fluvastatin are least likely to cause myopathy
      Initiate re-trial of statin therapy with a different statin, considering drug interactions and statin lipophilicity, at equivalent dosing
      a) 43% tolerated the new statin without reporting symptoms [14]
II. If failure to statin re-trial, initiate a "drug holiday" and retrial statin therapy with a more potent statin alternative at a lower dose
   A. Atorvastatin and rosuvastatin are the two more potent statins
   B. Studies have demonstrated re-trial of more potent statin at a lower dose is effective LDL lowering therapy and majority of patients with previous statin intolerance are able tolerate this alternative [17]
III. If failure after the first two alternatives and patient has risk factors for vitamin D deficiency, assess vitamin D level
   A. Determine if treatment is necessary based on vitamin D level
   B. Vitamin D <30 ng/mL initiate supplementation [34]
      a) Loading dose: 50,000 IU of vitamin D orally once weekly for eight weeks
      b) Maintenance dose: daily dose of 800 to 2000 IU or more will be needed to avoid recurrent deficiency

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APPENDIX

Appendix A: Comparison of statin efficacy trials by patient risk [6]

Patient Risk Category	Trial	Type of Prevention	NNT
High	4S	Secondary	15
	Heart Protection Study	Primary and secondary	19
	PROVE-IT	Primary and secondary	26
Moderate	LIPID	Secondary	28
	CARE	Secondary	33
	PROSPER	Primary and secondary	48
Low	WOSCOP	Primary	42
	AFCAPS/TexCAPS	Primary	50
	JUPITER	Primary	83
	ASCOT-LLA	Primary	91
	MEGA	Primary	119

Patient risk is based on coronary heart disease event rate in the placebo group, low, <10%; moderate; 10-20%; high, >20%

Appendix B: Statin intensity based on risk factors [3]

Benefit Group		Statin Dose
Clinical ASCVD	≤ 75 years old >75 years old	High-intensity statin Moderate-intensity statin
Diabetes Mellitus (age 40-75 years)	ASCVD Score ≥7.5% ASCVD Score <7.5%	High-intensity statin Moderate-intensity statin
LDL-C	≥ 190mg/dL	High-intensity statin
No Diabetes Mellitus	≥7.5% ASCVD Risk (age 40- 75 years)	Moderate-to-high intensity statin

Appendix C: ATP III Recommendations on LDL, Total, and HDL Cholesterol (mg/dL)

LDL-Cholestrol-Primary Target of Therapy (mg/dL)	
<100	Optimal
100-129	Near optimal/above optimal
130-159	Borderline high
160-189	High
≥190	Very high
Total Cholesterol	
<200	Desirable
200-239	Borderline high
≥240	High
HDL Cholesterol	
<40	Low
≥60	High

Appendix D: Statin conversion chart. [36]

% LDL Reduction	Simvastatin (Zocor)	Lovastatin (Mevacor)	Pravastatin (Pravachol)	Fluvastatin (Lescol)	Atorvastatin (Lipitor)	Rosuvastatin (Crestor)
<24%	5mg	10mg	10mg	20mg		
25 26 27 28 29 30 31 32	10mg	20mg	20mg	40mg		
33 34 35 36 37 38 39	20mg	40mg	40mg	80mg	10mg	
40 41 42 43 44 45	40mg	80mg	80mg		20mg	5mg
48 49 50 51 52	80mg				40mg	10mg
55 56 57 58 59 60					80mg	20mg
61-63						40mg

Appendix E: Exclusion criteria meeting comorbid conditions that result in bone or muscle pain

- Diabetic sensory neuropathy
- Fibromyalgia
- Polymyalgia
- Rheumatica
- Arthritis
- Peripheral vascular disease
- Sensory neuropathy
- Hypothyroidism