AIMN review
Australasian Institute for Medical Nutrition
www.aimnutrition.org
DEC 2016

Vitamin D levels and Controversy

Introduction

There is an issue brewing in Integrative Medicine about what constitutes appropriate circulating levels of Vitamin D (25-hydroxyvitamin D).

A review of medical literature finds wide ranging opinion on this issue, but it is clear at this point that there is very little peer reviewed medical literature advocating very high levels.

A range of recommendations are made in the peer reviewed literature for circulating levels of 25-hydroxyvitamin D ranging from 50 nmol/L up to 80 nmol/L. Many IM doctors are advocating much higher levels than this so naturally questions arise about safety.

It is also clear that the pursuit of very high levels is not supported by the orthodoxy and that the chase for higher levels is beginning to attract attention from regulatory authorities.

As with all treatments in IM, it is worth noting these general guidelines:

- Things occasionally go wrong.
- If the dose/dose form you are using is not represented in peer reviewed literature it will be difficult to support your position if adverse events do occur.
- If you aim to achieve very high levels in every patient, and test every patient several times, you will probably attract attention.

Is there any agreement about what constitutes a minimum circulating level of 25-hydroxyvitamin D? Generally yes, 50 nmol/L.

“There is an issue brewing in Integrative Medicine about what constitutes appropriate circulating levels of Vitamin D (25-hydroxyvitamin D).”

So, looking at current literature, let’s ask these questions:

- Is there any agreement about what constitutes a **minimum** circulating level of 25-hydroxyvitamin D?
  - Generally yes, 50 nmol/L.
- Is there any agreement about what constitutes an **upper** circulating level of 25-hydroxyvitamin D?
  - Generally no, but significant literature supports levels up to and around 80 nmol/L.
- Is there any clear benefit form published literature (including cases) about very high levels being clearly superior to 80 nmol/L?
  - No, not really.
- Is there any literature that finds negative associations with very high levels of circulating 25-hydroxyvitamin D?
  - Yes there is.
- Are the methods used to measure circulating 25-hydroxyvitamin D accurate and reproducible with different tests?
  - No, apparently not. Different types of tests get different results.
- I get high levels of Vitamin C, why not Vitamin D too?
  - They are not the same thing!

Ok so let’s briefly look at the above points.
There have been many many people chewing over these same questions for years now so there is an abundance of opinion in the literature and no clear consensus, but in general these appear to be the main points.

Is there any agreement about what constitutes a minimum circulating level of 25-hydroxyvitamin D?

Position statements have been released by a variety of organisations, including in Australia and New Zealand.

IOM Dietary Reference Intakes for Calcium and Vitamin D[1]
http://www.iom.edu/Reports/2010/Dietary-Reference-Intakes-for-Calcium-and-Vitamin-D.aspx

This is a conservative and internationally accepted reference for Vitamin D, it is also an extremely thorough and complex document. Circulating levels are affected by many factors, such as sun exposure, dietary intake, skin type, geographical location, age etc. However literature reviewed in this document links a variety of disease states with various circulating 25-hydroxyvitamin D levels and comes to the conclusion that there is an "optimal" range for these levels. The recommendation from IOM is that 50 nmol/L is an optimal level that provides benefit for most of the population:

"A level of 40 nmol/L (16 ng/mL) was consistent with the intended nature of an average requirement, in that it reflects the desired level for a population median—it meets the needs of approximately half the population. Moreover, benefit for most in the population is associated with serum 25OHD levels of approximately 50 nmol/L (20 ng/mL), making this level a reasonable estimate for a value akin to "coverage" for nearly all the population."

50 nmol/L (20 ng/L) appears to be the current accepted orthodox norm for a safe and beneficial operating level for 25-hydroxyvitamin D.

Is there any agreement about what constitutes an upper circulating level of 25-hydroxyvitamin D?

Holick MF, Vitamin D deficiency. N. Engl. J. Med.. 2007 Jul; 357(3): 266-81. PMID: 17634462[2]

Holick in general reviews literature that supports a higher level of circulating 25-hydroxyvitamin D.

"As long as the combined total is 30 ng per milliliter or more (approx 80 nmol/L), the patient has sufficient vitamin D."

There is in general no agreement amongst experts about a safe upper level. Holick provides extensive evidence in the above review connecting low levels with various diseases and gives comprehensive strategies to treat Vitamin D deficiencies. This of course does not mean that achieving higher levels will treat these diseases; it is more a guideline to prevent deficiency and reduce risk of developing these diseases.

Melamed ML, Michos ED, Post W, Astor B, 25-hydroxyvitamin D levels and the risk of mortality in the general population. Arch. Intern. Med.. 2008 Aug; 168(15): 1629-37. PMID: 18695076[3]

> *50 nmol/L (20 ng/L) appears to be the current accepted orthodox norm for a safe and beneficial operating level for 25-hydroxyvitamin D.*

"A meta-analysis of 18 randomized clinical trials of vitamin D supplementation in mostly older individuals found that randomization to vitamin D was associated with lower all-cause mortality. The optimal level of 25(OH)D has been suggested to be ≥ 30 ng/ml (75 nmol/L), a level associated with maximal suppression of parathyroid hormone and reduced fracture rates and postulated to be associated with better health outcomes. Approximately 41% of men and 53% of women in the United States, however, have levels of 25(OH)D below 28 ng/ml (70 nmol/L)."

"Several authors have commented that the optimal levels of 25(OH)D should be greater than 30 ng/ml. In our observational study we found that there was a lower risk of mortality at levels 30-49 ng/ml but that at levels >50 ng/ml there was again a higher risk of mortality in women."

Is there any clear benefit form published literature (including cases) about very high levels being clearly superior to 80 nmol/L?

In the peer reviewed literature a case for higher levels can be made with a few diseases, including MS.

Lucas RM, Ponsonby AL, Dear K, Valery PC, Pender MP, Taylor BV, Kilpatrick TJ, Dwyer T, Coulthard A, Chapman C, van der Mei I, Williams D, McMichael AJ, Sun exposure and vitamin D are independent risk factors for CNS demyelination. Neurology. 2011 Feb; 76(6): 540-8. PMID: 21300969[4]

"Higher serum vitamin D status per 10 nmol/L increase in 25(OH)D) was independently associated with decreased FDE risk." (FDE – first demyelinating event)

The risk of a FDE was highest at 25-hydroxyvitamin D levels < approx 54 nmol/L and lowest at approx 87 nmol/L. At 104 nmol/L there was no increased benefit; in fact the data show a minimally higher risk. The full data are not published in the paper but these trends are evident in the graphs.

In this study it is not clear at all that above approx 85 nmol/L that benefit keeps increasing. And again, this is not a treatment study. It is looking at Vit D levels in relation to the risk of a first MS event.

Is there any literature that finds negative associations with very high levels of circulating 25-hydroxyvitamin D?

Durup D, Jørgensen HL, Christensen J, Schwarz P, Heegaard AM, Lind B, A reverse J-shaped association of all-cause mortality with serum 25-hydroxyvitamin D in general practice: the CopD study. J. Clin. Endocrinol. Metab.. 2012 Aug; 97(8): 2644-52. PMID: 22573406 [5]

"In this study from the general practice sector, a reverse J-shaped relation between the serum level of 25(OH)D and all-cause mortality was observed, indicating not only a lower limit but also an upper limit. **The lowest mortality risk was at 50–60 nmol/liter**. The study did not allow inference of causality, and further studies are needed to elucidate a possible causal relationship between 25(OH)D levels, especially higher levels, and mortality."

Melamed ML, Michos ED, Post W, Astor B, 25-hydroxyvitamin D levels and the risk of mortality in the general population. Arch. Intern. Med.. 2008 Aug; 168(15): 1629-37. PMID: 18695076 [3]

"In our observational study we found that there was a lower risk of mortality at levels 30-49 ng/ml but that at levels >50 ng/ml there was again a higher risk of mortality in women."

Tuohimaa P, Tenkanen L, Ahonen M, Lumme S, Jellum E, Hallmans G, Stattin P, Harvei S, Hakulinen T, Luostarinen T, Dillner J, Lehtinen M, Hakama M, Both high and low levels of blood vitamin D are associated with a higher prostate cancer risk: a longitudinal, nested case-control study in the Nordic countries. Int. J. Cancer. 2004 Jan; 108(1): 104-8. PMID: 14618623 [6]

"The normal average serum concentration of 25(OH)-vitamin D (40–60 nmol/l) comprises the lowest risk of prostate cancer. The U-shaped risk of prostate cancer might be due to similar 1,25-dihydroxyvitamin D availability within the prostate: low vitamin D serum concentration apparently leads to a low tissue concentration and to weakened mitotic control of target cells, whereas a high vitamin D level might lead to vitamin D resistance through increased inactivation by enhanced expression of 24-hydroxylase. It is recommended that vitamin D deficiency be supplemented, but too high vitamin D serum level might also enhance cancer development."

Are the methods used to measure circulating 25-hydroxyvitamin D accurate and reproducible with different tests?

Lai JK, Lucas RM, Clements MS, Harrison SL, Banks E, Assessing vitamin D status: pitfalls for the unwary. Mol Nutr Food Res. 2010 Aug; 54(8): 1062-71. PMID: 20397196 [7]

"...there remains a lack of consensus as to the 25(OH)D concentration that denotes vitamin D sufficiency or guides when treatment of insufficiency is necessary. Second, significant between-assay and between-laboratory variability persists. Thus, defining vitamin D deficiency according to a single universal cut-point is not currently appropriate and any single measure of 25(OH)D may not be reliable in detecting vitamin D deficiency."

I get high levels of Vitamin C, why not Vitamin D too?

The levels of Vitamin C typically achieved in an intravenous injection are well documented in the peer reviewed literature; corresponding concentrations can be achieved *in vivo* that have been shown to be of benefit in numerous *in vitro* studies. There is also significant clinical literature, including randomised controlled trials and other trials that support these doses in humans. For Vitamin C, the safe upper limits of concentration vary from patient to patient and are transient, i.e. the VC is quickly cleared and excreted and does not display appreciable toxicity.

This type of literature does not exist for Vitamin D, it is not a simple relationship that more is better, the levels stay high for prolonged periods and the literature about efficacy is essentially missing. So it is not at all a simple matter of giving more to get the job done.

Vitamin D levels, what do they mean?

It is important to note that this discussion is about circulating 25-hydroxyvitamin D levels, it is NOT about Vitamin D dose or dose forms. The dose and dose form are appropriate to the patient; some need more to achieve even normal levels. There is abundant literature on this aspect of dosing now, including guidelines:

Holick MF, Vitamin D deficiency. N. Engl. J. Med.. 2007 Jul; 357(3): 266-81. PMID: 17634462 [2]

Diamond TH, Ho KW, Rohl PG, Meerkin M, Annual intramuscular injection of a megadose of cholecalciferol for treatment of vitamin D deficiency: efficacy and safety data. Med. J. Aust.. 2005 Jul; 183(1): 10-2. PMID: 15992330 [8]

Lucas RM, Ponsonby AL, Dear K, Valery PC, Pender MP, Taylor BV, Kilpatrick TJ, Dwyer T, Coulthard A, Chapman C, van der Mei I, Williams D, McMichael AJ, Sun exposure and vitamin D are independent risk factors for CNS demyelination. Neurology. 2011 Feb; 76(6): 540-8. PMID: 21300969 [4]

"The lower serum 25(OH)D levels among FDE (first demyelination event) cases occurred despite higher vitamin D supplement use. At interview, 34.3% of FDE cases and 26.6% of matched controls were taking a vitamin D containing supplement."

The above quote from Lucas et al[4] shows us that patients are different and doses/protocols that raise levels for some may not raise them in others. So individual response, as always, plays a part in clinical approaches to dosing.

Individual response goes further; there are significant polymorphisms in the genes that code for various aspects of Vitamin D metabolism and binding such as variations in Vitamin D receptors and hydroxylation enzymes that convert circulating 25-hydroxyvitamin D into the active form. Some of these variations can cause severe Vitamin D deficiency[9] but others may be more benign, leading to seasonal variations in Vitamin D levels or an apparent mismatch between Vitamin D levels and Vitamin D function[10]. So it is quite possible that Vitamin D deficiency can persist despite "adequate" levels of 25-hydroxyvitamin D. Vitamin D deficiency for many people is seasonal, being worst in winter, and further to this the seasonal deficiency may be related to genetics. Kitanaka et al[10] report on a study in Japan that found that 70% of the variation in seasonal Vitamin D levels is due to genetic factors.

So it is reasonable then to see that it is not possible to make a blanket statement about what constitutes an adequate circulating 25-hydroxyvitamin D level for every person. While it is a good idea to get levels into at least a normal range, it is also ***not*** reasonable based on published negative evidence to aim to get the levels as high as possible.

Summary

The literature presented above in general represents the current state of the debate about what constitutes safe and beneficial circulating levels of 25-hydroxyvitamin D. The fact that there is peer reviewed evidence for a decreased benefit of very high levels should serve as a warning; if the goal is to pursue higher and higher levels there is published literature that says this is risky. Prevention and treatment trials at low and high levels have not been done; this argument is in its early days.

The literature reviewed generally portrays a safe and beneficial level from approx 50 nmol/L up to approx 80 nmol/L, no higher. There is at least one prostate cancer risk paper (*Tuohimaa et al*[6]) that finds that 80 nmol/L is above the ideal range for risk.

References:

[1] *IOM Dietary Reference Intakes for Calcium and Vitamin D http://www.iom.edu/Reports/2010/Dietary-Reference-Intakes-for-Calcium-and-Vitamin-D.aspx*

[2] Holick MF, Vitamin D deficiency. N. Engl. J. Med.. 2007 Jul; 357(3): 266-81. PMID: 17634462

[3] Melamed ML, Michos ED, Post W, Astor B, 25-hydroxyvitamin D levels and the risk of mortality in the general population. Arch. Intern. Med.. 2008 Aug; 168(15): 1629-37. PMID: 18695076

[4] Lucas RM, Ponsonby AL, Dear K, Valery PC, Pender MP, Taylor BV, Kilpatrick TJ, Dwyer T, Coulthard A, Chapman C, van der Mei I, Williams D, McMichael AJ, Sun exposure and vitamin D are independent risk factors for CNS demyelination. Neurology. 2011 Feb; 76(6): 540-8. PMID: 21300969

[5] Durup D, Jørgensen HL, Christensen J, Schwarz P, Heegaard AM, Lind B, A reverse J-shaped association of all-cause mortality with serum 25-hydroxyvitamin D in general practice: the CopD study. J. Clin. Endocrinol. Metab.. 2012 Aug; 97(8): 2644-52. PMID: 22573406

[6] Tuohimaa P, Tenkanen L, Ahonen M, Lumme S, Jellum E, Hallmans G, Stattin P, Harvei S, Hakulinen T, Luostarinen T, Dillner J, Lehtinen M, Hakama M, Both high and low levels of blood vitamin D are associated with a higher prostate cancer risk: a longitudinal, nested case-control study in the Nordic countries. Int. J. Cancer. 2004 Jan; 108(1): 104-8. PMID: 14618623

[7] Lai JK, Lucas RM, Clements MS, Harrison SL, Banks E, Assessing vitamin D status: pitfalls for the unwary. Mol Nutr Food Res. 2010 Aug; 54(8): 1062-71. PMID: 20397196

[8] Diamond TH, Ho KW, Rohl PG, Meerkin M, Annual intramuscular injection of a megadose of cholecalciferol for treatment of vitamin D deficiency: efficacy and safety data. Med. J. Aust.. 2005 Jul; 183(1): 10-2. PMID: 15992330

[9] Kim CJ, Kaplan LE, Perwad F, Huang N, Sharma A, Choi Y, Miller WL, Portale AA, Vitamin D 1alpha-hydroxylase gene mutations in patients with 1alpha-hydroxylase deficiency. J. Clin. Endocrinol. Metab.. 2007 Aug; 92(8): 3177-82. PMID: 17488797

[10] Kitanaka S, Isojima T, Takaki M, Numakura C, Hayasaka K, Igarashi T, Association of vitamin D-related gene polymorphisms with manifestation of vitamin D deficiency in children. Endocr. J.. 2012 07; 59(11): 1007-14. PMID: 22785457

Australasian Institute for Medical Nutrition

Version ID: AIMN_Review_Vitamin_D_Levels_Controversy_Dec_2016