Vitamin D and Lipids
Do We Really Need More Studies?
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The interest in vitamin D has exploded during the last decade, illustrated by the number of new vitamin D-related articles registered in PubMed, which is between 50 and 100 every week. This is also reflected in the lay press, with numerous articles promoting the beneficial effects of the D-lightful sunshine hormone vitamin D. If read uncritically, vitamin D appears to be good for almost any condition thinkable and is today the hottest magic cure. But why has this happened?

First of all, vitamin D is nature’s own product, an ancient hormone produced in the skin by sun exposure. It promotes the intestinal calcium absorption, has a well-known effect in preventing and curing rickets, and the role of vitamin D in calcium metabolism and skeletal health is indisputable. Secondly, the enzyme necessary for the final activation of vitamin D as well as the vitamin D receptor have recently been identified in tissues throughout the body, and extraskeletal effects of vitamin D were therefore to be expected. Thus, when methods for measuring 25(OH)D (the most abundant vitamin D metabolite and the one used to evaluate a subject’s vitamin D status) became widely available, numerous observational studies were published. And almost without exception, high serum 25(OH)D levels were associated with good health, whereas low levels were predictors of type II diabetes mellitus, cancer, cardiovascular disease, immunologic diseases, and even mortality. In 4751 participants in the Tromsø study from Northern Norway, over a follow-up period of 11 years those in the lowest serum 25(OH)D quartile had a 32% increased mortality risk as compared with those in the highest 25(OH)D quartile. And similarly, in the 1739 subjects in the Framingham Offspring Study followed for 5.4 years, those with serum 25(OH)D levels <10 ng/mL had a hazard ratio of 1.80 for a cardiovascular event as compared with those with levels >15 ng/mL. On the basis of these and numerous other observational studies, a great optimism for improving health with vitamin D supplementation was created. And, indeed, if there is a causal relation between low serum 25(OH)D levels and common diseases like cancer and cardiovascular disease, the impact of vitamin D supplementation, which is cheap and simple to perform, could be formidable. Although there is no consensus on what are optimal serum 25(OH)D levels, there is no disagreement that vitamin D deficiency is prevalent not only in countries with low UV exposure but also in countries close to the equator because of clothing habits. Accordingly, vitamin D supplementation could potentially be beneficial to billions of people, but still, hard evidence is lacking.

The association between vitamin D and cardiovascular disease could be explained by a lipid-lowering effect of vitamin D. This has been substantiated in several cross-sectional studies, and there is a general agreement that high serum 25(OH)D levels are associated with a favorable serum lipid profile. However, associations derived from observational studies are no proof of causality, particularly for vitamin D. People in good health stay outdoors more and therefore get more sunshine and vitamin D production in the skin, and they may also have more healthy food habits. Their higher serum 25(OH)D levels may therefore be the result and not the cause of good health. To avoid this bias and to address the key question on causality, the traditional approach has been randomized clinical trials (RCTs), which are, however, time-consuming and expensive. For hard end points like cardiovascular disease or death the number of patients needed in such trials is usually from 5000 to 10 000, and even for a surrogate end point like serum lipids the number needed is substantial. Thus, if wanting to show a 5% decrease in low-density lipoprotein (LDL) cholesterol levels, which corresponds to the difference between subjects with serum 25(OH)D <20 ng/mL and subjects with levels >30 ng/mL reported in the present issue of Circulation by Ponda et al, one would have to include at least 1200 subjects if wanting a power of 0.80 and a significance level of 0.05. A more realistic expectation would be a lowering of 2.5%, and then one would have to include close to 4000 subjects. Ponda et al present another approach which, with its cost-effectiveness, is highly attractive. Based on >4 million patient laboratory test results they were able to select a group of 108 711 subjects who had repeated serum 25(OH)D and lipid testing 4 to 26 weeks apart. In both men and women there was with increasing 25(OH)D strata a modest but highly significant decrease in total cholesterol, LDL cholesterol, and triglycerides, and an increase in high-density lipoprotein cholesterol. This is basically confirmatory of what has been published by others as summarized in two recent reviews on vitamin D and lipids. More interesting, however, are the results from the interventional or longitudinal part of the study. Among the 108 711 subjects, 6260 had serum 25(OH)D levels <20

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levels differed significantly between the two groups. Also, the subjects in the repletion group were more likely to have a diagnosis of lipid disorder or hypertension than the control group, and accordingly, more likely to receive some sort of treatment or advice regarding lipids than the controls. And, most important, subjects with serum 25(OH)D levels <20 ng/mL are probably advised (or should be) to take some sort or vitamin D supplementation. It is highly unlikely that the subjects who followed that advice (or who had the initiative to ask for the result of the 25(OH)D measurement, or who had a physician who took the responsibility to follow-up low serum 25(OH)D levels) are identical to the subjects who did not receive or follow advice on vitamin D substitution. An improvement in the serum lipid levels could therefore have been expected in the repletion group unrelated to an effect of the vitamin D substitution. However, that was not seen. One could therefore suspect that a negative effect of vitamin D on the serum lipids, as indicated in the vitamin D meta-analysis,12 was masked in the present study. Furthermore, as emphasized by the authors, no information on medication was available, which in this study was particularly important as statins by themselves may affect the serum 25(OH)D levels.13

In spite of the above objections and shortcomings, the study by Ponda et al10 is of great importance as it underscores that cross-sectional results are not necessarily reproduced in prospective studies and that cross-sectional data cannot and should never be taken as evidence of causality. This lesson applies not only to the relation between vitamin D and lipids but practically to the entire clinical vitamin D field. As stated by the Institute of Medicine,14 there is at present no solid evidence for a protective effect of vitamin D on major extraskeletal diseases, and it should be recalled that vitamin D is not the only substance that has been associated with positive health outcomes. Cures with \( \beta \)-carotene, vitamin A, C, and E, and selenium have all been promising but on proper testing turned out to be disappointing.15

A similar approach as the one presented by Ponda et al10 could be used by others who have access to large databases with laboratory test results from more than 1 time point, and particularly if the data can be merged with databases with clinical information and outcomes. However, if doing so one should bear in mind that this approach can never be used as a substitute for an RCT and that there are, as in the present case, many pit-falls in the interpretation. It should also be mentioned that the impressive size of the study by Ponda et al10 may give it an unjustified impact and demotivate other researchers from doing the proper RCTs. It is therefore to the credit of the authors that they have chosen a very cautious title of their paper: “Vitamin D May Not Improve Lipid Levels.”

There are a number of large and well-designed RCTs with vitamin D on its way, and within a few years we will know whether the effects of vitamin D are as D-lightful as the observational data indicate. Until then, there is no need to rush recommendations on vitamin D supplementation based on associations and speculations. So this editorial, as almost every article written on effects of vitamin D, has to conclude that large RCTs are still needed, and for the effects on lipids,
subjects with a combination of vitamin D deficiency and hyperlipidemia should in particular be studied.

**Disclosures**

None.

**References**


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