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Technical Report

Target Serum Levels and Optimal Dosing of Vitamin D

A response to the IOM Report

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A Response to the IOM Report

Research supporting vitamin D supplementation has increased dramatically over the past decade and has significantly revitalized interest in this important nutrient. While in the past, vitamin D was recognized mainly for its role in bone health, recent epidemiological and randomized-controlled trials have uncovered relationships between low levels of vitamin D and a number of chronic conditions, including muscle pain and weakness, autoimmune diseases such as type 1 diabetes, colorectal cancer, cardiovascular disease, inflammatory bowel disease, and multiple sclerosis. These significant and widespread findings have prompted new controversy in defining "optimal" serum levels of vitamin D, as well as the doses needed to achieve them. This paper will review key conclusions of the recent Institute of Medicine (IOM) report on vitamin D and will address the question of optimal dosing of vitamin D for the prevention of chronic disease.

The dietary reference intakes (DRIs) for vitamins are established by the IOM with the intention of serving as a guide for good nutrition and to provide the basis for nutrient guidelines in the U.S. and Canada. In the case of vitamin D, the process of establishing recommendations for intake levels is more complex, for several reasons. Unlike other vitamins, serum levels of vitamin D are the result of both dietary intake, mainly through fatty fish, eggs, beef, supplements and synthesis of the nutrient within the skin after exposure to UVB sunlight. Both of these factors vary from person to person, though sun exposure is the source of 90–95% of vitamin D for the majority of the population not consuming supplements.[1] Like dietary intake, exposure to the sun is variable and is quite often significantly reduced as a result of increased sunscreen use and more time spent indoors, adding to the complexity of formulating recommendations for intake.

Note: Except during the summer months, the skin makes little if any vitamin D from the sun at latitudes above 37 degrees north (in the United States, the shaded region in the map) or below 37 degrees south of the equator. People who live in these areas are at relatively greater risk for vitamin D deficiency[2]

In light of newly emerging data, the recently issued IOM report[3] on Vitamin D has recommended increasing vitamin D intake for all age groups, as follows:

- Doubling intake for infants to 400 IU
- Tripling intake those ages 1 - 50 to 600 IU
- Doubling intake for those aged 51-70 to 600 IU
- Increasing intake by 33% for those older than 71 years old, up to 800 IU.

According to the IOM report, the average total intake of vitamin D is indeed below the median requirement. Furthermore, the majority of Americans and Canadians currently receive adequate amounts of vitamin D, with average blood levels above the target level of 20 ng/mL (50 nmol/L), the level deemed necessary by the IOM for the general population, based on bone health studies. In addition, the IOM report highlights "emerging evidence that too much (vitamin D)…may be harmful," and warns that once intakes of vitamin D surpass the upper limit (UL) of 4,000 IUs per day, the risk for harm begins to increase, with very high levels known to cause kidney and tissue damage.

Response to the IOM report

The changes made to recommended dosages of vitamin D by the IOM are conservative, and have come as a surprise to many researchers and physicians who have questioned the relevance of these new DRIs in the clinical setting. While the increases in vitamin D may have a beneficial effect overall, they do not reflect the large body of evidence that demonstrates a need for intake to be *at least* 2,000 IU/day for the prevention of chronic diseases in adults. Part of this discrepancy is due to the fact that the committee considered only studies on vitamin D and bone health and neglected to include research on other chronic conditions, such as colorectal cancer, citing conflicting data. The report also neglected to mention large segments of the population which have inadequate vitamin D status, such as minority populations, despite the data from the National Health and Nutritional Examination Surveys (NHANES) that examined over 15,390 participants and found that serum levels of 25(OH)D are below the recommended levels for a large portion of the general adult population.

The IOM committee also raised concerns about vitamin D toxicity, however, the number of reports on such occurrences is very small, while reports of deficiency have reached epidemic numbers. The kidney's ability to limit production of calcitriol, the active form of vitamin D, is also a tightly controlled mechanism, thus concern about toxicity may be disproportionate compared to evidence for risk of deficiency.

Laboratory values

The IOM report emphasized that the current measurements, or cut-off points, of sufficiency and deficiency of 25(OH) D in use by laboratories have not been set using rigorous scientific studies. They suggest that since no central authority has determined which cut-off points to use, reports of deficiency may be skewed and numbers overestimated. In fact, laboratory reference ranges for serum 25(OH)D levels have long been based upon average values from populations of healthy individuals and it is the recent research, suggesting that health-based cutoff values be aimed at preventing secondary hyperparathyroidism and bone loss, which pushed for the numbers to be increased.[4] Furthermore, recent evaluations have detected an improvement in the clinical measurement of vitamin D, and it is projected that the availability of reference materials from the National Institute of Standards and Technology will further improve confidence in these measurements.[5] However, it is important to note that values deemed sufficient by major laboratories differ from those recommended in the latest research.

Target serum levels

The IOM report references data which suggest that sun exposure contributes meaningful amounts of vitamin D to North Americans (indicating that a majority of the population is meeting its needs for vitamin D). In addition to the geographical limits on sun exposure experienced by many North Americans, this conclusion is based upon a low target serum level of 20 ng/ml (50 nmol/L--to convert from ng/mL to nmol/l, simply multiply by 2.5), shown in recent studies to be insufficient for the prevention of chronic vitamin D-associated diseases. However, there is increasing agreement among vitamin D researchers that values less than approximately 30-32 ng/mL (75-80 nmol/l) should be classified as "low," making low Vitamin D status extremely common worldwide.[5] Interestingly, even the now higher levels recommended by the IOM seem to be insufficient for bone health. Two 2009 meta-analyses of double-blind randomized controlled trials have found 20 ng/ml (50 nmol/l) to be insufficient for fracture or fall reduction based on achieved 25(OH)D levels in the treatment groups.[6,7] Furthermore, the 2010 position paper of the International Osteoporosis Foundation (IOF) has recommended a threshold of 30 ng/ml (75 nmol/l) for optimal fall and fracture reduction and a dietary intake of 800 to 1,000 IU of vitamin D per day for seniors age 60 years and older.[8]

While benefits of serum concentrations higher than 20 ng/ml (50 nmol/l) on endpoints other than bone health have not been documented by randomized trials, the evidence for benefit is quite strong for certain conditions, especially colorectal cancer.[9] Studies from areas of epidemiology, molecular and cellular biology have shown increasing support for serum concentrations of 25(OH)D higher than 28 ng/ml (70 nmol/L) as being both natural and beneficial to human health.[10,11] A report from the Office of Dietary Supplements of the National Institutes of Health has also further concluded that there is currently not enough evidence to recommend a specific upper limit of serum 25(OH)D that would indicate vitamin D sufficiency.

Optimal dosages

Many U.S. experts consider 30 ng/mL (75 nmol/L) 25(OH)D to be an optimal of vitamin D, such as Michael Holick, one of the world's leading researchers on vitamin D, who agrees that 30 ng/mL (75 nmol/L) "*is required to maximize vitamin D's beneficial effects for health.*" When using this functional target of 28-30 ng/mL (70-75 nmol/L), an intake of 600 IU (the new adult DRI) is insufficient for most to achieve such levels and the question arises as to what dose of vitamin D is needed to attain this higher target in most patients. Based on the suggestion that 1 mcg or 40 IU per day increases 25(OH)D by an average of 0.4 ng/mL (1 nmol/L)[10,12], lower intakes in the range of 200-600 IU (5-15 mcg) per day would not increase levels in a sufficient manner.[13-15]

According to a 2008 review,

> *"Supplementation with 1000 IU per day [of cholecalciferol] will usually result in about a 10 ng/mL elevationof serum 25(OH)D when given over 3-4 months. Therefore, a normal weight, healthy adult with an initial level of 10 ng/mL would generally require about 2000 IU per day to achieve a level of 30 ng/mL in the absence of cutaneous UVB exposure. However its kinetics are not linear; 1000 IU per day will substantially raise low baseline levels but a similar dose will not increase higher baseline levels by a similar increment (that is, 2000 IU per day may not raise 30 ng/mL to 50 ng/mL). In the absence of significant UVB exposure, input from diet and supplements of approximately 1000 IU (25 mcg) per day for every 15 kg of body weight may be needed, i.e. an obese 150-kg adult may require up to 10,000 IU per day to achieve a 25(OH)D level of 50 ng/mL."*[16]

A recent study from the *American Journal of Clinical Nutrition*[17] examined what the optimal dose of vitamin D would need to be in order to raise serum 25(OH)D levels to greater than 30 ng/mL

(75 nmol/L) without exceeding 88ng/mL (220 nmol/L). The 6-month, randomized, double-blind, placebo-controlled trial enrolled 138 healthy men (n=26) and women (n=112) ages 18-65 and initial doses of vitamin D were determined from baseline status. Individuals with a 25(OH)D baseline concentration between 20-32 ng/mL (50-80 nmol/L) were given 50 μg/day of vitamin D3 (2000 IU) and those with a baseline concentration below 20 ng/mL (50 nmol/L) were given 100 μg/day of vitamin D3 (4000 IU). The patients were followed at 8 week intervals and the dose was adjusted after each visit, and increased or decreased in 50 μg or 20 μg increments. The mean daily dose given was 86 μg/day (3440 IU) of vitamin D3. After optimization through computer modeling, an optimal daily dose of 115 μg/day (4600 IU) of supplemental vitamin D3 was found to be necessary for most patients in order to maintain serum 25(OH)D levels between the range of 30-88 ng/mL (75-220 nmol/L). When the observations from this study were projected onto the population of the 3rd National Health and Nutrition Examination Survey (NHANES III), an optimal dose of 3800 IU of vitamin D/day was found to be necessary for those above a baseline reading of 55nmol/L, and a dose of 5000 IU for those below the baseline.

In the case of more severe vitamin D deficiency,[18] some studies have suggested loading doses of 50,000 IU once weekly for 2-3 months or 3 times weekly for one month, with added doses of 800-2000 IU per day regardless of dosing pattern, to prevent recurrent deficiency; one study which looked at daily, weekly and monthly protocols of vitamin D3 supplementation with an outcome measure of 25(OH)D found that all three patterns of dosing and supplementation are equally beneficial.[19] The dosing approach should be selected based on patient adherence and should take into account personal health goals, ethnic background, age, geographic location and the season.

Vitamin D2 or D3

Studies from the 1930s on rickets prevention led to the long term assumption that vitamin D2 and D3 are equally effective in humans.[20] However, previous results were often skewed by the stability of preparations used in the studies and there is a lack of consistent and objective evidence that the two forms of the vitamin are equivalent with regards to increasing 25(OH)D levels.[20] Since the serum half life of D3 is longer, it is the clearly preferred form if administered less than once weekly.[18] A growing number of studies over the past decade have also found evidence that D3 increases serum 25(OH)D levels more efficiently than D2.[20,21] One group found the increase in blood levels with vitamin D3 to be 70% greater (1.7 times) than the increase provided by D2. In addition, a recent 2010 study found that in 33 adults, after 12 weeks of weekly supplementation with 50,000 IU of vitamin D, levels increased significantly more in the D3 group than in the D2 group, with D3 being 87% more potent in raising serum concentrations, and with 2-3 fold greater storage in the tissues than D2.[12,22]

The Vitamin K question

Vitamin K has also been increasingly linked to bone health in recent years and has spurred a new interest among clinicians in the supplementation of the vitamin together with vitamin D and calcium in many bone support protocols.[23] A growing number of epidemiological studies have highlighted a key role of vitamin K in optimizing bone heath.[24] Low vitamin K intake and low plasma levels of the vitamin have repeatedly been associated with low bone mineral density as well as increased osteoporotic fractures in postmenopausal women,[25-28] however other randomized controlled trials have shown mixed results.[23,29] Newer research has found that vitamin D and K work in synergy to support bone health.[30 31,32] One suggests that high doses of vitamin D may increase the demand for vitamin K. This model suggests that the administration of doses of vitamin D beyond the upper limit could cause a functional deficiency of vitamin K, based upon the role of Vitamin D in upregulating the expression of Gla-proteins, while osteocalcin activation depends on vitamin K-

mediated carboxylation.[33] Such literature suggested that vitamin K should be supplemented together with vitamin D, though no conclusive randomized controlled trials support this hypothesis to date.[34] Despite the lack of evidence, the synergistic relationship of vitamins K and D warrants the monitoring of serum K or uncarboxylated osteocalcin levels, and supplementating of dosages of vitamin K, as necessary.

Conclusion

While the IOM has done well to recognize the need for increased vitamin D consumption by all Americans, optimal vitamin D levels will likely not be achieved (for all of vitamin D's benefits) with the new recommendations. We recommend a target goal of 30 ng/mL for all patients and suggest that serum level of 40-70 ng/mL may be needed in various vitamin D related chronic health conditions. The following are recommendations for assessing serum levels and recommending vitamin D3 dosages for different age groups.

A. Serum 25-OH vitamin D levels

	ng/mL	nmol/L
Deficiency	**10 to 15**	25 to 37
Insufficiency	**15 to 30**	37 to 75
Minimum target	**30**	75
Therapeutic*	**40 to 70**	100 to 175
Upper limit	**100**	250
Excessive	**over 100**	over 250

* - May be considered "optimal" in patients with specific, vitamin-D mediated chronic disease conditions. Evidence is lacking for specific recommendations. The Vitamin D Council recommends a target level of 50-80 ng/mL, year-round.

B. Recommended daily dosages of vitamin D3 (IU) [35,36]

	1 & younger	**1 & older**	**Adults**	**71 & older**	**Blood testing**
The Point Institute*	Not more than 1000	1000	2000-5000	2000-5000	every 6 months
Institute of Medicine	400	600	600	800	
Dr. Michael Holick	1000	1000	2000-3000	2000-3000	
Vitamin D Council	1000	1000 per 25 lbs	5000	5000	every 2-3 months

*- Dose should be monitored by testing and adjusted based on sunlight exposure.

Other points to remember:

- Serum vitamin D testing should be for 25-OH not 1,25 OH vitamin D
- When supplementing vitamin D, choose D3 over D2
- Add vitamin K as necessary; if possible, monitor blood levels
- Obesity increases the need for vitamin D supplementation; weight loss may reduce need for vitamin D supplementation

References:

1. Holick MF. The vitamin D epidemic and its health consequences. *J Nutr.* Nov 2005;135(11):2739S-2748S.
2. Harvard University. http://www.health.harvard.edu/newsweek/time-for-more-vitamin-d.htm.
3. Institute of Medicine. http://www.iom.edu/Reports/2010/Dietary-Reference-Intakes-for-Calcium-and-Vitamin-D/Report-Brief.aspx?page=2.
4. State O. http://lpi.oregonstate.edu/infocenter/vitamins/vitaminD/.
5. Binkley N, Ramamurthy R, Krueger D. Low vitamin D status: definition, prevalence, consequences, and correction. *Endocrinol Metab Clin North Am.* Jun 2010;39(2):287-301, table of contents.
6. Bischoff-Ferrari HA, Willett WC, Wong JB, et al. Prevention of nonvertebral fractures with oral vitamin D and dose dependency: a meta-analysis of randomized controlled trials. *Arch Intern Med.* Mar 23 2009;169(6):551-561.
7. Bischoff-Ferrari HA, Dawson-Hughes B, Staehelin HB, et al. Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. *BMJ.* 2009;339:b3692.
8. Dawson-Hughes B, Mithal A, Bonjour JP, et al. IOF position statement: vitamin D recommendations for older adults. *Osteoporos Int.* Jul 2010;21(7):1151-1154.
9. Giovannucci E. Epidemiological evidence for vitamin D and colorectal cancer. *J Bone Miner Res.* Dec 2007;22 Suppl 2:V81-85.
10. Vieth R. Why the optimal requirement for Vitamin D3 is probably much higher than what is officially recommended for adults. *J Steroid Biochem Mol Biol.* May 2004;89-90(1-5):575-579.
11. Mosekilde L. Vitamin D requirement and setting recommendation levels: long-term perspectives. *Nutr Rev.* Oct 2008;66(10 Suppl 2):S170-177.
12. R.P. Heany KMD, T.C. Chen, M.F. Holick, M.J. Barger-Lux. Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. *Am J Clin Nutr.* 2003;77:204-210.
13. FM Gloth III JT, SS Sherman, BW Hollis. Is the recommended daily allowance for Vitamin D too low for the homebound elderly? *J. Am. Geriatr. Soc.* . 1991;39:137-141.
14. H. Glerup KM, L. Poulsen, et al. Hypovitaminosis D myopathy without biochemical signs of osteomalacic bone involvement. *Calcif Tissue Int.* 2000;66(419-424).
15. R. Vieth DC, GA Hawker, HM Trang, LA Rubin. Wintertime Vitamin D insufficiency is common in young Canadian women and their vitamin D intake does not prevent it. *Eur. J Clin Nut.* 2001;55(1091-1097).
16. Cannell JJ, Hollis BW. Use of vitamin D in clinical practice. *Altern Med Rev.* Mar 2008;13(1):6-20.
17. Aloia JF, Patel M, Dimaano R, et al. Vitamin D intake to attain a desired serum 25-hydroxyvitamin D concentration. *Am J Clin Nutr.* Jun 2008;87(6):1952-1958.
18. Kennel KA, Drake MT, Hurley DL. Vitamin D deficiency in adults: when to test and how to treat. *Mayo Clin Proc.* Aug 2010;85(8):752-757; quiz 757-758.
19. Ish-Shalom S, Segal E, Salganik T, Raz B, Bromberg IL, Vieth R. Comparison of daily, weekly, and monthly vitamin D3 in ethanol dosing protocols for two months in elderly hip fracture patients. *J Clin Endocrinol Metab.* Sep 2008;93(9):3430-3435.
20. Trang HM, Cole DE, Rubin LA, Pierratos A, Siu S, Vieth R. Evidence that vitamin D3 increases serum 25-hydroxyvitamin D more efficiently than does vitamin D2. *Am J Clin Nutr.* Oct 1998;68(4):854-858.
21. Heaney RP, Recker RR, Grote J, Horst RL, Armas LA. Vitamin D3 Is More Potent Than Vitamin D2 in Humans. *J Clin Endocrinol Metab*2010.

22. Heaney RP, Recker RR, Grote J, Horst RL, Armas LA. Vitamin D3 Is More Potent Than Vitamin D2 in Humans. *J Clin Endocrinol Metab.* Dec 22 2010.
23. Cheung AM, Tile L, Lee Y, et al. Vitamin K supplementation in postmenopausal women with osteopenia (ECKO trial): a randomized controlled trial. *PLoS Med.* Oct 14 2008;5(10):e196.
24. Lanham-New SA. Importance of calcium, vitamin D and vitamin K for osteoporosis prevention and treatment. *Proceedings of the Nutrition Society.* 2008;67(02).
25. Feskanich D, Weber P, Willett WC, Rockett H, Booth SL, Colditz GA. Vitamin K intake and hip fractures in women: a prospective study. *Am J.Clin.Nutr.* 1999;69(1):74-79.
26. Hodges SJ AK, Vergnaud P, Obrant K, Delmas PD , . Circulating levels of vitamins K1 and K2 decreased in elderly women with hip fracture. *J Bone Miner Res.* 1993;8:1241–1245.
27. Hodges SJ PM, Stamp TC, Catterall A, Shearer MJ, et al. . Depressed levels of circulating menaquinones in patients with osteoporotic fractures of the spine and femoral neck. . *Bone* 1991;12:387-389.
28. Bitensky L HJ, Catterall A, Hodges SJ, Pilkington MJ, et al. . Circulating vitamin K levels in patients with fractures. *J Bone Joint Surg BR.* 1988;70:663–664.
29. Purwosunu Y, Rachman IA, Reksoprodjo S, Sekizawa A. Vitamin K2 treatment for postmenopausal osteoporosis in Indonesia. *Journal of Obstetrics and Gynaecology Research.* 2006;32(2):230-234.
30. Bolton-Smith C, McMurdo ME, Paterson CR, et al. Two-year randomized controlled trial of vitamin K1 (phylloquinone) and vitamin D3 plus calcium on the bone health of older women. *J Bone Miner.Res.* 2007;22(4):509-519.
31. Iwamoto J, Takeda T, Ichimura S. Treatment with vitamin D3 and/or vitamin K2 for postmenopausal osteoporosis. *Keio J Med.* Sep 2003;52(3):147-150.
32. Braam LA, Knapen MH, Geusens P, et al. Vitamin K1 supplementation retards bone loss in postmenopausal women between 50 and 60 years of age. *Calcif Tissue Int.* Jul 2003;73(1):21-26.
33. Pizzorno L. Vitamin D and Vitamin K Team Up to Lower CVD Risk: Part II. http://www.lmreview.com/articles/view/vitamin-d-and-vitamin-k-team-up-to-lower-cvd-risk-part-II/#fn-44-72.
34. Masterjohn C. Vitamin D toxicity redefined: Vitamin K and the molecular mechanism. *Medical Hypotheses.* 2007;68(5):1026-1034.
35. Holick MF. Vitamin D Deficiency. *New Engl. J. Med.* 2007;357:266-281.
36. Vitamin D Council. http://www.vitamindcouncil.org/.