Vitamin D and Lipids: Do We Really Need More Studies?

Running title: Jorde et al.; Vitamin D and lipids

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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 sun-shine 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 vitamin D’s role in calcium metabolism and skeletal health is indisputable.\(^1\) Secondly, the enzyme necessary for the final activation of vitamin D as well as the vitamin D receptor (VDR) have recently been identified in tissues throughout the body, and extra-skeletal effects of vitamin D were therefore to be expected.\(^2\) 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, while low levels were predictors of type II diabetes, cancer, cardiovascular disease (CVD), immunological diseases and even mortality.\(^3\) In 4751 participants in the Tromsø study from Northern Norway, those in the lowest serum 25(OH)D quartile had over a follow-up period of 11 years a 32 % increased mortality risk as compared to those in the highest 25(OH)D quartile.\(^4\) 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 to those with levels > 15 ng/ml.\(^5\) Based on 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 been low serum 25(OH)D
levels and common diseases like cancer and CVD, 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.6 Accordingly, vitamin D supplementation could potentially be beneficial to billions of people, but still, hard evidence is lacking.

The association between vitamin D and CVD 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 favourable serum lipid profile.7-9 However, associations derived from observational studies are no proof of causality, particularly for vitamin D. People in good health stay more out-doors and therefore get more sunshine and vitamin D production in the skin, and 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 however are time consuming and expensive. For hard endpoints like CVD or death the number of patients needed in such trials is usually from 5,000 to 10,000, and even for a “surrogate” endpoint like serum lipids the number needed is substantial. Thus, if wanting to show a 5% decrease in 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.,10 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 that with its cost-effectiveness is highly attractive.\textsuperscript{10} Based on more than 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 HDL cholesterol. This is basically confirmatory of what has been published by others as summarized in two recent reviews on vitamin D and lipids\textsuperscript{8,9}

More interesting, however, are the results from the “interventional” or longitudinal part of the study. Among the 108,711 subjects, 6,260 had serum 25(OH)D levels < 20 ng/ml that after 4 to 26 weeks had increased to between 30 and 100 ng/ml (“repletion” group), and 2,332 patients had 25(OH)D levels < 20 ng/ml at both measurements (“control” group). In the “repletion” group there was an increase in serum 25(OH)D of 27.3 ng/ml, whereas the increase in the “control” group was only 0.9 ng/ml. The assay used by the authors separated 25(OH)D\textsubscript{2} (which almost exclusively comes from vitamin D\textsubscript{2} supplements) from 25(OH)D\textsubscript{3} (which predominantly comes from cutaneous vitamin D\textsubscript{3} production), and 81\% of the increase in 25(OH)D in the “repletion” group represented 25(OH)D\textsubscript{2}. This shows that the increase in the “repletion” group was mainly the result of vitamin D\textsubscript{2} supplementation, and if vitamin D supplementation has any clinically significant effect on serum lipids, one should in this setting have a reasonably good chance of detecting it. However, the results were disappointing in the sense that there was no improvement in the lipid profile by vitamin D. Compared with the “controls” there was a marginal but significant increase in total and HDL cholesterol of 0.8 mg/dl and 0.4 mg/dl, respectively, and no significant effect on LDL cholesterol and triglycerides.

So, does this rule out a beneficial effect of vitamin D on the serum lipid profile and make
the large, expensive, time- and effort-consuming RCTs unnecessary? And just as important, does it rule out a negative effect of vitamin D substitution on serum lipids? In this context it should be recalled that there are emerging indications for a U shaped-dose response curve for serum 25(OH)D with increased risk of death in those with low as well as high 25(OH)D levels.11

To address the first question, how do their longitudinal (“intervention”) results compare to other studies? So far there is only one published meta-analysis on vitamin D intervention and serum lipids that included 12 clinical trials with 1346 participants.12 The only effect on the lipid profile that reached statistical significance was a small increase in LDL cholesterol of 3.23 mg/ml, whereas there was a non-significant increase in total cholesterol of 1.52 mg/dl, a reduction in HDL cholesterol of 0.14 mg/dl, and a reduction in triglycerides of 1.92 mg/dl.

However, most of the studies included were small, the doses of vitamin D given ranged from 300 IU to ~ 6000 IU per day, the duration ranged from 8 weeks to 3 years, none of them had high lipid levels as inclusion criteria, and at baseline the majority of the subjects were not vitamin D deficient. In spite of these short-comings, when this meta-analysis is considered together with the results reported by Ponda et al.,10 it appears highly unlikely that oral supplementation with vitamin D will have any clinically significant positive effect on the serum lipid levels, with the possible reservation that subjects with a combination of vitamin D deficiency and hyperlipidemia still need to be studied.

Then on the other hand, is it possible that the study by Ponda et al.,10 due to its design, masks significant and important negative effects of vitamin D? As the authors themselves point out, they have performed an observational study which is critically different from an RCT. The subjects were not randomized and to no surprise there were important differences between the “repletion” and “control” groups at baseline. The first serum LDL cholesterol and triglyceride
levels differed significantly between the two groups. Also, the subjects in the “repletion” group were more likely to have a diagnosis of lipid disorder and/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 below 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, was masked in the present study.

Furthermore, as emphasised 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. In spite of the above objections and shortcomings, the study by Ponda et al. 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 for 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 (IOM), there is at present no solid evidence for a protective effect of vitamin D on major extra-skeletal 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.\textsuperscript{15}

A similar approach as the one presented by Ponda et al.\textsuperscript{10} could be used by others who have access to large databases with laboratory test results from more than one time point, and particularly if the data can be merged with data bases 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, as in the present case, are many pit-falls in the interpretation. It should also be mentioned that the impressive size of the study by Ponda et al.\textsuperscript{10} may give it an unjustified impact and de-motivate 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 if 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 paper 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.

Conflict of Interest Disclosures: None.

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