The statin D-lemma

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Yavuz et al.\textsuperscript{1} in 2009 reported that patients with hyperlipidemia who were in a prospective study evaluating rosuvastatin in hyperlipidemic patients made an unexpected observation. Blood concentrations of 25-hydroxyvitamin D \([25(\text{OH})D]\) and 1,25-dihydroxyvitamin D \([1,25(\text{OH})_2D]\) increased after 8 weeks of treatment. In addition they observed the expected significant declines in total cholesterol, LDL cholesterol and triglycerides. In a follow up study to determine whether this observation could be generalized to other statins Ertugrul et al.\textsuperscript{2} compared the effect of rosuvastatin 10 mg daily to fluvastatin 80 mg daily for 8 weeks on serum \(25(\text{OH})D\) concentrations and parameters of bone metabolism. They reported that rosuvastatin was significantly more effective than fluvastatin in lowering total and LDL cholesterol levels. The group receiving rosuvastatin demonstrated a significant increase in serum \(25(\text{OH})D\) concentrations whereas no significant change was observed in the group receiving fluvastatin. The authors suggested that the observed increase in serum \(25(\text{OH})D\) concentrations was not a class drug effect but rather specific for rosuvastatin. They were unable to show that rosuvastatin had any influence on circulating levels of \(1,25(\text{OH})_2D\) that had been previously reported by the same group.\textsuperscript{1}

There has been concern that because statins inhibit cholesterol biosynthesis that they may also influence the cutaneous production of vitamin D\textsubscript{3} from its cholesterol precursor, 7-dehydrocholesterol. However most of the vitamin D\textsubscript{3} produced in the skin occurs in the bloodless epidermis\textsuperscript{3} and as a result statins do not appear to have any influence on cholesterol biosynthesis in the epidermis nor influence the cutaneous production of vitamin D\textsubscript{3}. Both Yavuz et al.\textsuperscript{1} and Ertugrul et al.\textsuperscript{2} conducted their studies in the late fall and winter to minimize the influence of sun exposure on circulating levels of \(25(\text{OH})D\). Although they did not document dietary intake for vitamin D they did note that there was very little vitamin D in the diet of their patients. The \(25(\text{OH})D\) was measured by a radioimmunoassay.

This remarkable and unexpected observation was critically analyzed by Glossman and Blumenthaler.\textsuperscript{4} It is true that during the winter at 39.6° N latitude essentially no vitamin D is produced in the skin from sun exposure due to the increased zenith angle of the sun.\textsuperscript{5} However Glossman and Blumenthaler\textsuperscript{4} correctly point out that Ankara has a mean elevation of 938 meters (3077 feet) and therefore there is a significant increase in the amount of UV radiation that reaches Ankara compared with a lower altitude such as in Istanbul (288 meters) and therefore it was possible that vitamin D\textsubscript{3} could have been produced in the skin of the subjects which could have influenced the outcome of the study. Holick et al.\textsuperscript{6} reported that in November at a latitude of 27° N in India very little vitamin D\textsubscript{3} was produced in Agra whereas at approximately 3,000 feet altitude at the same latitude there was a 3-fold increase in the production of vitamin D\textsubscript{3}. Therefore it was possible that environmental factors independent of the statin intervention could have influenced the circulating concentrations of \(25(\text{OH})D\). However it is doubtful that this would’ve had such a dramatic effect on the circulating levels of \(25(\text{OH})D\) since it’s unlikely that the sun exposure habits would have been that much different between the groups.

A more important issue however is whether a metabolite of rosuvastatin...
interfered with the antibody assay that was used to measure circulating 25(OH)D concentrations as noted by Glossman and Blumenthal. This study would have been greatly strengthened if they had verified by liquid chromatography tandem mass spectroscopy that the observed 25(OH)D was indeed 25(OH)D.

Glossman and Blumenthal have also raised several other valid criticisms regarding the design of the two studies reporting that rosuvastatin dramatically increased the blood concentrations of 25(OH)D. Furthermore a recent study by Demir et al. was unable to confirm the observations by Yavuz et al. and Ertrugul et al.

It would have been very interesting if the authors had reported on the change in circulating concentrations of 25(OH)D for each of the individual subjects to determine individual responses. It is quite remarkable that the blood levels could have increased so dramatically in just 8 weeks. Furthermore it is surprising that blood levels as high as 100 ng/mL was achieved in subjects receiving rosuvastatin especially when the baseline levels were 11.8 ng/mL. As noted by Glossman and Blumenthal this would require ingesting 9,000 IU vitamin D daily for at least 6 weeks. For every 100 IU ingested the circulating level of 25(OH)D increases by ~1 ng/mL.

In response to these criticisms Yavuz and Ertrugul thoughtfully provide a variety of mechanisms that could explain the dramatic increase in circulating concentrations of 25(OH)D but they themselves admit that their observation is surprising and that a randomized controlled multicenter study should be conducted to determine whether rosuvastatin can have a dual role in improving cardiovascular health by reducing cholesterol and triglycerides while at the same time enhancing vitamin D status.

I must admit that after reading Ertrugul et al. I began reviewing blood levels of 25(OH)D in my patients who are on rosuvastatin and vitamin D compared with patients on the same amount of vitamin D who were not taking this statin. Anecdotally I did not see any significant increase in the blood level of 25(OH)D above what would have been expected from the vitamin D that I was treating them with. Therefore the serious doubts raised by Glossman and Blumenthal D-serve further attention.

Acknowledgments
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