Commentary

Possible mechanisms of interaction between statins and vitamin D

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Introduction

Myalgia, the most common statin-related complaint, may affect 10–15% of patients on statins¹ and affect patient compliance. There have been several reports regarding the relationship between vitamin D deficiencies and statin-induced myalgia.²⁻⁶ In addition, vitamin D levels have been reported to affect the lipid lowering actions of some statins.⁸,⁹ The mechanism of these interactions is poorly understood and is believed to contradict the expected action of vitamin D on statin metabolism.⁷ In a published review,⁷ authors speculate that vitamin D, by activating CYP3A4, should decrease atorvastatin levels and the efficacy of atorvastatin in reducing total and LDL cholesterol, but the opposite has been observed.⁸ In this article, we have tried to connect the missing links between the statin metabolism and the actions of vitamin D in inducing statin metabolism. We researched the chemistry and metabolism of the statins especially in terms of the role of Cytochrome P-450 (CYP). Since not all the statins are metabolized similarly, the effect of vitamin D on their metabolism is not universal.

Literature survey

Vitamin D levels and statin effectiveness

Some research data suggest that there is a relationship between vitamin D levels and statin effectiveness. One research has suggested that adequate vitamin D levels >30 nmol/l may be required for atorvastatin to reduce lipid levels⁸ because 63 vitamin D-deficient patients did not respond to low- or high dose of atorvastatin in terms of total cholesterol or LDL at 12 months while patients with insufficient and normal levels of vitamin D showed expected reduction in cholesterol. In one additional study,⁹ supplemental vitamin D (800 IU/day) enhanced the effect of atorvastatin therapy on total and LDL cholesterol (P < 0.005).

Vitamin D deficiency and statin myopathy

There is also evidence for the relationship of vitamin D deficiency to statin myopathy.²⁻⁶ One study³ reported resolution of myalgia (92%) after restoring vitamin D levels in vitamin D-deficient patients. The authors speculated that patients with concurrent vitamin D deficiency may reflect a reversible interaction between vitamin D deficiency and statins on skeletal muscles. Another report suggests that vitamin D deficiency potentiates statin-induced myalgia or causes drug-unrelated myalgia in a subset of statin-treated patients.⁶

Vitamin D as an inducer of CYP enzymes

Vitamin D is known to activate CYP3A4.¹⁰,¹¹ 1α, 25-(OH)₂D₃ is an inducer of CYP3A4 in human hepatocytes, as previously observed by researchers in intestinal cell lines.¹¹,¹² The fully
active dihydroxylated metabolite of vitamin D3 induces the expression of not only CYP3A4, but also CYP2B6 and CYP2C9 in primary human hepatocytes. Hydroxylated vitamin D derivatives also possess 3-hydroxy-3-methyl-glutaryl-Coenzyme A (HMG-CoA) reductase activity.

**Statin metabolism and its clinical significance**

There are seven statins currently marketed. Statins can be classified as lipophilic or hydrophilic. Atorvastatin, simvastatin, lovastatin, fluvastatin and pitavastatin are lipophilic and undergo first-pass metabolism by gut and liver. Pravastatin and rosuvastatin are hydrophilic statins with good oral bioavailability. Not all statins are metabolized in a similar way. Three of the statins are metabolized primarily by CYP3A4: simvastatin, atorvastatin and lovastatin; fluvastatin is metabolized by CYP2C9, and pravastatin and rosuvastatin are not significantly metabolized by CYP enzymes. Pitavastatin is marginally metabolized by CYP2C9 and to a lesser extent by CYP2C8.

Atorvastatin undergoes aromatic hydroxylation at the p and o positions of the phenyl ring connected to the carboxamide group by CYP3A4 (Figure 1). These metabolites are both active and are responsible for the clinical activity of the drug.

Lovastatin and simvastatin metabolites are inactive (Figure 2).

CYP2C9 is the major metabolic pathway for fluvastatin. CYP2C9 hydroxylates the indole ring of fluvastatin to produce active metabolites. In addition, fluvastatin also undergoes CYP2C9-mediated dealkylation of the indole nitrogen and hydroxylation of the isopropyl group on the indole ring to provide additional active metabolites. None of these active metabolites is believed to contribute to the observed activity of this statin (Figure 3).

Rosuvastatin is only modestly metabolized by CYP and the enzyme inhibitors do not increase the clinically significant toxicity.

There are significant drug–food interactions with statins and CYP enzyme inhibitors indicating the relationship between statin metabolism and the development of myopathy. Grapefruit juice inhibits CYP enzymes in the intestinal mucosa and liver and increased toxicity has been observed when statins have been consumed with grapefruit juice. The inhibition of first-pass metabolism of lovastatin or simvastatin could result in 10–20-fold elevations (oral bioavailability increasing from 5% to 100%) in steady-state concentrations with a marked liability to drug toxicity. Some other inhibitors of statin metabolism are cyclosporine, itraconazole, gemfibrozil, etc. The incidence of muscle disorder increases >10-fold when statins are given with these drugs.
Discussion

While CYP enzyme inhibitors increase the toxicity of CYP metabolized statins, the CYP enzyme inducers will enhance the metabolism resulting in less toxic metabolites. Since vitamin D is an inducer of CYP3A4 and CYP2C9, it can be expected that it will help in the metabolism of certain statins and reduce their toxic side effects. This is exactly what has been observed in the previously cited reports and studies.

CYP3A4 and CYP2C9 are both involved in the oxidative metabolism of the various statins, but there is little consistency in the chemical nature or pharmacological activity of the metabolites. The metabolic rate and the impact of that metabolism

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Figure 2. Inactive metabolites of lovastatin and simvastatin.

Figure 3. Hydroxylation of fluvastatin by CYP2C9.
on potency and duration of action must be evaluated separately for each statin drug. The fact that vitamin D is a known inducer of CYP3A4 and the metabolites are responsible for pharmacologic activity explains the enhanced enzyme activity and reduced toxicity of atorvastatin after vitamin D supplementation. CYP3A4 metabolites of lovastatin and simvastatin are inactive. Since inhibition of CYP3A4 metabolism results in increased toxicity,\textsuperscript{29,30} enhancing CYP3A4 metabolism should result in fast metabolism and less drug availability for muscle toxicity. However, the increased lipid lowering action by atorvastatin will not be expected in the case of simvastatin and lovastatin. Fluvastatin is metabolized into active ingredients by CYP2C9. Even though these metabolites are not supposed to be responsible for the action of fluvastatin, there is a possibility of food and drug interaction with CYP2C9 enzyme inhibitors or inducers. Vitamin D is also known to induce transcription of CYP2C9.\textsuperscript{11} Thus, vitamin D supplementation with fluvastatin would mean increased metabolism and reduced toxicity of fluvastatin. Since these metabolites are not active, we cannot expect the increase in lipid lowering effects as seen in the case of atorvastatin.

Pravastatin and rosvastatin are hydrophilic statins with good oral bioavailability and better safety profile. Since pravastatin, rosuvastatin and Pitavastatin are not metabolized by cytochromes to any appreciable extent, enzyme induction or vitamin D supplementation would not enhance their activity or reduce myalgia caused by them.

Conclusions

Statins, a proven class of drugs that lower cholesterol levels, reduce the threat of cardiovascular diseases (CVDs). However, statins are also related with unpleasant side effects like myalgia. Interestingly, deficiency in vitamin D has also been known to cause muscle pain that initiated the study of possible interactions between statins and vitamin D. That there are several contradicting reports of the effect of vitamin D levels on statin function and myalgia makes the case for reviewing the mechanism of interaction between vitamin D and statins.

Insufficient CYP enzyme activity related to vitamin D deficiency may be responsible for inactivity and increased toxicity of CYP metabolized statins in some patients. Based on above explained mechanisms, we suggest that the concurrent prescription of vitamin D along with atorvastatin might reduce dosage requirements of the drug. Vitamin D may also lessen the risk of adverse effects including myopathy in case of atorvastatin, simvastatin, fluvastatin and lovastatin. Vitamin D supplement may have moderate or no effect on the dosage requirement or side effects of pravastatin, rosvastatin and pitavastatin. Since vitamin D has mild HMG-CoA reductase activity, it will work synergistically with all statins. In accordance with current findings regarding the role of vitamin D in CADs, supplementation with vitamin D will also provide additional protection against stroke,\textsuperscript{31} as well as economic benefits from lower drug costs.

Although we have tried to address one aspect of vitamin D–statin interaction in this article, i.e. the effect of vitamin D levels on statin performance and toxicity, the entire picture of interaction between statins and vitamin D is enigmatic at best. In different studies, statins have shown variable effects on vitamin D levels in humans.\textsuperscript{34–37} For example, rosuvastatin robustly increases vitamin D levels\textsuperscript{36} and it has been proposed that the reported beneficial effects of rosuvastatin in the Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) were in part related to a statin-induced elevation of vitamin D blood levels in a vitamin D-insufficient population.\textsuperscript{39} In summary, the mechanism of statin-induced vitamin D levels is still a gray area to be explored.

It is thus imperative that there is a need for research based on individual statin, including matched blinded controls and placebo controls to determine a causal association between vitamin D and statins. It would be wise to extrapolate from this research and future research may use these findings as a stepping stone toward more complex statin–vitamin D interactions.

References


