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Resolution of Statin-induced Myalgias by Correcting Vitamin D Deficiency

David S. H. Bell, MD

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Abstract and Introduction

Abstract

Correction of hyperlipidemia with statins is often limited by the side-effect of statin-induced myalgias. Vitamin D deficiency is also associated with myalgias that resolve with correction of the vitamin D deficiency. Myalgias associated with statin therapy may also resolve with correction of vitamin D deficiency. This case report presents a case where cardioprotective lipid levels were achieved with a powerful statin only after correction of vitamin D deficiency.

Introduction

Vitamin D deficiency is endemic in Western society and a strong correlation between low vitamin D levels and myalgias has been reported.[1,2] Indeed, myalgias resulting from vitamin D deficiency are often misdiagnosed as fibromyalgia.[3] Voluntary muscle has a highly specific nuclear receptor for 1-25 (OH) vitamin D and correction of vitamin D deficiency through its action on this receptor improves muscle strength, physical performance, and myalgias.[4]

Statins are commonly associated with myalgias, less commonly with myositis, and rarely with rhabdomyolysis.[5] The statins that are most commonly associated with myalgias (simvastatin and atorvastatin) inhibit the enzyme CYP3A4. Water soluble statins such as pravastatin, fluvastatin, and rosuvastatin are metabolized by CYP2C9 and are less likely to cause myalgias. The clinical experience of many endocrinologists and cardiologists is that the myalgias associated with statin therapy can often be resolved by correcting vitamin D deficiency.[6] To date there have been reports of correction of muscle weakness and myopathy with resolution of vitamin D deficiency and associations of vitamin D deficiency and myalgias in statin-treated patients who were studied retrospectively.[7,8] However, to date only one prospective study has reported that the correction of vitamin D deficiency will lead to the resolution of statin-induced myalgias in some patients.[9] In this small case series, four of six patients with statin-induced myalgias and vitamin D deficiency on rechallenge with the same statin following vitamin D repletion and statin therapy was tolerated for at least six months. This report presents a case where, after many years of suboptimal therapy for hyperlipidemia, the identification and correction of vitamin D deficiency resulted in a successful rechallenge with effective statin therapy and for the first time control of hyperlipidemia.

Clinical Presentation

A 52-year-old white female, who at age 30 was found to have a total cholesterol of 308 mg/dL, which increased to 511 mg/dL while pregnant at age 35, presented for a second opinion on how her hyperlipidemia could be controlled. Every time that she had tried to use a statin, she developed intolerable muscle pains, cramps, and weakness. The statins which she had attempted to use were pravastatin, simvastatin, lovastatin, atorvastatin, and rosuvastatin. In addition, because of flushing, she had not been able to tolerate nicotinic acid, and the only medication that she had found to be tolerable was ezetimibe. Ezetimibe was relatively ineffective, since on ezetimibe 10 mg daily her total cholesterol was 391 mg/dL, calculated low density lipoprotein (LDL) cholesterol 307 mg/dL, high density lipoprotein (HDL) cholesterol 47 mg/dL, non-HDL cholesterol 344 mg/dL, triglyceride 187 mg/dL, and the triglyceride to HDL ratio 4:0. Her renal function was normal, and she did not have proteinuria. She was euthyroidal and euglycemic and had no evidence of hepatic or renal impairment and was not taking medications that would cause hyperlipidemia. She did not drink alcoholic beverages.

She had a positive family history of cholesterol levels above 300 mg/dL in her mother, sister, and son but not in her brother. Her fasting glucose was 78 mg/dL and there was no family history of diabetes, premature cardiovascular disease, or hypertension.

Following the initial assessment, it was found that she could tolerate the weak hydrophilic statin- extended release fluvastatin 80 mg, and this, in conjunction with ezetimibe 10 mg, colesevelam 1250 mg three times daily after meals, and high dose omega 3 fatty acids after three years, reduced her total cholesterol to 275 mg/dL, calculated LDL cholesterol to 189 mg/dL, non-HDL cholesterol to 221 mg/dL, and triglyceride to 158 mg/dL with her HDL increasing to 54 mg/dL (Fig. 1).

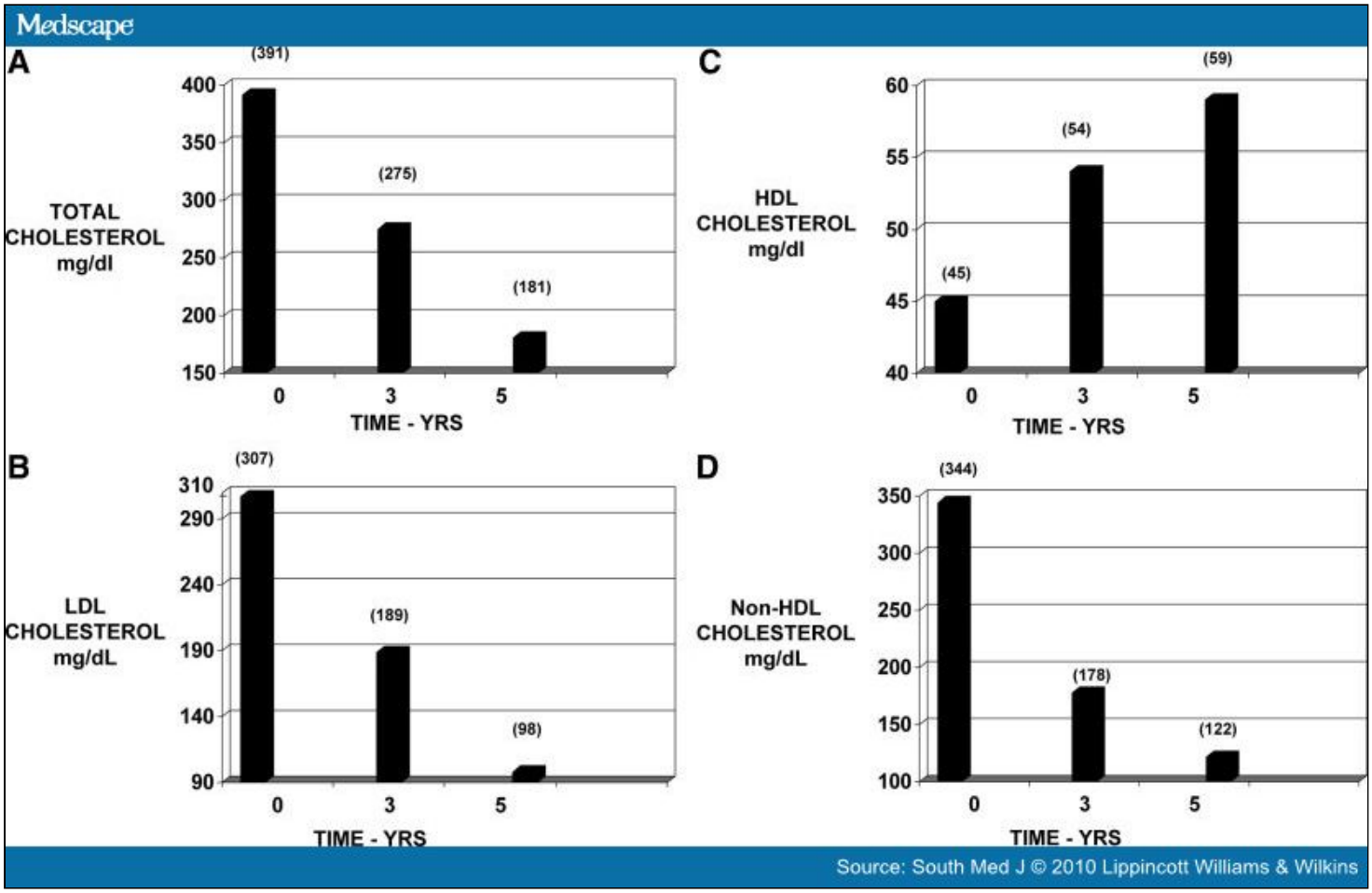

Figure 1.

A, Total and low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and non-HDL cholesterol at baseline on ezetimibe only, after three years on ezetimibe, fluvastatin and colesevelam. *B*, Low-density lipoprotein. *C*, High-density lipoprotein. *D*, Non-high-density lipoprotein cholesterol.

Five years after the initial consultation, her 25-OH vitamin D was checked and found to be 17 ng/mL (normal above 30 ng/mL). This was treated with 100,000 units of vitamin D_2 weekly, and three months later her 250-OH vitamin D level was 42.2 ng/mL. Correcting her vitamin D level raised the possibility that she would be able to tolerate a more powerful statin, and the extended-release fluvastatin was replaced with rosuvastatin 10 mg daily. Three months later her total cholesterol was 181 mg/dL, calculated LDL cholesterol 98 mg/dL, HDL cholesterol 59 mg/dL, non-HDL cholesterol 122 mg/dL, and triglyceride 122 mg/dL (Figs. 1–4). She reported no muscle pain, cramps or weakness.

Discussion

This case shows that statin-induced myalgias, which previously prohibited the use of much needed effective and powerful statin therapy, resolved with the correction of vitamin D deficiency, thus facilitating the use of an effective statin which could previously not be tolerated. This patient may be one of many patients who need effective and even lifesaving statin therapy but are prohibited from utilizing powerful statin therapy because of myalgias associated with unrecognized vitamin D deficiency.

Many patients develop myalgias due to statin induced myositis. In the more severe cases of myositis creatinine kinase (CPK), levels are elevated. In less severe cases, CPK levels are normal. However, even without an elevation of CPK, muscle biopsies have shown inflammation without statin-induced muscle damage. More definitive studies with electromicroscopy have shown that even in mild cases of statin-induced myositis there is a breakdown of the T-tubular system and subsarcolemmal rupture.[10] In addition, an upregulation of the expression of the ryanodine receptor 3 indicating an intracellular leak is associated with vitamin D deficiency.[11] Since statins are, in general, anti-inflammatory molecules, the inflammatory infiltrate, due to muscle damage, is seen in these muscles and localized.[12]

The effects of vitamin D on muscle are mediated through the attachment of 1–25 OH vitamin D to its nuclear receptor, resulting in changes in gene transcription that generate messenger RNA and stimulate protein synthesis.[13] Presumably, with vitamin D

deficiency, the generation of proteins that are needed for repair of the T-tubular system and prevention of subsarcolemmal rupture does not occur.

Therapies used to avoid statin-induced myalgias, such as the weaker hydrophilic statins, fluvastatin, and pravastatin, have been less than satisfactory in obtaining the goals of anti-lipid therapy, as have nondaily dosing regimens.[14] The results of the use of CoQ10 to treat or avoid the symptoms of tenderness, myalgias, cramping, and elevated CPK has at best been equivocal.[15] Therefore, the possibility that the correction of vitamin D deficiency will liberate the victims of statin myopathy so that their cardiovascular risk and cardiovascular events can be decreased and their life expectancy increased is an exciting prospect for an otherwise recalcitrant complication of statin therapy.

Conclusion

I have described a hyperlipidemic patient whose ability to utilize statins was previously compromised by statin-induced myalgias which did not recur following the correction of her vitamin D deficiency. Patients who are intolerant of statin therapy should be evaluated for vitamin D deficiency since vitamin D therapy has the potential to enable hyperlipidemic subjects to utilize these life saving drugs.

Sidebar

Key Points

- Therapy with statins is often limited by the common side effect of statin-induced myalgias.
- Vitamin D deficiency is common and is associated with myalgias.
- In this case, correction of vitamin D deficiency permitted the use of a powerful statin and correction of hyperlipidemia.
- When statin-induced myalgias occur, check for vitamin D deficiency.

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