Appendix 1: Criticisms and Response
Vitamin D is Essential for Optimal Health: Are You Getting Enough?

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The information herein is for educational purposes only and is not to be taken as medical advice; please consult a healthcare professional for personal advice.

We welcome constructive criticism because that is part of rational scientific discourse. Appendix 1 addresses criticisms received.

Appendix 1 - Peer Review Commentary and Responses

Criticism. The authors fail "*to reference or promote the current US & Canada guidelines that were established in 2011 by IOM"* (Institute of Medicine).[1]

Response. Health Canada's recommendations for VitD range from 400 IU (10 µg) with an upper tolerable limit of 1000 IU (25 µg) for infants 0-6 months, to 800 IU (20 µg) with an upper tolerable limit of 4,000 IU (100 µg) for adults > 70 years. We included Health Canada's reference guidelines but did not promote them because while they are sufficient for bone health, they are too low for optimal function of many other VitD actions. We cited the MS Society target levels of *serum 25-hydroxyvitamin D (25OHD/calcidiol) = 50−125 nMol/L, requiring intake of 600–4,000 IU vitamin D/day."*[2,3]

The recommended daily allowance by the IOM report appears to have been based on an erroneous calculation according to Veugelers and Ekwaru (2014).[4] These authors estimated that 8,895 IU would be required for 97.5% of individuals achieve serum calcidiol of 50 nMol/L.

Criticism. ***"IOM concluded that 25-OH-D <25-30 nmol/L is truly deficient; 30-50 nmol/L is a level that needs treatment; and there is no insufficiency as there are no symptoms."***

Response. Most MDs would disagree with the notion that lack of symptoms equals lack of a problem. This statement also implies that 50 nMol/L calcifediol (25-OH-VitD3, calcidiol) represents full sufficiency, which is inconsistent with most recent literature. Thus, the graphs of Quraishi *et al.* (2014)[5] and Borshe *et al*. (2021)[6] show regression line extrapolations intersecting the abscissa at ~45-50 ng/ml or ~110-125 nMol/L. This indicates that ~125 nMol/L should be considered VitD sufficiency for bacterial and viral infection prophylaxis; less than 100 nMol/L would increase the risk of infections. For diabetes mellitus type 2, the VitD level for protection appeared to be ~125 nMol/L but for cardiovascular diseases ~50 nMol/L seemed to be sufficient.[7]

As early as 2007, Bischoff-Ferrari suggested calcidiol levels of at least 75 nMol/L for adequate bone mineral density, fracture prevention, lower extremity function, and cancer prevention.[8]

The higher target level of calcidiol (125 nMol/L) advocated in our document is the same as that recommended in Chapter 4 of the book by David Anderson and David Grimes (2023) entitled "Vitamin D3 and the Great Biology Reset."[9] This indicates that the guidelines established in 2011 by IOM have been modified upwards by subsequent evidence that has been generated by VitD investigators.

Criticism. Your group *"promotes extreme ideas proposed by" …Drs. X, Y and Z … "who are currently viewed as outsiders and whose ideas were dismissed by IOM. They promote normal target levels often in excess of 80-125 nMol/L."*

Response. Our group has stated "*This means raising the bar above the amount required for bone health. The evidence currently available for immune health indicates a target of 125-150 nMol/L*." This is within the values suggested by Jones (2008),[10] "*hypercalcemia only results when 25(OH)D3 concentrations have consistently been above 375–500 nMol/L.*" We also agree with Jones' suggestion that the target range for VitD could be up to ~250 nMol/L, "the wealth of animal studies and human anecdotal reports of vitamin D intoxication indicate that plasma 25(OH)D3 is a good biomarker for toxicity, and the threshold for toxic symptoms is ~750 nmol/L. This threshold value implies that vitamin 25(OH)D concentrations up to the currently considered upper limit of the normal range, namely 250 nMol/L, are safe and still leave a broad margin for error because values significantly higher than this value have never been associated with toxicity."

We wrote- "*In summary, a daily dose of 4,000-6,000 IU should be safe for the population and fulfill much of the human health needs. This is above the 400-800 IU/d currently recommended by Health Canada*." This is not promoting **"extreme ideas"** as these values seem to be in line with many of the statements made in the 2011 IOM review.[1] Our statements do not seem out of line with the work being attributed to DeLuca and others in Chapter 6 of "Dietary Reference Intakes for Calcium and Vitamin D."[11] DeLuca (2009) concluded that, overall, the toxicity of hypercalcemia becomes evident at vitamin D intakes above 25,000 IU/day, corresponding to a serum 25OHD level of about 500 nmol/L.[12] Hathcock *et al.* (2007), [13] following an analysis of more than 20 publications, concluded that there was no association between harm and intakes of

10,000 IU/day. Although toxic effects associated with 400 IU/day seem implausible, the diverse range of intakes and serum 25OHD levels is notable. Most reports suggest that the toxicity threshold is between 10,000 and 40,000 IU of vitamin D per day. Also, most do not identify toxicity until serum 25OHD levels of 500 to 600 nMol/L or higher are reached; frank toxicity has been associated with a serum 25OHD level of 750 nMol/L."[10, 12]

Our suggestion of up to 6,000 IU seems reasonable given that the Burt *et al*. (2019),[14] showed that 10,000 IU/day resulted in an increase in calcidiol from 78.4 to 188.0 nMol/L, which is still below the safe upper limit of 250 nMol/L, mentioned above.

For **effectiveness and safety** reasons we advocated VitD testing - "R*equest that* ***vitamin D testing*** *be covered by provincial health plans to help citizens take appropriate doses of vitamin D*."

Criticism. Several negative publications showing no benefit of VitD were omitted.

Response. We admitted that we could not include every VitD publication. Below are publications that were brought to our attention.

Burt *et al.* (2019)[14] in their VitD Supplemental Trial studied some 300 individuals who received 400, 4000 or 10,000 IU/day for 3 years and concluded that the high dose of VitD causes a bone loss in some individuals, which would be an adverse effect of concern for higher doses (10,000 IU/d) of VitD.

Response. A significant problem with this trial is the study population. The baseline levels of calcidiol for participants in this trial averaged 76.3 to 81.3 nmol/L. For comparison in the Cui *et al*. (2023) large, international study, 76% of subjects had less than 75 nMol/L.[15] In the graph shown by Quraishi *et al.* (2014),[16] this baseline level of VitD would leave less than 10% of the theoretical effect available for detection with supplemental VitD. This almost guarantees failure of VitD supplements. Also, bone loss would be predicted if VitD was taken without vitamin K2 as suggested from Capozzi *et al.* (2020).[17]

Manson *et al.* (2019) in their clinical study tested 25,871 participants to determine if 2000 IU/day of VitD protected against cardiovascular disease or cancer over a median follow-up of 5.3 years.[18] They concluded that supplemental VitD had no effect on incidence of CVD or cancers; in that sense, it was negative study.

Response. This trial also enrolled a population with substantial VitD levels upon entry with a mean of 77 nMol/L. Like the Burt trial above,[14] that would make it difficult to detect a positive effect of VitD supplementation. Despite this handicap, they observed that the VitD treated group had fewer cancer deaths after the first two years. This delay in effect is unsurprising because cancers are slow to develop and detection of beneficial effects such as reduction in deaths are anticipated to take time. Detection of any benefit in this study population seems remarkable.

In Manson's defence, she has written (as co-author) extensive discussions about the evidence describing the nuances that can affect the detection of beneficial of VitD in colon cancer.[19]

John Bilezikian and Andrea Giustina reviewed several of the controversial issues that you raised (*e.g.,* COVID-19 and vitamin D). These associations between low vitamin D levels and various diseases do not establish cause and effect.

Response. Bilezikian *et al*. (2023)[20] in their 2023 paper "Consensus and Controversial Aspects of Vitamin D and COVID-19" stated "*There is quite consistent evidence for an association between low 25 OH vitamin D (25(OH)D) levels and poor COVID-19 outcomes, despite heterogeneous publications of variable quality*."

We agree that association does not prove causation and that the gold standard for clinical trials is the RCT, which is used for the introduction of novel drugs. In drug trials, the controls can have a serum drug level of zero, but it is not possible to recruit subjects with a null level of VitD, which complicates trial design. Nevertheless, Bradford-Hill (1965) published a set of criteria that can be applied to observational trials.[21] These are often used as indicators of a cause and effect relationship. We consider that the many associations between low VitD levels and diseases are indicative of cause because of the consistency of Bradford-Hill's criteria across a substantial

breadth of studies. Again, we are not alone in applying the Bradford-Hill criteria to the subject at hand as Walsh *et al.* (2022).[22]

Another issue that has been raised is the possibility of reverse causality wherein the onset of disease produced a decrease in serum VitD. This has been determined to be non-existent or minimal by various authors including Borsche *et al.* (2021).[23]

Martineau *et al.* (2019) conducted a meta-analysis that included 10,933 participants and determined that VitD supplementation reduced acute respiratory infections (ARI) significantly (adjusted Odds Ratio 0.88, 95% CI 0.81 to 0.96; p = 0.003 in 25 studies).[24]

Response. This was not a negative study and the beneficial effects were greatest among those whose baseline levels of calcidiol were <25 nMol/l compared with ≥ 25 nMol/l (p = 0.006). This is also relevant to the studies above in which the baseline levels of calcidiol exceeded 70 nMol/L. By the Cochrane criteria, the evidence used herein was assessed as being of high quality.

Epilogue. After reading many but certainly not all papers on VitD, we suggest consideration of some factors apply particularly to VitD. One would be to consider the necessity for metabolic activation of VitD; in some studies, determination of effects was conducted without allowing time for VitD to become active. Secondly, the variability of VitD pharmacokinetics among individuals should be considered in the design of clinical trials. There is great variability in the calcidiol levels among people receiving the same dose of VitD. Rather than dose of VitD, perhaps calcidiol level should be the independent variable.

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