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Why did we end up having so few vitamin D answers and what can we do about it? A provocative and narrative review

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ABSTRACT

In spite of numerous vitamin D publications, including thousands of RCTs, meta-analyses, review papers and editorials, we still do not have answers to the most basic vitamin D questions. The recommendations for vitamin D intake are based on a few and questionable studies, and according to the latest Endocrine Society Guidelines from 2024, there is no clinical trial evidence for establishing serum 25-hydroxyvitamin D (25OHD) thresholds to define vitamin D deficiency. Furthermore, large and impressive vitamin D RCTs, some with more than 20,000 participants, have failed to show significant effects on disease prevention. However, there are indications that vitamin D may have a small preventive effect on type 2 diabetes and auto-immune diseases, and vitamin D may also improve cancer survival. In general, the RCTs have been under-powered, and most subjects included were already vitamin D sufficient. The time for new vitamin D mega trials is probably over, and in the future, we have to design our RCTs smarter. One should mainly include subjects with low serum 25OHD levels, use individual dosing to reach a preset 25OHD level [treat-to-target), use realistic power calculations, and we should use similar study designs to facilitate individual patient data meta-analyses. We must be willing to realize that we have failed, we must be willing to change, and we must be willing to pull our forces together. A vitamin D consensus conference is highly needed. We cannot accept that in 2025 we do not know what is a sufficient serum 25OHD level.

1. Introduction

The number of vitamin D publications is huge. If using the search term "vitamin D" in PubMed the number of hits is 110,924 [1]. If restricting the search to publications with "vitamin D" in the title the number of hits, 45,486, is still impressive. Among these 45,486 publications 7385 are classified as review papers, 2447 as randomized controlled trials (RCT), 1347 as meta-analyses, and 912 as editorials. The peak year was in 2021 with 3006 publications with "vitamin D" in the title, thereafter gradually decreasing to 2418 in 2024 [1]. Among the RCTs there are several huge and impressive studies like the VITAL, D-Health, VIDA, FIND and D2D trials with 25,871, 21,315, 5108, 2495, and 2423 participants, respectively [2–6]. With this background, one would assume that we had answers to the most basic vitamin D questions like: What is a sufficient or optimal level of serum 25-hydroxyvitamin D (25OHD, the metabolite used to evaluate a subject's vitamin D status), and how much vitamin D do we need? Is vitamin D important for more than preventing rickets in children and osteomalacia in adults? The truth is, we do not know.

2. Vitamin D guidelines

2.1. The Institute of Medicine report from 2011

These questions have been addressed in three important vitamin D guidelines, The Institute of Medicine (IOM) report from 2011 on dietary reference intakes for calcium and vitamin D [7], and the two Endocrine Society guidelines from 2011 and 2024 [8,9].

Based on bone health outcomes (mainly osteomalacia), the IOM considered that a serum 25OHD level of 50 nmol/L would be necessary to prevent osteomalacia in at least 97.5 % of the population. To achieve this, daily intakes of 600 IU/day for adults up to 70 years old, and an intake of 800 IU/day for those older, were estimated [7]. This threshold of 50 nmol/L for vitamin D deficiency has reached almost universal acceptance. In this context it should be mentioned that the IOM recommendations were based on studies exclusively performed in Caucasian populations. It is known that African Americans have lower calcium excretion, higher serum PTH and lower 25OHD levels, and thus may have different vitamin D needs than a Caucasian population [10].

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Moreover, most studies were designed to test a drug and not a nutrient, which may partly explain the non-linear curves in the observational trials.

2.2. The endocrine society guidelines

The Endocrine Society guidelines from 2011 supported this deficiency cut-off, but additionally considered serum 25OHD levels in the range 50 – 75 nmol/L as insufficient. The latter was based both on bone health studies as well as suppression of serum PTH with increasing serum 25OHD level. Thus, targeting a higher 25OHD value of 75 nmol/L was considered prudent in order to reduce multiple adverse consequences of vitamin D deficiency at low cost with minimal toxicity risk [8].

However, the new Endocrine Society guidelines from 2024 did not find clinical trial evidence that would support establishing distinct 25OHD thresholds to define neither vitamin D sufficiency, insufficiency, nor deficiency. Accordingly, the previous recommendation of a serum 25OHD levels of 75 nmol/L or higher was no longer endorsed [9]. On the other hand, the recommended daily intake of vitamin D established by the IOM in 2011 was not questioned, even though that was indeed based on a 25OHD threshold of 50 nmol/L. Thus, the guideline panel assumed that all should follow the IOM established vitamin D intake recommendation. In addition to this basic intake, vitamin D supplementation was recommended in pregnancy, in persons with prediabetes, and in those 75 year or older. The strength of these recommendations was considered to be conditional only (that is, desirable consequences probably outweigh undesirable consequences), and the certainty considered moderate or limited. The supplementation should be "empiric", meaning that the supplementation should be given without prior testing for serum 25OHD level and without need for 25OHD monitoring thereafter. Furthermore, specific dose recommendations could not be given due to the various doses used in the trials on which the recommendations were based [9].

And most surprisingly, the panel did not find evidence showing that potential benefit was restricted to those with low 25OHD levels. In other words, vitamin D supplementation, where indicated, works whether you lack vitamin D or not.

This is by no means a criticism of the 2024 guidelines. These guidelines simply reflect how little evidence we have regarding clinical vitamin D effects.

3. How to find a serum 25OHD threshold for vitamin D deficiency/sufficiency

3.1. Osteomalacia and serum 25OHD threshold

To give recommendations for vitamin D intake, one has to, for practical purposes, base this on the serum 25OHD threshold for deficiency/sufficiency. Knowing this threshold is also important for how to interpret a serum 25OHD measurement. The threshold has to be decided in relation to known clinical vitamin D effects. We do know that vitamin D is vital for intestinal calcium absorption, and that severe vitamin D deficiency may lead to rickets in children and to osteomalacia in adults [11]. Apart from this, there is no SOLID evidence for skeletal or non-skeletal vitamin D effects. This was acknowledged by the IOM when they made their 2011 report, and they therefore focused on bone health, in particular prevention of osteomalacia [7].

However, the serum 25OHD level necessary for preventing osteomalacia is uncertain. Thus, the IOM 25OHD threshold estimate of 50 nmol/L in adults was mainly based on the observational study by Priemel et al. that included 675 iliac crest biopsies taken at autopsy [12]. The biopsies were examined for osteomalacia, and related to serum 25OHD levels in blood samples drawn post-mortem. This study has been criticized for several reasons, in particular for using a non-standardized serum 25OHD assay. The radioimmunoassays at that time were known for inaccuracy, and the serum samples unfortunately not re-analyzed. Again, this is not a criticism of the work done by the IOM who made evaluations from the best data available. However, in 2025 we cannot have vitamin D intake recommendations for billons of people based on a single, questionable study. New vitamin D and osteomalacia studies are a must.

3.2. Biochemical diagnosis of osteomalacia

Observational studies on osteomalacia are very few for the simple reason that a definite diagnosis requires a bone biopsy which is not easy to obtain. One option could be to use the same design as Priemel at al. with biopsies taken at autopsies [12], or biopsies taken in connection with surgical procedures [13]. Another approach would be to diagnose osteomalacia based on serum levels of calcium, phosphate and bone-specific alkaline phosphate (BALP), so-called "biochemical osteomalacia" [14,15]. This is very promising, but diagnostic criteria for biochemical osteomalacia have yet to be verified by histological examinations. When and if biochemical parameters are accepted for diagnosing osteomalacia, large observational studies can easily be performed and be very helpful in finding a threshold for vitamin D sufficiency.

On the other hand, for osteomalacia vitamin D RCTs would not be suitable to define serum 25OHD thresholds as that would imply including subjects with very low 25OHD levels (< 20 nmol/L) followed for years. That would clearly be unethical, and for osteomalacia we therefore have to rely on observational studies.

4. Effects of vitamin D other than prevention of osteomalacia

4.1. Importance of performing RCTs

From laboratory and observational studies there are strong indications for vitamin D effects other than prevention of osteomalacia. Thus, the vitamin D receptor (VDR) and the machinery for vitamin D hydroxylation and activation are present in numerous tissues, and low serum 25OHD levels are associated with various adverse health outcomes [11,16]. It is not unlikely that the 25OHD threshold for such effects may differ between outcomes, and could well be substantially higher than that needed for prevention of osteomalacia. To prove such effects is therefore important, for which one has to perform RCTs. Vitamin D RCTs are numerous, but in general the corresponding meta-analyses and reviews conclude that no significant effects are found [17].

4.2. Why have the RCTs failed

There are some obvious explanations [17,18]. Firstly, there may not be any positive effect of vitamin D supplementation apart from prevention of rickets and osteomalacia. Secondly, the effect of vitamin D may be very small and the RCTs under-powered. Thirdly, the subjects included in most RCTs were already vitamin D sufficient and may not have been at risk of the outcome. It should also be mentioned that the effect of vitamin D supplementation may differ between populations as seen for whites and African Americans, as well as for obese and non-obese regarding cancer in the VITAL study [2].

4.2.1. Lack of power

An example of lack of power is the RCTs designed to see if vitamin D supplementation could prevent people with prediabetes from progression to diabetes. Three large RCTs from Norway, USA and Japan were specifically designed for that purpose and included 511, 2423 and 1256 subjects with prediabetes, respectively [6,19,20]. All showed a non-significant effect of 10–13 % on prevention of diabetes. However, they were designed to detect an effect of 25–30 %, and statistical significance was only achieved when the three studies were analyzed

together with individual patient data [21].

4.2.2. Inclusion of vitamin D sufficient subjects

As for inclusion criteria, it is obvious that an effect of vitamin D is most likely if given to subjects with low serum 25OHD levels. Unfortunately, that has only been done in a few studies, and in none of the large RCTs [17]. Thus, the participants in the VITAL, D-Health, VIDA, FIND and D2D studies had mean baseline serum 25OHD levels of 77, 77, 63, 74 and 70 nmol/L, respectively [2–6]. One can therefore say that we have tried to show an effect of vitamin D in subjects who do not need more vitamin D.

4.2.2.1. Ethical consideration on inclusion criteria. The reasons for inclusion of vitamin D sufficient subjects might have been in the optimistic belief that "the more vitamin D the better", or more likely for ethical reasons. Thus, it was considered unethical to knowingly include subjects with vitamin D deficiency in long lasting studies. Therefore, serum 25OHD samples taken at screening/inclusion were not measured before the study was over.

In retrospect that was a reasonable approach. The IOM-introduced serum 25OHD threshold of 50 nmol/L had a profound impact both in the scientific and lay community. It made it hard to get ethical approval for long-term intervention studies on vitamin D deficient subjects. Also, it would be hard to include subjects if they were told their 25OHD level was low and they might risk receiving placebo. Furthermore, if told they were vitamin D deficient, it could be tempting to take vitamin D supplements in addition to the study drugs.

4.2.2.2. Why one today can include subjects with low 25OHD in RCTs. It is the nature of any RCT that those in the placebo group will not get the potential benefit of the intervention drug. However, today we know that the effect of vitamin D, if present at all, is very small and thus the risk with being in the placebo group negligible.

Furthermore, we also know that the risk of osteomalacia is minimal with serum 25OHD levels > 30 nmol/L [17]. Even though the IOM set a threshold of 50 nmol/L, they also stated that: "a significant number of subjects displaying the mineralization defect was not observed until the serum 25OHD level had decreased below 30 nmol/L. A number of subjects continued to achieve adequate bone mineralization even at very low levels of 25OHD" [7]. In addition, with the possibility of making a biochemical osteomalacia diagnosis, subjects can be screened for this at baseline, and if present excluded [15,16]. For extra safety, that can also be monitored during the study.

Accordingly, there can today be no reasonable, ethical objections to including subjects with serum 25OHD levels as low as 30 nmol/L, even in long-term studies. Baseline screening could also identify subjects with critically low 25OHD levels, and thus avoid that such subjects are given placebo for years before treatment is started. And indeed, RCTs on subjects with low 25OHD levels is repeatedly asked for in the 2024 guidelines [9], and they should be included in treat-to-target studies.

5. Future vitamin D RCTs

5.1. The need for more RCTs

Practically all reviews and meta-analyses ask for more studies. Given all the negative studies so far, it is likely that the time for large vitamin D RCTs is over. Such studies are very expensive and funding would be hard to get. Accordingly, no new mega-studies are in the pipeline [22]. However, more studies are needed as documentation of even small effects could have a huge impact on public health given the large number of subjects with presumed vitamin D deficiency [23].

5.2. Treat-to-target

Similar to inclusion of subjects with low serum 25OHD levels, treat-to-target studies have been asked for in the 2024 guidelines [9].

As mentioned for osteomalacia, setting 25OHD thresholds based on observational studies depends on a strong causal relation between vitamin D and outcome, which apparently only exists for vitamin D and osteomalacia. For all others outcomes, the effect will be too small and inflicted by numerous confounding factors. Therefore, thresholds for outcomes other than osteomalacia have to be set by RCTs. Of note, RCTs using only one dose given to everyone, cannot be used in this respect. One dose for all will only give a "yes" or "no" answer and result in a wide range of achieved serum 25OHD levels. Relating the 25OHD levels within the vitamin D group to eventual effects cannot be analyzed as an RCT, but as an observational study with all the inherit limitations.

Thus, for the purpose of finding a threshold, the design has to be treat-to-target. To do that, one has to decide the desired serum 25OHD level, which may differ for different clinical outcomes. Serum 25OHD has to be measured repeatedly during the study, and the vitamin D dose increased or decreased accordingly. Different people are likely to require different doses and thereby more 25OHD measurements, adding to the cost of the study. If a positive effect is seen with a certain 25OHD target level, the true threshold is probably lower. If no effect is found, the target was set too low or the effect not existing. Accordingly, it is unlikely that a true threshold can be found from just one study or one applied target level.

Selection of which clinical outcomes to study will require strict prioritization. In this regard, one should not only consider previous clinical studies, but also Mendelian randomization studies that have provided strong evidence for a causal link between low serum 25OHD levels and several pathologies, in particular multiple sclerosis [24].

It has to be acknowledged that a treat-to-target approach to find serum 25OHD thresholds will be expensive. Hopefully federal agencies will see the need for such studies and contribute financially.

5.3. Guidelines for future vitamin D RCTs

We cannot continue as today with small RCTs in a multitude of diseases performed with a great variety of designs. If we do that, we will forever end up with too many unanswered questions. We have to be smarter. We should pull our resources together and do studies in a similar manner to facilitate meta-analyses based on individual patient data. Small RCTs that cannot be incorporated in meta-analyses are research waste. The following RCT-guideline are therefore suggested:

1. To increase chances of a positive result, only include subjects with low baseline serum 25OHD, preferably in the range 30 – 40 nmol/L.
2. Treat-to-target. Ideally two targets should be set, one close to the assumed threshold (like serum 25OHD 50 nmol/L) and one higher like 80 nmol/L.
3. If treat-to-target is impossible, like in an add-on-study in cancer treatment, use 3000 IU per day. This is a safe dose and will in most subject increase serum 25OHD sufficiently. The use of different doses will, even if all show a positive effect, make results more difficult to implement in clinical practice. This was one of the reasons why the American Diabetes Organization (ADA) did not endorse vitamin D supplementation in prediabetes [25].
4. Include subjects at risk of the disease in question, like subjects with prediabetes if want to see effect on diabetes prevention, subjects with positive thyroid antisera (anti-TPO) if want to prevent hypothyroidism and so on.
5. Focus on conditions where previous studies most strongly have indicated a positive effect of vitamin D like prediabetes [9], pregnancy [9], mortality [9], cancer survival [2], and autoimmune diseases [26].

6. Use daily doses of vitamin D (cholecalciferol). Intermittent high doses should be avoided [9].
7. Use realistic power calculations. The effect looking for is most likely very small. If one cannot include a sufficient number, collaborate with others, or do not do the study.
8. Use 25OHD as measure of vitamin D status which is widely accepted. Other measures like free 25OHD or various ratios may be of theoretical interest but has to be evaluated against a gold standard (known levels of vitamin D status) that do not exist.
9. Serum 25OHD should be measured with an LC-MS/MS assay which today is the gold standard. Serum samples should be kept for re-analyses if results are questioned.
10. Include stratification for BMI in the protocol since for unknown reasons vitamin D effects might be BMI related [21].
11. Include stratification for race/ethnicity since the vitamin D response for some outcomes may be race dependent [2].
12. The length of the intervention should depend on the outcome. For outcomes where subjects at risk can be identified (prediabetes, auto-antibodies), the intervention period should be five years. For outcomes like cancer, where subjects at risk are hard to identify, the intervention period should be longer, preferably 10 years.
13. If the RCT is long lasting, continue follow-up for at least one year since the vitamin D group will have higher serum 25OHD for a prolonged time [17,27].

6. Implementation

Such vitamin D RCT guidelines are of value only if they are implemented. For that to happen, there must be a consensus within the vitamin D research community. Therefore, a consensus conference is needed. If a consensus is reached, a vitamin D RCT guideline could serve as a reference document not only for researcher, but also for funding agencies, ethics committees and editorial boards.

7. Conclusion

This narrative review was written with the purpose to provoke, not to criticize. However, we have to realize and accept that despite formidable efforts, we still have huge gaps in basic vitamin D knowledge. Furthermore, we have to realize that these gaps will not be filled unless we do things differently. The time to act is now, while there still is interest in vitamin D research. We owe that to future generations.

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Rolf Jorde: Writing – original draft, Investigation, Conceptualization.

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Declaration of Competing Interest

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