What Have We Learned About Vitamin D Dosing?

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Over the past several years, the surprising prevalence of vitamin D deficiency has become broadly recognized. A number of studies have attempted to determine the minimum, optimum, and toxic dosages, while others have used supplemental vitamin D to prevent and treat a diverse range of diseases. And, as might be expected, drug companies are investing substantial research dollars to find patentable vitamin D analogues, with some notable successes.

There have been several excellent review articles on the efficacy of vitamin D (including in *IMCJ*: see "Vitamin D [Cholecalciferol]: A Paradigm Shift With Implications for All Healthcare Providers" in *IMCJ* 2004;3.5: 44-54 and "Preparing Patients for Proper Sun Exposure" in *IMCJ* 2009;8.4:52-54), so I see no need to replicate that now. However, the issue of dosing has not yet been, in my opinion, adequately addressed. Here I will review the research on vitamin D dosing. In addition, I will present some initial results from a very exciting, ground-breaking corporate wellness program in Canada that I am involved in where we are fully applying the principles of natural/functional/integrative medicine to a group of blue-collar workers. As part of the project, we are running several laboratory tests to evaluate nutritional status and toxic load. One of the nutrients we have tested, supplemented, and followed is vitamin D. This project is quite important for integrative medicine as we are able to objectively measure the impact of our interventions in a large population of 1500 workers.

Incidence of Deficiency

In addition to the well-known osteoporosis connection, low vitamin D levels are associated with, for example, increased incidence of cardiovascular disease, cancer, autoimmune diseases such as multiple sclerosis, pain, loss of cognitive function, and decreased strength.[1,2] An 8.7-year follow-up study on 13 331 adults aged 20 years or older found that those in the lowest quartile of $25(OH)D_3$ have a 26% increased rate of all-cause mortality.[3] New research continues to add to this list.

Deficiency of vitamin D is now recognized as a pandemic, with more than half of the world's population currently at risk.[4] Research in the United States shows vitamin D deficiency in 36% of healthy young adults, 80% of healthy Caucasian infants, and 52% of adolescent African Americans and Hispanic children.[5] In addition, rickets is resurfacing in the 21st century as a major public health problem.

We still do not definitively know the incidence of vitamin D deficiency. At this time, it appears to me that approximately 50% of the "healthy" North American population and greater than 80% of those with a chronic disease are deficient.

Minimum Versus Optimal Level

At this time, there is no consensus on minimum, optimal, or toxic levels of vitamin D. However, I believe the body of research is now large enough that some guidelines can be set.

A comprehensive review study focused on estimating the optimal serum level of $25(OH)D_3$ for a range of measures such as disease incidence, neurological function, and bone density.[6] Included in their review was the observation that normal, healthy levels in outdoor workers such as farmers is 135 nmol/L and for lifeguards 163 nmol/L.

The researchers found that bone density in males aged 20 to 49 increased in proportion to increased $25(OH)D_3$ blood levels throughout the measured range: max 180 nmol/L for Caucasians, while for Hispanics it peaked at 118 nmol/L and African Americans at 90 nmol/L. Risk of fracture decreased proportionately with serum vitamin D levels throughout the measured range, so optimal levels were probably not achieved.

Lower-extremity function in the elderly (average age 71 years), as measured by the 8-foot walk and sit-to-stand tests, found that walk time increased through the range (max 220 nmol/L), while sit-to-stand optimized at 130.

For periodontal disease, the degree of bone loss and tooth loss found was progressively lower in proportion to the level range measured. Since the study only measured up to 100 nmol/L, the likely higher optimal level to mitigate this disease is not known.

For colon cancer, the risk decreased throughout the measured range. Those with $25(OH)D_3$ >91.5 nmol/L have 27% the incidence of colon cancer compared with those below 48.0.

My suggestion for the optimum level of vitamin D as measured by $25(OH)D_3$ is Caucasians, 125 to 175 nmol/L; Hispanics, 100 to 150 nmol/L; and African Americans, 80 to 120 nmol/L. I was not able to determine in this review why the optimal range appears to differ according to ethnic background.

Loading Versus Maintenance Dose

There is no widely accepted upper limit to daily vitamin D dosage. In the past, the US Institute of Medicine recommended an upper limit of 2000 IU/d. However, a comprehensive review found, "The clinical trial evidence shows that a prolonged intake of 250 µg (10 000 IU)/d of vitamin D_3) is likely to pose no risk of adverse effects in almost all individuals in the general population."[7] However, almost all articles supporting this dosage as universally safe are written by a single author.

Several studies have looked at the impact of oral vitamin D supplementation and changes in serum $25(OH)D_3$ levels. One study measured dose response (nmol/L) in post-menopausal African American women given 800 IU/d for 2 years and then 2000 IU/d for another year. They found that 2000 IU/d was enough to reach a 50 nmol/L blood level but not enough to reach the more desirable 75 nmol/L the researchers had targeted.[8]

A comprehensive study looked for the dosage necessary to achieve a $25(OH)D_3$ level of at least 75 nmol/L. Those above a

baseline of 55 nmol/L were initially given 3800 IU/d while those under were given 5000 IU/d. Dosages were then modified periodically for each person in order to achieve a target level of >75 nmol/L. The required dosage ranged from a low of 800 IU/d to a high of 6800 IU/d. Through data analysis and an algorithm, researchers determined that the average person needed a dosage of 4600 IU/d to achieve at least 75 nmol/L.[9] Only 1 person (dosage unspecified) exceeded 200 nmol/L, peaking at 220.

Perhaps the best study of dosage and safety was a 2007 report in which 12 patients with multiple sclerosis where treated with escalating dosages of vitamin D starting at 4000 IU/d and increasing to 40 000 IU/d over 28 weeks.[10] Comprehensive testing was done to detect toxicity: serum calcium, urinary calcium/creatine, liver enzymes, serum creatinine, electrolytes, serum protein, and parathyroid hormone. The only change researchers detected was a decrease in parathyroid hormone (and a remarkable 55% decrease in spinal lesions!). The effect of the various dosages can be seen in Table 1 (multiply by 40 to convert to IUs).

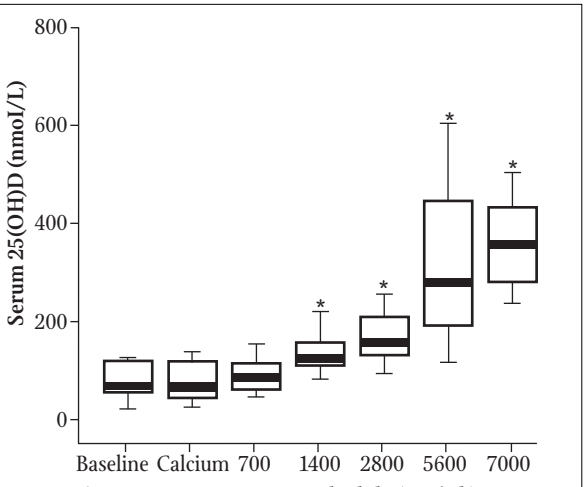

Figure. Vitamin D_3 Dose Schedule (mg/wk)
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As can be seen, the dosage that caused serum 25(OH)D_3 to exceed the totally safe level of 200 in a significant portion of the study group was 16 000 IU/d. The limitations of this study are that it was short term (only 4 weeks per dosage level) and in patients known to especially need vitamin D. Nonetheless, this appears to be the definitive study at this time.

When following the effect of vitamin D dosing (whether oral or sun exposure), keep in mind the following half lives:

Ingested D_3 (food or supplement)	2 to 6 hours in the blood before depositing in tissues
Tissue D_3	2 months (sun-produced form)
25(OH)D_3	15 days (circulating form)
$1,25(OH)_2D_3$	15 hours (most active form)

Toxic Dose

For ethical reasons, no systematic studies have examined vitamin D intoxication in humans. However, there have been numerous anecdotal reports that have described accidental poisoning with either vitamin D_3 or vitamin D_2.

One recent study specifically looked for the dosage threshold for causing hypercalcemia. They found that hypercalcemia only results when 25(OH)D_3 concentrations have consistently been above 375 to 500 nmol/L. The maximum safe level of vitamin has been estimated as 275 nmol/L with a persistent level of 375 causing hypercalcemia.[11,12]

Representative toxicity reports are as follows:

- A 3-month-old girl given 320 000 IU/d for 8 days; result = hypercalcemia.[13]
- A 7-year-old boy given 300 000 IU/d for 8 days; result = anorexia, nausea, vomiting, polydypsia, polyuria, constipation, and hypercalcemia.[14]
- A 58-year-old woman with diabetes mellitus and rheumatoid arthritis given 188 640 IU of vitamin D_3 for 60 days; result = fatigue, constipation, back pain, forgetfulness, nausea, vomiting, and hypercalcemia. Her 25(OH)D_3 was 1171 nmol/L.[15]
- A 77-year-old woman given 50 000 IU/d for 6 days; result = hypercalcemia.[16]
- Eight patients drinking milk from the same dairy that had made an error in vitamin D fortification. Dosages ranged from 116 000 to 464 000 IU/d. Result = 7 had hypercalcemia, and 1 had hypercalciuria but normocalcemia. The 25(OH)D_3 ranged from 297 to 1168 nmol/L.[11]
- Patient age and vitamin D dosage not specified. Of note in this study is that the initial 25(OH)D_3 was 570 nmol/L and calcium did not stabilize until it dropped to 285 nmol/L.[12]

A large public health study was done in Boston where a dairy that provided home deliveries accidentally enriched the milk with 70 to 600 times the maximum legal amount of vitamin D; 11 000 households were delivered the overdosed milk.[17] Searching hospital records found 56 people with hypercalcinosis; 2 died. Following were their symptoms:

Anorexia	32%
Weight loss	27%
Weakness	27%
Fatigue	21%
Disorientation	14%
Vomiting	14%
Dehydration	14%
Polyuria	12%
Constipation	11%
Asymptomatic	12%

Contraindications, Adverse Events, and Drug Interactions

Sarcoidosis patients react poorly to vitamin D supplementation. It appears to interact with the fundamental pathophysiology resulting in over production of $1,25(OH)_2D_3$ and increased granuloma production. Even summer sunlight exposure can increase D levels high enough to cause hypercalcemia in these patients.

The most significant drug interactions appear to be with the vitamin D analogues. There are some moderate interactions that are not contraindications but rather indicate the need for attention. Vitamin D increases the absorption of aluminum from

aluminum-containing antacids and statins; increases the activity of digoxin since it increases calcium absorption—same problem with other calcium-channel inhibitors as well as diuretics that increase calcium retention; and increases the activity of CYP3A4 so drugs metabolized by this liver enzyme will be cleared more quickly. Drugs.com has a useful list of potential interactions that can be quickly checked.

Adverse reactions to vitamin D supplementation appear to primarily occur only at accidental dosages as noted above.

A more subtle potential problem with large dosages of vitamin D is its dependence on adequate amounts of vitamins A and K_2. It is beyond the scope of this editorial to address this in depth. The key is that vitamins A, D, and K_2 work intricately together in a surprisingly diverse range of physiological functions. As vitamin D levels normalize, deficiencies of vitamins A or K_2 become clinically apparent. The paradox of soft-tissue calcium deposition in patients with osteoporosis appears largely due to this imbalance between vitamins D, A, and K_2. Similarly, much of the toxicity associated with high dosages of vitamin A appear to be due to inadequate vitamin D. Bottom line, when supplementing with vitamin D, be sure to include modest amounts of vitamins A and K_2.

Direct Experience With 1500 Canadians

This review of the research is interesting, but what happens when applied to a blue-collar population? As noted above, I have the privilege of applying integrative medicine principles to a large population of Canadians primarily located in a single province. Following is what we learned about vitamin D.

Using a cutoff of 80 nmol/L (32.0 ng/L), we found that a surprising 81% of the study group were deficient. Our intervention was to first provide a 1-page educational handout to the participants and to then provide a no-cost supplemental vitamin D in the form of capsules or liquid drops. The challenge was determining a loading dose that would normalize most of the group with minimal risk of excess in any and to then determine a maintenance dose. Early on, we were recommending 2000 to 4000 IU/day, but, as we looked at the emerging research on vitamin D, we soon realized we needed much larger loading and maintenance dosages. Thus, we began recommending a loading dose of 8000 to 15 000 IU/d typically for 3 months and then an average daily maintenance dose of 5000 IU/d. An average of a year later we asked if they took the vitamin D we provided them and remeasured their serum 25(OH)D_3. Remarkably, 90% took the vitamin D we prescribed them. This unprecedented compliance resulted in their average serum 25(OH)D_3 increasing 41% and the number below 80 nmol/L decreasing to 53%. Of particular importance, no one's vitamin D level went into the toxic range. Only a few were over 200, with 3 exceeding our preferred upper limit of 250: 269, 275, and 283. No adverse events were reported.

A key question, then, is what factors should be taken into consideration when recommending a loading and maintenance dose? Although 90% took their vitamin D, only 35% made it into the normal range. Obvious factors to consider include age, weight/body-mass index (BMI), dosage and duration, and, just for the heck of it, blood mercury. The only correlations I found were for dose and duration (0.41) and age (0.16). There were several surprises here. I had expected older participants to have more difficulty absorbing vitamin D, but the opposite appeared to be the case. However, a closer look at the data revealed that older participants were better at taking their vitamin D. I had also expected weight/BMI to be negative factors, but BMI correlation, while negative as expected, was weak. The mercury long shot also did not show a correlation. While more definitive multiple correlation analysis may show us something new, the bottom line appears to be simply that dosage and duration are the primary factors.

What does this tell us about vitamin D dosages? That a loading dose of 10 000 IU/d for 3 months and maintenance of 5000 IU/d is not enough for most people in northern climes; after 1 year of intervention, most of the participants had still not improved into normal range (let alone optimal range) with this regime. Based on the research I reviewed above, I think a maintenance dose of 5000 is still probably about right. However, the loading dose needs to be much higher, perhaps 20 000 IU for 3 to 6 months. The only way to be sure is to periodically measure your patient's serum 25(OH)D_3.

Finally, of clinical significance are the anecdotes and reports of improved "energy" of the participants and objective measures of improved health. Obviously, we did not only provide them vitamin D, but also lifestyle counseling, a multivitamin, etc. The bottom line is that applying the principles promulgated by this journal is well received and effective.

Personal Experience

As part of the project, all of us involved in design and implementation are running the same lab tests on ourselves as we are on the participants. I was quite surprised to find that my vitamin D levels were also low, despite my healthy diet, love of the sun (yes, we do occasionally get sun in Seattle), and regular use of a good-quality multivitamin. Thus began my own adventure finding my right dosage. At this time, all I can say is that a daily dose of 5000 is not enough to maintain my levels at 80 nmol/L, let alone get it into my self-determined optimal range for Caucasians of 125 to 175 nmol/L. And for my wife Lara, after 2 years of continuously losing bone despite everything I knew to do—including supplementation with vitamin D—we decided to run a genomic test on her to look at various genes involved in bone health. We found she has the VDR BB variant, meaning she has trouble absorbing and using vitamin D. Two years of experimenting with increasing dosages of vitamin D supplementation finally revealed that for her to maintain a normal serum 25(OH)D_3 level of 100 to 150 nmol/L requires a surprising 10 000 IU/d. We do live in Seattle, so sunlight is hard to come by.

Cost Effectiveness

This is a no-brainer. I found 1 study that showed those with vitamin D deficiency experiencing 39% higher annual health care costs than those with normal levels.[18] Vitamin D is cheap—for example a bottle of 360 capsules at 2000 IU/capsule costs around $12.00. So a person taking 5000 IU/d would spend only $30.00 a year and likely prevent several orders of magnitude more in health-care costs.

Summary

After looking at the research and considering our experience with 1500 blue-collar workers, I am making the following observations and recommendations:

1. The incidence of deficiency in the general population is apparently greater than 50% and likely less than 10% have optimal levels of vitamin D. These numbers are all worse in those who suffer almost any chronic disease as well as those with dark skin—though the story is still developing, so on this latter observation the research is mixed.
2. Interpretation of serum 25(OH)D_3 levels is as follows (divide by 2.5 to get ng/L):
   - minimum: 80 nmol/L;
   - optimum: Caucasians, 125 to 175 nmol/L; Hispanics, 100 to 150 nmol/L; African Americans, 80 to 120 nmol/L;
   - safe upper limit: 250 nmol/L;
   - lowest level with any documented toxicity: 375 nmol/L;
   - certain toxic level: 500 nmol/L.
3. The only way to determine the proper vitamin D supplementation is by periodically measuring serum 25(OH)D_3—no specific dosage regime meets the needs of everyone.
4. The average loading dose appears to be 20 000 IU for 3 to 6 months.
5. The average maintenance dose appears to be 5000 IU/d—less during the summer for those who get sun exposure.
6. Ensure your patient's vitamins A and K_2 levels are adequate and check for possible drug interactions.
7. Contraindicated in those with sarcoidosis and other granulomatous diseases.

What have we learned about vitamin D dosing? Increase the dosage a lot—4 to 10 times the current RDI recommendations.

In This Issue

As usual at the end of the year, we include our annual index. In this we compile articles—listed by both author and topic—for all issues in 2009 (8.1-8.6). We are sure this will be a useful tool for years to come.

We continue our periodic articles on nutrient and herbs. Kathy Abascal, JD, RH (AHG), and Eric Yarnell, ND, RH (AHG), present to us cinnamon—note I do not use the scientific name and therein lies part of the story they tell us. The German Commission E has approved this herb to treat loss of appetite and dyspeptic complaints such as mild spastic conditions of the gastrointestinal tract, bloating, and flatulence. The article also outlines cinnamon's history and folk use; chemical composition; pharmacology; clinical applications; dosages; and safety, including drug interactions. I am disappointed that there does not appear to be research on so many of its traditional uses. For example, one of the traditional uses taught me by my mentor John Bastyr, ND, was to use powdered cinnamon as a topical styptic.

For original research, Doddabele Madhavi, PhD, and Daniel Kagan, PhD, provide "A Study on the Bioavailability of a Sustained-release Coenzyme Q_{10}-β-Cyclodextrin Complex (MicroActive Co-Q_{10})." They compare the relative bioavailability of an improved coQ_{10} bound to cyclodextrin inclusion with both a conventional coQ_{10} softgel formulation and a crystalline co-Q_{10}. The results of the first study indicated that MicroActive Co-Q_{10} showed a sustained release and that its bioavailability was significantly better than the crystalline form, while in the second study, the 0- to 24-hour absorption confirmed the sustained-release property of the MicroActive Co-Q_{10} complex as well as the significantly higher and uniform bioavailability. Also, all the subjects in the accumulation phase of this second study showed a minimum of doubling in the plasma co-Q_{10} levels after 21 days of MicroActive Co-Q_{10} supplementation, which represents a 100% response rate.

Now that he has completed his careful study of the Standardized Information on Dietary Ingredients (SIDI) Program, Rick Liva, ND, RPh, returns with his critique, which will run in 2 parts. The SIDI program was developed by the Joint Standardized Ingredient Information Protocol (SIIP) Working Group, a joint trade association effort with participants representing both ingredient suppliers and finished product manufacturers. The objective of the working group is to develop standardized quality-control guidelines that ingredient suppliers can voluntarily use to help convey relevant and required information to their customers or manufacturers. The resulting SIDI guidelines are both comprehensive and flexible so as to be applicable across multiple product categories (eg, vitamins, minerals, botanicals, and other dietary ingredients). There are, however, some limitations. Rick delves into the pros and cons of SIDI in this issue and in the next will take a look at the sample Botanical Template filled in by the SIIP Working Group and will offer suggestions as to what would make the templates stronger.

Our interview this month is unusual as we address an area we have not covered before. James V. Hardt, PhD, has spent more than 3 decades studying the electrophysiological basis of spiritual states. He has published research in such scholarly journals as *Science, Psychophysiology* and the *Journal of Experimental Psychology* and has coauthored or has pending more than 30 patents for the technology he has developed based on electroencephalography measurement and feedback. I think you will find "Deciphering the Electrophysiological Basis of Spiritual States" quite interesting. I had the great fortune of spending a week studying with him, using his technology to increase my alpha waves. I found it a life-changing experience.

With seemingly everything in flux in health care, John Weeks's Industry Insights is an important read. Really, how will this healthcare reform play out for us integrative medicine folks?

I continue to be astounded by the insights Bill Benda, MD, brings in BackTalk. While I may not always agree with him, he certainly makes me think. The issue of titles is indeed fraught with social, financial, legal, and practice complications. As usual, no easy solutions.

Last, I am sorry to report that W. John Diamond, MD, author of "Allostatic Medicine: Bringing Stress, Coping, and Chronic Disease into Focus" (published last issue, *IMCJ* 2009;8.6:40-44) passed away in December of 2009 while we were doing the final edits on Part II. We are working with his son, David Diamond, to

publish the second half of his article, and you will find that coming in the next issue, Apr/May 2010. We most regret the loss of Dr Diamond, whose work we greatly respect, and apologize for the disruption in sequentiality of his article.

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References

1. Bordelon P, Ghetu MV, Langan RC. Recognition and management of vitamin D deficiency. *Am Fam Physician.* 2009;80(8):841-846.
2. Stechschulte SA, Kirsner RS, Federman DG. Vitamin D: bone and beyond, rationale and recommendations for supplementation. *Am J Med.* 2009;122(9):793-802.
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;168(15):1629-1637.
4. Holick MF, Chen TC. Vitamin D deficiency: a worldwide problem with health consequences. *Am J Clin Nutr.* 2008;87(4):1080S-1086S
5. Goldstein D. The epidemic of vitamin D deficiency. *J Pediatr Nurs.* 2009;24(4):345-346.
6. Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. *Am J Clin Nutr.* 2006;84(1):18-28.
7. Vieth R. Vitamin D toxicity, policy, and science. *J Bone Miner Res.* 2007;22 Suppl 2:V64-V68.
8. Talwar SA, Aloia JF, Pollack S, Yeh JK. Dose response to vitamin D supplementation among postmenopausal African American women. *Am J Clin Nutr.* 2007;86(6):1657-1662.
9. Aloia JF, Patel M, Dimaano R, et al. Vitamin D intake to attain a desired serum 25-hydroxyvitamin D concentration. *Am J Clin Nutr.* 2008;87(6):1952-1958.
10. Kimball SM, Ursell MR, O'Connor P, Vieth R. Safety of vitamin D3 in adults with multiple sclerosis. *Am J Clin Nutr,* 2007;86(3):645-651.
11. Jacobus CH, Holick MF, Shao Q, et al. Hypervitaminosis D associated with drinking milk. *N Engl J Med.* 1992;326(18):1173-1177.
12. Lilienfeld-Toal H, Messerschmidt W, Sturm B, Ochs H. 25-hydroxy-vitamin D levels in a patient with hypervitaminosis D. *Klin Wochenschr.* 1978;56(14):715-717.
13. Ezgu FS, Buyan N, Gündüz M, Tümer L, Okur I, Hasanoglu A. Vitamin D intoxication and hypercalcaemia in an infant treated with pamidronate infusions. *Eur J Pediatr.* 2004;163(3):163-165.
14. Barrueto F Jr, Wang-Flores HH, Howland MA, Hoffman RS, Nelson LS. Acute vitamin D intoxication in a child. *Pediatrics.* 2005;116(3):e453-e456.
15. Klontz KC, Acheson DW. Dietary supplement–induced vitamin D intoxication. *N Engl J Med.* 2007;357(3):308-309.
16. Lee DC, Lee GY. The use of pamidronate for hypercalcemia secondary to acute vitamin D intoxication. *J Toxicol Clin Toxicol.* 1998;36(7):719-721.
17. Blank S, Scanlon KS, Sinks TH, Lett S, Falk H. An outbreak of hypervitaminosis D associated with the overfortification of milk from a home-delivery dairy. *Am J Pub Health.* 1995;85(5):656-659.
18. Peiris AN, Bailey BA, Manning T. The relationship of vitamin D deficiency to health care costs in veterans. *Mil Med.* 2008;173(12):1214-1218.