The Vitamin D Gap

Estimating an adequate intake of vitamin D.

By Laurence Montgomery, ND and George Tardik, ND

Vitamin D intake guidelines were established to prevent rickets in children and osteomalacia in adults, diseases that resolve when the serum concentration of 25(OH)D reaches 25nmol/L (Wharton 2003). Emerging research has shown that raising vitamin D levels even further in the general population could have a far-reaching preventive impact on a variety of illnesses including: malignancy; musculoskeletal conditions; autoimmune conditions (diabetes, rheumatoid arthritis, and multiple sclerosis); cardiovascular conditions (hypertension, stroke, peripheral arterial disease); respiratory illness; and gynecological conditions (pre-eclampsia and gestational diabetes). The beneficial effects of vitamin D on these conditions appear at a higher threshold, often 75nmol/L or greater. The higher doses required to obtain theses levels are known to be safe in the short term, but the long term effects of maintaining the general population at between 75 and 100nmol/L through oral supplementation have not been thoroughly studied. The result is that although clinicians are being urged by many researchers to aim for higher serum concentrations of vitamin D, they are simultaneously being advised to prescribe supplemental doses that cannot meet those targets. We refer to this persistent case of circular epidemiology as the 'vitamin D gap'.

SPECIAL POPULATIONS AT RISK FOR LOW VITAMIN D STATUS

The attention paid to groups at higher risk for lower vitamin D status has somewhat obscured the vitamin D gap. In addition to the well-known relationship between latitude and vitamin D status, other factors known to lower vitamin D status include:

- Darker skin color (Nesby-O'Dell 2002)
- Older age (Hirani 2010, Linnebur 2007)
- Smoking (Brot 1999)
- Winter/Seasonality (Brot 1999)
- Obesity (Alemzadeh 2008, Vilarrasa 2007, Yanoff 2006)

continued on page 65 >

Laurence Montgomery, BSc, ND
Integra Health and Wellness Clinic

623a Mount Pleasant Road
Toronto, Ontario, Canada M4S 2M9
lmontgomery@ccnm.edu

George Tardik, ND
Preventive Medical Health Centre

271 Spring Street
Cobourg, Ontario, Canada K9A 3K3
pmhc_nd@yahoo.com

The existence of special higher risk groups for vitamin D deficiency does not imply, however, that the general population is at an optimal or even healthy level. On initial screening, 46.2% of adults in Duluth, Minnesota had a vitamin D level less than 60nmol/L (Arvold 2009). A group of 'healthy' male adolescents living in a suburb north of Paris had an average 25(OH)D concentration of 20.6nmol/L at the end of the winter (Guillemant 1999). Table 1 reveals that the deficiencies faced by specific populations exist in the context of a generally low vitamin D status of the population at large.

ESTABLISHING AN OPTIMAL TARGET FOR VITAMIN D LEVELS

Although 'deficiency' and 'sufficiency' are terms that lack consensus in the literature, the trend over the past few decades has been for the threshold to increase. Multiple studies have been published attempting to establish a 'minimum' level of 25(OH) D for the general population. Many experts have suggested that a concentration of 75nmol/L should serve as the minimum level within the general population (Bischoff-Ferrari 2006). Suggested upper limits run as high as 220nmol/L (Aloia 2008).

However, establishing an optimal concentration of 25(OH)D for patients who are at higher risk for certain diseases appears to be more complicated. In these cases, the 'minimum' 75nmol/L may not be an appropriate target. As an example, Table 2 illustrates concentrations required to prevent secondary hyperparathyroidism is twofold greater than the concentration required to prevent rickets. Additionally, for those at risk of colon cancer, the maintenance concentration required for prevention appears to be twice as high again. For the practitioner of preventive medicine, the evidence points towards individual target ranges depending on individual therapeutic goals.

THE RIGHT DOSE TO REACH THE RIGHT TARGET

Assuming a goal of 75nmol/L for the general population (or perhaps a higher range for specific disease prevention) the relevant clinical question becomes: How can the chosen goal be met?

Regardless of starting levels, serum 25(OH)D rises approximately 2.5nmol/L for every additional 100 IU given (Heaney 2003, Holick 2008). To raise a serum 25(OH)D from 50nmol/L to 75nmol/L typically requires an additional 1,000 IU above current intake. Using the same estimate, raising the level from 25nmol/L to 75nmol/L would require an additional 2,000 IU per day.

Table 1. Vitamin D Status of selected populations

25(OH)D	Population at Risk	Source
<75nmol/L	81% of adults with cystic fibrosis	Boyle 2005
<75nmol/L	98% of obese 13-16 year olds (Wisconsin, Winter)	Alemzadeh 2008
<75nmol/L	50% of 'healthy' mothers	Lee 2007
<75nmol/L	65% of 'healthy' newborn infants	Lee 2007
<60nmol/L	46% of adults (Duluth, February)	Arvold 2009
<60nmol/L	50% of all Canadians age 12-19	Statistics Canada 2009
<50nmol/L	75% of female acute admissions over 65 (Ireland)	DeLappe 2006
<50nmol/L	51% Dutch men and women aged 60-87 (Winter)	van Dam 2007
<50nmol/L	48% adolescent girls (Maine – Winter)	Sullivan 2005
<50nmol/L	17% adolescent girls (Maine – Summer)	Sullivan 2005
<50nmol/L	28% female osteoporosis patients (Global)	Lips 2001
<40nmol/L	59% of obese blacks (Washington, DC)	Yanoff 2006
<40nmol/L	18% of obese whites (Washington, DC)	Yanoff 2006
<40nmol/L	51% of morbidly obese women (Barcelona)	Vilarrasa 2007
<40nmol/L	48% of blacks aged 15-49 (USA – Winter)	Looker 2002
<30nmol/L	79% nursing home residents (Netherlands)	Brot 1999
< 30nmol/L	5% of all Canadians aged 6-79	Statistics Canada 2009
<25nmol/L	8% of women being treated for osteoporosis (Europe)	Lips 2001

More recently, the above 'rule-of-thumb' was studied to see if a dose response exists and if such a dose response might be affected by age, gender or race. The objective of the study was to investigate an algorithm for raising 25(OH)D concentrations to between 80 and 140nmol/L. The authors performed a six-month, prospective, randomized, double blind, controlled study of vitamin D3 supplementation in healthy white and African American men and women 18-65 years (Aloia 2008).

Those with a basal concentration of 25(OH)D between 50 and 80nmol/L were started on 2,000 IU/d, whereas those with a basal concentration <50nmol/L were started on 4,000 IU/d. The results revealed that by week 18 approximately 90% of both African American and white male and females achieved or exceeded 75nmol/L, with the bulk of the increase occurring within the first two months. Although people starting with a lower level required a higher dose, age, race, body mass index, and percentage body fat did not significantly influence the response to vitamin D. Interestingly, there was a striking intersubject variation in response to vitamin D, with a tenfold difference in response between the highest and lowest responders. This variation did not correlate with any of the traditional risk factors for poor vitamin D status (Aloia 2008).

Table 2. Concentrations of 25(OH)D Associated with Specific Health Outcomes

25(OH)D	Therapeutic Goals	Source
120nmol/L	Associated with 50% risk reduction for breast cancer	Garland 2007
100nmol/L	Associated with 80% reduction in risk for colon cancer	Garland 1989
	Associated with 51% reduction in risk for multiple sclerosis	Munger 2006
90nmol/L	Minimum recommended for prevention of hip fractures	Bischoff-Ferrari 2006
	Minimum recommended for prevention of colorectal cancer	Bischoff-Ferrari 2006
80nmol/L	Significant (odds ratio=2.1) reduction in risk of aggressive prostate cancer	Li 2007
50nmol/L	Required to prevent secondary hyperparathyroidism	Robinson 2006
40nmol/L	Significantly (odds ratio=1.62) decreased risk of cardiovascular events	Wang 2008
25nmol/L	Resolution of rickets	Wharton and Bishop 2003
	Children 11 times less likely to suffer acute lower respiratory infection	Wayse 2004

Table 3. Some Typical Recommended Vitamin D Intakes

Daily Doses	Claim/Recommendation	Source
1,000 IU	Safe tolerable upper intake level	Expert Group on Vitamins and Minerals 2003
600 IU	Adequate intake upper range Adequate intake for Canadians >71 years old	Food and Nutrition Board 1997
400 IU	Adequate intake for Canadians aged 51-70.	Health Canada 2004
200 IU	Adequate intake lower range Adequate intake for Canadians aged 2-50 years	Health Canada 2009

Table 4. Average Additional Vitamin D Intakes Required to Raise Serum 25(OH)D Above 75nmol/L

Daily Dose	Claim/Recommendation	Source
4,000 IU	To attain and maintain >75nmol/L if starting below 50nmol/L	Aloia 2008
2,000 IU	To attain and maintain >75nmol/L if starting above 50nmol/L	Aloia 2008

Aloia and colleagues have confirmed that the daily additional dose required to obtain and maintain >75nmol/L is much higher than typical recommended intakes. More importantly, their work calls into question the wisdom of setting uniform requirements for vitamin D, given the known differences in starting levels and the previously unknown large variability in dose response – not between groups, but between individuals.

Although this paper is concerned mostly with the optimal preventive daily intake of vitamin D, much can be learned from the ongoing therapeutic failure of high dose repletion regimes. A recent evaluation of commonly prescribed repletion protocols has revealed that, to take just one example, 50,000 IU of D2 once a week for four weeks followed by 50,000 IU monthly for five months failed to obtain 75nmol/L for 62% of patients (Pepper 2009). This regime, which provided 450,000 IU over six months was less effective than the 112,000 IU provided by Aloia to subjects assigned to 2000 IU/d in the first eight weeks of their trial (Aloia 2008). Indeed, Aloia and colleagues found that response rates tended to decrease with escalating doses. A direct comparison with the high dose repletion regimes may not be fair, given that they tend to use synthetic D2 on older patients with known deficiency. However, a reasonable inference for the time being is that smaller daily doses of vitamin D3 are more effective in preventing vitamin D deficiency than larger, less frequent doses of D2 are at correcting a vitamin D deficiency. To employ an aphorism, an ounce of D3 prevention may be worth a pound of D2 cure.

A common obstacle encountered by clinicians is that patients often expect that sunlight 'should be' an adequate source of vitamin D. Indeed it is theoretically possible to get the equivalent of 20,000 IU or more per day from the sun. Holick has termed 20,000 IU the "minimal erythemal dose", because this is the equivalent amount obtained from exposing one's whole body to the sun until the entire body develops a slight redness. Skin pigmentation, latitude, season, and concerns over skin cancer prevent the average patient from getting anywhere near this amount of exposure (Holick 2007).

Compared to the 20,000 IU or more that our ancestors produced from being in the sun, 400 IU a day seems unreasonably low, and adding 2,000-4,000 IU per day to our existing intake seems less intimidating for both the patient and the clinician.

SAFETY CONCERNS

And yet there is strong resistance to increasing a daily intake by a factor of ten, even though the highest chronic daily oral intake of vitamin D that poses no risk of adverse effects for most healthy adults has never been determined. One of the greatest clinical concerns with high dosages of vitamin D supplementation is toxicity (hypervitaminosis D) leading to abnormally high serum calcium levels (hypercalcemia), which could result in kidney stones, and calcification of organs like the heart and kidneys if untreated over a long period of time. When the Food and Nutrition Board of the Institute of Medicine established the tolerable upper intake level for vitamin D, documentation of the lowest intake of vitamin D that would induce hypercalcemia was very limited. Because the consequences of hypercalcemia are severe, the Food and Nutrition Board established a very conservative upper limit of 2,000 IU/day for children and adults. Research published since suggests that this upper limit for adults is likely overly conservative and that vitamin D toxicity is very unlikely in healthy people at intake levels lower than 10,000 IU/day (Heaney 2003, Maalouf 2008, Vieth 2000).

The short term studies summarised in Table 5 show no ill effects with even higher doses of vitamin D that raise blood levels up to 643nmol/L. Regardless, the long term consequences of supplementing the entire population to the 75-100nmol/L range have not been studied to the point where authorities have deemed it safe to raise recommended intakes accordingly.

Closing the vitamin D gap with new intake recommendations will require detailed study of multiple subpopulations. However, separate recommendations based on race, latitude, season, BMI, age, etc may not be feasible. Moreover, although knowledge of these environmental factors might be used to make allowances for different starting levels in specific populations, the large personal variations in dose response reported in the literature still need to be accounted for. Until all of the above occurs, a one-size-fits-all style of recommendation may not be appropriate, and closing the vitamin D gap may have to proceed one patient at a time.

Table 5. Short Term Effects of High Dose Vitamin D (adapted from Hathcock 2007)

Study	Study Population	Dosage and Design	Duration	Outcome
Stern 1981	Healthy adults (N=24) and children (N=12)	Adults: 100,000 IU vitamin D3/d Children: 37.5μg · kg^{-1} d^{-1} randomized controlled	4 days	Significant increase in serum 25(OH)D; no significant change in serum calcium or phosphorous. Duration was too short to assess chronic intake effect.
Trivedi 2003	Elderly adults (N=2686)	100,000 IU bolus doses D3 provided once every four months with no acute toxicity reported; long duration (5 years), but not representative of daily exposure at this level; randomized controlled.	5 years	Significant increase in serum 25(OH)D; serum and urinary calcium not measured; no adverse effects reported.
Kimball 2006	Adult multiple sclerosis patients (N=12)	Up to 50,000 IU vitamin D3/d; randomized; dosing during cold months with little sun exposure.	8 weeks (56 days)	Significant dose-dependent increase in serum 25(OH)D (643nmol/L at highest dose); no significant change in serum calcium.
Heaney 2003	Healthy men (N=67)	Up to 10,000 vitamin D3/d; randomized controlled; dosing during cold months with little sun exposure expected.	20 weeks (140 days)	Significant dose-dependent increase in serum 25(OH)D (to 220nmol/L at highest dose); no significant change in serum calcium.

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