

Statins and vitamin D

A hot topic that will be discussed for a long time

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Recently, evidence regarding the link between increased cardiovascular events and vitamin D is accumulating. The effect of statins, which are very well known to have protective cardiovascular effects, on vitamin D is one of these research topics attracting interest lately. However, the findings of the studies examining the influence of different statins on vitamin D levels are controversial.

We reviewed the paper of Glossmann et al. regarding our articles about statins and vitamin D. The authors were right indicating that the magnitude of the rise in 25-hydroxy vitamin D observed with rosuvastatin treatment is surprising and our hypothesis that a common catabolic pathway, cannot explain this magnitude of increase alone. In our first study, after 8 weeks of rosuvastatin therapy, mean 25-hydroxy vitamin D levels rose from 14.0 ng/ml to 36.3 ng/ml by a mechanism which could not be clearly explained by then.¹ This amount of rise in 25-hydroxy vitamin D was an unexpected result. At that time, the mechanism underlying this high magnitude effect could not exactly be clarified. In the light of several studies in this field which took place in the literature since 2009 (the year our article was published) a novel hypothesis discussed below has been created. After observing the results of this first study, we wondered whether this effect is a group effect of statins or an effect specific to rosuvastatin. Therefore, we planned the second study to compare the effect of rosuvastatin and fluvastatin on 25-hydroxy vitamin D. In this second study, the observed rise of mean 25-hydroxy vitamin D was from 11.8 ng/ml to 35.2 ng/ml

after 8 weeks of rosuvastatin therapy, whereas 8 weeks of fluvastatin therapy did not show a significant rise.² A similar magnitude of rise in vitamin D levels in rosuvastatin groups was observed in both studies.

Our second study was a prospective, randomized clinical trial. The patients were randomized by simple randomization method into rosuvastatin and fluvastatin groups. These groups were followed prospectively through 8 weeks. Patients receiving oral vitamin D supplementation and all other phosphorus-calcium modifying drugs were excluded from the study as mentioned in the article. One demographic finding that was not mentioned in the articles is about clothing habits. Within the total sample which was 134 patients, 85 were female, and within the female patients 66 (77.6%) of them were covered due to religious reasons. However, as the study was conducted during the winter season (October 1, 2008–March 2, 2009), all of the patients were clothed compatible with winter conditions which causes diminished exposure to sunlight. Furthermore, even if some UV light is present during winter in Ankara, people are avoiding staying outside due to cold weather. Therefore, vitamin D deficiency is a common feature in our area in winter months. The results of our study showed that frequency of vitamin D deficiency was extremely high in the study group. Vitamin D levels of 64 patients (47.8%) were below or equal to 10 ng/ml and the median 25-hydroxy vitamin D levels were 11.8 ng/ml at baseline. In Ankara Kecioren region, most of the patients and the staff working in our hospital (including

Keywords: statin, vitamin D, rosuvastatin, fluvastatin, pleotropic effects

Submitted: 12/09/11

Accepted: 03/28/12

<http://dx.doi.org/10.4161/derm.20188>

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ourselves) are vitamin D deficient during winter. Our government is planning to enrich dairy products with vitamin D supplementation because of this reason. If statins are increasing vitamin D levels, this effect would be best observed in vitamin deficient populations. This may be the reason of the big magnitude of rise of 25-hydroxyvitamin D levels in our studies. In USA and Europe, most of the states are supplementing at least some of the dairy products with vitamin D. Therefore, it is difficult to compare our results with studies from these countries. Both of our studies were conducted at the same hospital, during the same months of different years, examining the patients residing at the same region with similar cultural, rural, and environmental features. Therefore, when viewed from this aspect, the finding that comorbidities, mean age, and some demographic properties being similar in both studies is not a surprising result.

We are still wondering how rosuvastatin increases 25-hydroxyvitamin D levels. We

suggest another hypothesis about this. Scavenger Receptor class B type I (SR-BI), Cluster Determinant 36 (CD36), and Niemann-Pick C1 Like 1 (NPC1L1) membrane transporters are involved in cholesterol transport across enterocyte membranes. Reboul et al. have recently showed that intestinal absorption of vitamin D is not occurring only by a simple passive diffusion process, but also some membrane transporters such as SR-BI, CD36 and NPC1L1 may be involved in this phenomenon.³ It was previously shown that administration of atorvastatin for 6 weeks resulted in 50% increase in SR-BI mRNA levels in rabbits.⁴ Furthermore, SR-BI mRNA expression was negatively correlated with the serum total cholesterol levels. In vitro experiment by the same group also showed that atorvastatin induced a significantly increased SR-BI mRNA expression in a dose-dependent manner. Compared with that at baseline, atorvastatin at 0.1, 1.0 and 10 mol/l induced 76.2%, 105.8% and 161.9% increase in SR-BI mRNA

levels ($p < 0.01$), respectively. Therefore, our initial hypothesis that rosuvastatin may be increasing vitamin D levels by interfering with the metabolism of vitamin D, may be an inadequate explanation. We propose that some statins may be increasing the absorption of vitamin D by stimulating the expressions of cholesterol transporters. This effect, which was shown with atorvastatin, can be studied with rosuvastatin, and may open up a horizon to explain the link between statins and vitamin D.

In conclusion, our study published by Ertugrul et al. regarding the influence of rosuvastatin and fluvastatin on 25-hydroxy vitamin D was a randomized, prospective clinical trial. It naturally has some limitations like every study. One of them was being a single centered study. This subject has become a hot topic and it seems that it will be discussed for a long time. A multicentered, randomized, placebo controlled, and double blinded trial with a large sample should be designed to clarify the effect of statins on vitamin D levels.

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