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ORIGINAL ARTICLE

Implications for 25-Hydroxyvitamin D testing of public health policies about the benefits and risks of Vitamin D fortification and supplementation

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Abstract

Vitamin D status is of interest to physicians caring for patients in poor general health. The tool for assessing vitamin D status is the serum 25-hydroxyvitamin D (25(OH)D) concentration. Based on clinical trials and epidemiology the low end of the desirable concentration of this analyte generally ranges from 50 nmol/L to 75 nmol/L. Based on clinical trials, the high end of the safe concentration for 25(OH)D is at about 225 nmol/L, with an unspecified margin of safety beyond that. In the absence of sunlight, 225 nmol/L is achieved with prolonged consumption of about 10,000 IU/day (250 μg/day) of vitamin D3. Hence that intake should be regarded as safe, and in the absence of sunshine, comparable vitamin D-wise to abundant sun exposure. Government policy is very conservative, and consequently, the latest advice from the Institute of Medicine for Canada and the USA specifies that in the absence of sunshine, a recommended dietary allowance (RDA) of 600 IU/day (15 μg/day) of vitamin D will provide a serum 25(OH)D concentration of at least 50 nmol/L. Dietary-vitamin D-intake statistics for adult populations show that average intakes from food and supplements are 200–400 IU/day (5–10 μg/day), respectively. Therefore, adult populations are consuming vitamin D in amounts far below the RDA. Even if adults were to consume the RDA for vitamin D, it would still not be enough to ensure 25(OH)D >50 nmol/L. The implication of all these things for the clinical laboratory is that there will continue to be a demand for 25(OH)D measurements for many years to come.

Introduction

The purpose of what is presented here is to address policy recommendations about vitamin D, and to discuss the implications of public health policy for vitamin D nutrition as it relates to the laboratory measurement of 25-hydroxyvitamin D (25(OH)D) concentration[1]. The political benefits and risks of government health policies are as pertinent to the advice as are the scientific health-related implications of the nutrient. The thesis presented here is that the demand for 25(OH)D laboratory testing will stay high until government health policies provide societies with sufficient vitamin D nutrition to obviate the need for the laboratory test. A major reason for the high demand for 25(OH)D laboratory measurements is that health policies are resistant to change and fail to ensure S-25(OH)D above even the minimum target levels.

It needs to be clear from the outset, that anything will be toxic if consumed in excess. Therefore, unless the context is established, about the specific interval of vitamin D intake that is at issue, discussion can only remain vague and inconclusive. Several excellent reviews have balanced the medical benefits and medical risks of vitamin D supplementation. They largely focused on establishing the maximum dose of vitamin D that could be consumed without any risk of harm to the individual [1–3]. The underlying premise for each of these reviews has been that the natural, physiologic acquisition of vitamin D through exposure to sunshine is not harmful. Since the amount of vitamin D acquired from sunshine cannot be measured directly, the estimate of physiologic vitamin D production is based on the S-25(OH)D observed in the sun-rich populations of interest. The S-25(OH)D of people whose

[1]In this document the notation S-25(OH)D refers to the serum concentration of the sum of 25(OH)D3 and 25(OH)D2 concentrations which is the quantity generally measured.

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skin is exposed to abundant sunshine or UVB light are commonly higher than 100 nmol/liter, ranging up to 225 nmol/liter [4,5]; therefore, the intake of vitamin D orally that can bring about such levels of S-25(OH)D should be regarded as physiologic and safe. This interval of safety has been confirmed through many clinical trials that have demonstrated no adversity attributable to the doses of vitamin D that deliver S-25(OH)D concentrations of at least 225 nmol/liter (Table I).

Although many of the clinical trials listed in Table I show health benefits, it remains a subjective decision as to whether the evidence of benefits beyond musculoskeletal health are compelling enough to warrant serious consideration for health-policy makers. To my knowledge, all of the national agencies that address vitamin D nutritional recommendations recognize only the bone-health outcomes as relevant to dietary advice and health policy. The ratio of benefit and risk would surely shift dramatically if non-bone outcomes were accepted. At the present time, insulin responsiveness is among the more likely non-bone-health relationships of vitamin D that should warrant official acceptance, based on the growing evidence of double blind, placebo-controlled clinical trials. The perceived ratio of benefit to risk would also shift dramatically if the upper amount of vitamin D consumption were to increase to more than the 2,000 to 4,000 IU/day values currently prevalent [3,25]. Table I summarizes high-level evidence for vitamin D benefits on depression/wellbeing, and insulin responsiveness, and it should be noted that the risk of adverse events with vitamin D doses averaging 2,000–4,000 IU/day (to as high as 40,000 IU once weekly) never been reported as anything different from the risks of adverse events observed with placebo.

Dietary guidelines, and current intakes

In 2011, the Institutes of Medicine (IOM) published its final report on recommendations for dietary guidelines for vitamin D and calcium. Because the IOM is only an advisory body, the advice of the IOM still needs to be applied by the appropriate agencies of the United States and the Canadian governments to incorporate the advice into public-health policy. Among the many issues that need to be addressed by policymakers are the questions of whether any new advice even needs to be given to the public to increase intakes of vitamin D. Such advice would need to be balanced against the question of whether there is a risk-to-benefit ratio that warrants changes to public-health policy. To be clear about some of the distinctions that policy makers need to consider, fortification is the addition of a nutrient to food, while supplementation is the intake of a nutrient in relatively pure form, typically as a pill, liquid or powder preparation. The difference between fortification and supplementation is semantic, but the difference has broad implications for national food policies [26].

Until recently, Canada was unique among countries, because it's Food Guide specified the need for a dietary supplement, vitamin D, along with the balanced intake of healthy fruits, vegetables, protein sources, and dairy products. This advice for normal, healthy adults to supplement was remarkable, because dietary guidance generally starts from the principle that a healthy diet provides all of the nutrition required for health, and that normally, there is no need for a supplement. However, since the average intake of vitamin D by Canadians hovers around 200 IU/day (5 μg/day) (Figure 1), it is very difficult to ensure even the old adequate intake of vitamin D (400 IU/day; 10 μg/day) for those over 50 years of age. Now that the IOM has tripled its vitamin D recommendation for children and adults, it becomes even more difficult for people to acquire the 600 IU/day (15 μg/day) RDA by diet alone. Unless fortification with vitamin D were to increased dramatically, the need for supplementation will remain unavoidable. A new report on dietary guidance for vitamin D for Austria, Germany and Switzerland advises that a vitamin D supplement may be required in those countries as well, to ensure that S-25(OH)D remain above 50 nmol/L (25).

The reasons why several national-policy recommendations advise consumption of a vitamin D supplement are illustrated by the data represented in Figure 1. The data are for Canada, a country in which milk is fortified with vitamin D at approximately 400 IU/L (10 μg/L), with a lesser amount in margarine [27]. And they show that even with higher amount of fortification than other countries, the typical Canadian diet provides only about 200 IU/day of vitamin D. The vitamin D intake of Canadians is almost double that of Germans, whose data from the National Nutrition Survey II (NVS II, 2005–2006) shows that vitamin D intake in men (the highest intake group) was at a median intake of 2.9 μg/day, and the 95th percentile value of 9.6 μg/day (396 IU/day). These data show that in both Canada and in Germany the intakes of vitamin D through diet, with or without supplementation, fall severely short of their respective latest recommendation guidelines of 600 IU/day or 800 IU/day respectively. Presently, the only way to overcome this shortfall between actual intakes and the RDA for vitamin D in North America is to advise that the population specifically take a vitamin D supplement. However, this strategy is not a realistic approach to making a meaningful contribution to public health, because it would require a substantial social and cultural shift toward the use of supplements to achieve the vitamin D intakes that

Table I. Clinical trials of vitamin D3 supplementation > 800 IU/day (> 20 μg/day) and the attributable benefits and risks.

Clinical trial	Study subjects	Treatment dose and duration	Primary outcome	Treatment effect (a secondary outcome if different from the primary one)	Type of control (double-blind unless stated otherwise)	Control treatment S-25(OH)D nmol/L mean (SD) or median (interquartile range)		Primary outcome improved with vitamin D	A secondary outcome improved	Adverse effect attributed to treatment
Aloia 2010 [6]	Men and women ages 20–80	4,000 IU/day for 4 months with or without 1,200 mg calcium	Characterize interaction of calcium and vitamin D on bone-turnover markers	No effect of vitamin D on PTH or bone turnover markers. Calcium alone lowered these.	Double placebo, without calcium or vitamin D	66 (24)	112 (30) (active D, placebo Ca group)	No	No	None
Amir 2010 [7]	Women with metastatic breast cancer	10,000 IU/day for 4 months	Overall pain scores	No effect on overall pain or bone turnover markers, but significantly fewer pain sites	Single-arm trial	70 (19–169)	162 (74–226)	No	Yes	None
Burton 2010 [8]	Patients with multiple sclerosis	Average 14,000 IU/day over 12 months (doses ranged up to 40,000 IU/day)	Safety and exploratory outcomes	Lower risk of progression of disability score	Open label untreated group (many took up to 4,000 IU/day vitamin D)	83 (27)	179 (76), at 12 months (varied through study)	NA since Phase 1–2 clinical trial.	Yes	None
El-Haj Fuleihan 2006 [9]	Pre-menarcheal girls	2,000 IU/day for 12 months	Bone density	Greater gains in hip and vertebral bone density, and lean body mass	Placebo	27 (15)	70 (23)	Yes	Yes	None
Hitz 2007 [10]	Hip-fracture patients	1,400 IU/day plus 1,200 mg calcium for 12 months	Bone density	Improved lumbar spine BMD	200 IU vitamin D only	53 (17)	82 (19)	Yes	No	None
Hitz 2007 [10]	Patients with lower-extremity fracture	1,400 IU/day plus 1,200 mg calcium for 12 months	Bone density	Improved lumbar spine BMD	200 IU vitamin D only	77 (18)	90 (24)	Yes	No	None
Jorde 2008 [11]	Adults wit BMI > 28	weekly 20,000 IU or 40,000 IU vs placebo for 1 yr	Weigh loss	Lower (improved] Beck Depression Index	placebo group	50.0 (20–100)	88 (51–162) and 112 (47–193)	NA	Yes	None

Jorde 2010 [12]	Same as above, Jorde 2008	Weekly 20,000 IU or 40,000 IU vs placebo for 1 yr	Cardiovascular and diabetes outcomes	No effect	Placebo group	60 (22)	101 (21) or 140 (34)	No	No	None
Lappe 2007 [13]	Women over age 65	1,100 IU/day, plus 1000 mg/day calcium, 4 yrs	Bone density	Lower rates of new cancer diagnosis	Placebo	71 (20)	96 (21)	NA	Yes	None
Martineau 2011 [14]	Tuberculosis		Time to sputum conversion					Yes (for a subgroup]	No	None
Mitri 2011 [15]	BMI 25–40 and glucose intolerance early diabetes	2,000 IU/d for 16 wk	Beta-cell function	Improved beta cell function	Double blind with or without calcium	46 (19)	77 (20)	Yes	No	None
Mocanu 2009 [16]	Nursing-home residents	5,000 IU/day for 12 months, single-arm study	Bone density	Increase in bone density at both in hip and vertebral spine	Baseline of same group	29 (20–36)	125 (104–150)	Yes	No	None
Nagpal 2009 [17]	Men, middle aged centrally obese	120,000 IU vit D3 every wk for 6 wks (8571 IU/d for 6 wk)	Insulin responsiveness	Improved oral glucose insulin sensitivity	Double-blind placebo	30 (13)	72 (27)	Yes	None	None
Nursyam 2006 [18]	Pulmonary tuberculosis patients	10,000 IU/day for 6 weeks	TB Sputum Clearance	Radiological improvement	Placebo group	Not measured	Not measured	Yes	Yes	None
Saunders 2010 [19]	Women > 70yr at risk of fracture	Once each year, a bolus dose of 500,000 IU for 4 yr	Falls and fractures both increased (worsened)	No secondary outcomes,	Double-blind placebo	49 (40–63)	49 (40–63)	No, greater falls and fractures intreated arm	None	Yes, increased falls and fracture
Smith 2009 [20]	Men and women through the South Pole winter	2,000 IU/day or 1,000 IU/ day for 5 months	Effect on serum 25(OH]D	NA	Group receiving 400 IU/day	57 (18)	71 (23)	NA	NA	None
Stubbs 2010 [21]	End-stage renal disease	50,000 IU/wk for 8 wk but adjusted so 25(OH]D was 112–150 nM	Cytokine concentrations	Lower inflammatory cytokines	Single-arm trial	35	135	Yes		None

(*Continued*)

Table I. (*Continued*).

Clinical trial	Study subjects	Treatment dose and duration	Primary outcome	Treatment effect (a secondary outcome if different from the primary one)	Type of control (double-blind unless stated otherwise)	Control treatment S-25(OH)D nmol/L mean (SD) or median (interquartile range)	Primary outcome improved with vitamin D	A secondary outcome improved	Adverse effect attributed to treatment
Urashima 2010 [22]	School children 6–15y	1,200 IU/day for 4 months through winter	Incidence of influenza A	Lower risk of influenza A and lower risk of asthma attacks	Placebo	Not measured / Not measured	Yes	Yes	None
Vieth 2004 [23]	Well thyroid clinic outpatients	4,000 IU/day for 3 months and 15 months	Wellbeing and mood in February	Wellbeing scores improved into winter	Lower dose group, 600 IU/d	79 (30) / 112 (41)	Yes	No	None
von Hurst 2009 [24]	Insulin resistant Asian women	4,000 IU/day vs 600 IU/day for 6 months	Insulin responseiveness	Improved insulin responsiveness vs placebo	Placebo group	21 (11–40) / 75 (50–84)	Yes	No	None

would align with the latest recommendations. The more practical option is to introduce much higher levels of fortification with vitamin D into the food system in Canada, Germany and elsewhere. But fortification policies carry with them political risk, similar to what continues to be experienced with water fluoridation.

Recent reports that supplementation with multivitamins have failed to show a net health benefit have been discouraging. A recent analysis by Mursu et al. concludes, "Based on existing evidence, we see little justification for the general and widespread use of dietary supplements. We recommend that they be used with strong medically based cause, such as symptomatic nutrient deficiency disease." [28]. Furthermore, policy makers often cite the meta-analysis of high-dose vitamin E showing increased mortality at higher doses [29] or they refer to the suggestion of greater mortality and cancer risk with beta carotene in smokers in Finland [30]. When it comes to vitamin D, the problem in making analogies to multivitamins other nutrients, is that the analogies are simplistic, and neither scientific, nor relevant to the specific decision about whether or not to supplement with vitamin D.

The adverse associations with vitamin E and beta carotene were seen in clinical trials that had used those nutrients in amounts that were an order of magnitude greater than what could be acquired in the normal course of daily living. In contrast, if outdoor activity can generate a S-25(OH)D as high as 225 nmol/L, then this represents an input of vitamin D in the order of 5,000–10,000 IU/day. The analogy to "high" doses of the antioxidants pertains to approximately a 10-fold intake beyond what would be acquired through normal living. In the context of vitamin D, the analogy of what constitutes a "high" degree of nutrient consumption should be interpreted as a sustained daily vitamin D intake of at least 50,000 IU (1,250 μg). If there is a concern about "high" intakes of vitamin E or beta carotene, then the analogous concern about a "high" vitamin D intake should be addressing the question of vitamin D supplementation at a rate higher than 20,000 IU/day. That high an intake of vitamin D is far beyond any serious discussion about vitamin D as a nutrient. Vitamin D intakes pertinent to the present discussion are up to the amounts listed in the trials summarized in Table I.

It should be evident from other presentations in this symposium, that there are many reasons to expect that, higher levels of vitamin D consumption will eventually be recognized as necessary for sun-deprived societies. To be effective, this greater consumption will need to be achieved through greater levels of food fortification with vitamin D, instead of advising all of society to take vitamin D supplements. There are many advantages to greater fortification of foods with vitamin D: Firstly, the financial cost of

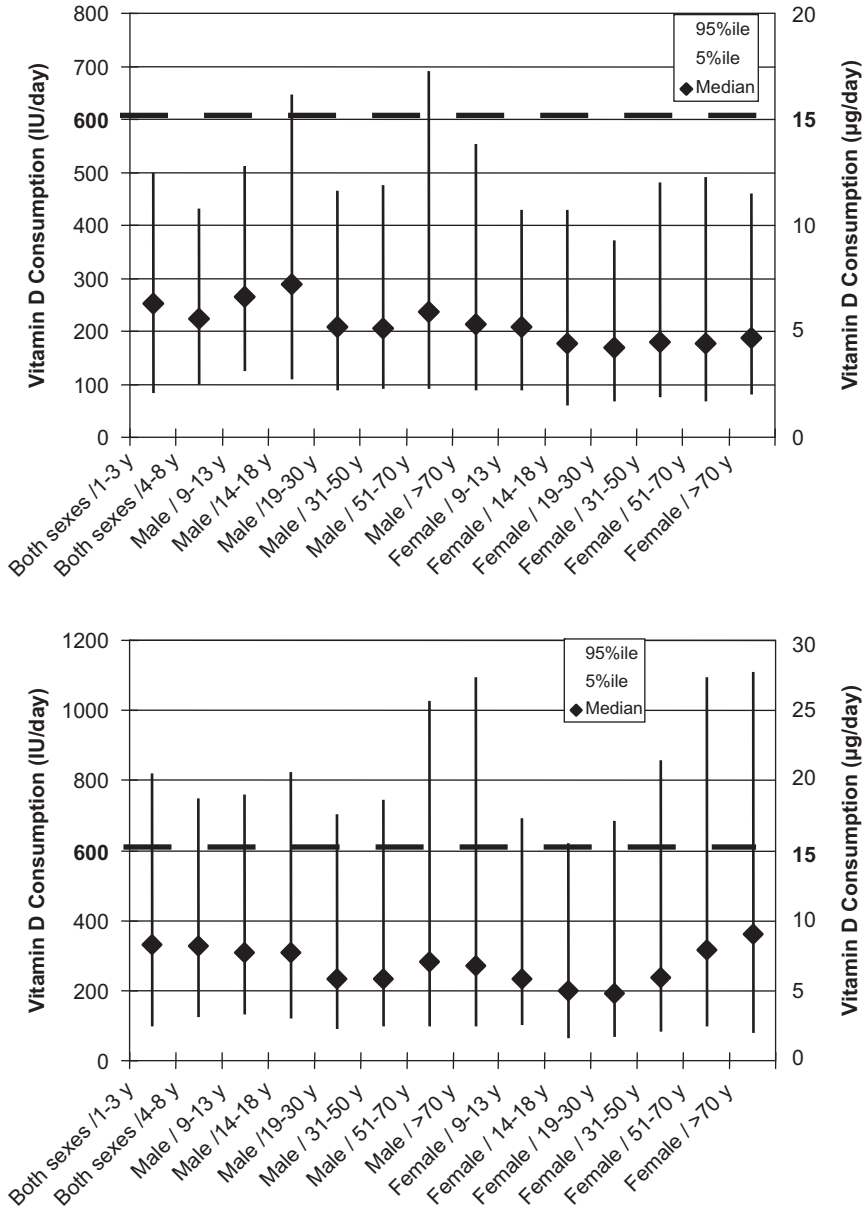

Figure 1. Vitamin D intake from food alone (Top panel) and from food plus dietary supplements (Bottom panel) in Canada. These data on vitamin D consumption in Canada, which has relatively high levels of food fortification (Top) and consumption of vitamin supplements (Bottom, which shows the total of food plus supplements) shows that most of the population does not attain the RDA intake for vitamin D. These data were obtained from the Canadian Community Health Survey - HS - 2004 - Cycle 2.2, which collected information from over 35,000 respondents of all ages from across Canada residing in private households [27]. The dashed line in each panel indicates the adult RDA (600 IU/day; 15 µg/day) according to the IOM, and that the median intakes are consistently well below the RDA for all segments of the population.

fortification is far less than the cost of widespread needs to purchase supplements. Secondly, the adherence of healthy people to taking a supplement is likely to be poor, while the consumption of vitamin D-fortified foods would be relatively consistent, and more effective across the broader population [26,31]. Examples of successful fortification policies include iodine in table salt and folic acid in flour used for baking. Iodine fortification started in the 1920s and led to remarkable reduction in rates of goitre. Folic acid fortification has reduced rates of spina bifida in recent years. Although fluoridation of water as a form of fortification does reduce rates of dental caries, it has remained a contentious issue, and stands as an example of the political difficulties that can result from fortification [26].

The context of my discussion here is related firstly to current guidance for health policy, such as that of the IOM and the Deutsche Gesellschaft für Ernährung, Österreichische Gesellschaft für Ernährung, Schweizerische Gesellschaft für Ernährungsforschung. Secondly, my context is to relate the different advice about vitamin D from medical groups including the Endocrine Society in the United States, and Osteoporosis Canada that propose intakes of 1,500–2,000 IU/day. Lastly, I will

address the benefit/risk of vitamin D supplement intakes of 2,000–4,000 IU/day, as currently used in clinical trials, and that may be a possible future RDA. The risk/benefit profile is different for those who might be perceived to benefit from higher S-25(OH) D within the physiologic range (up to 225 nmol/L).

Supplementation vs Fortification as possible alternate solutions to providing vitamin D to the broader population, to ensure S-25(OH) D > 50 nmol/L

Without even higher levels of fortification, it is not feasible for public health policy to advise more consumption of the existing food sources of vitamin D. Higher levels of fortification of food would minimize of the prevalence of S-25(OH)D < 50 nmol/L in the population, with minimal risk of exceeding the UL on the basis of the quantities of vitamin D in the present food supply. However, many people do not consume enough fortified milk or eat fish in amounts that could deliver the new recommended intakes of vitamin D. There are several barriers to increased milk intake, including cultural habits and perceived lactose intolerance. In addition, education alone, to increase consumption of specific foods would not address potential cost barriers to improved diet among those at low socio-economic levels.

One key advantage of encouraging supplementation is that it would make it unnecessary for people to change dietary patterns or for the industry to change the food supply through fortification. Supplementation could deliver a dose precisely, and minimize the risk of exceeding the UL. The drawbacks to supplementation are that it is more expensive than food fortification, and supplementation would require high levels of adherence by the population. The most vulnerable population groups are the ones least likely to be taking vitamin D supplements because of cost, lack of awareness of the need, and possibly lack of belief in the benefits.

There are important advantages to fortifying foods with vitamin D. Fortification of appropriate dietary sources with vitamin D will certainly reach a wider population than supplementation. Foods beyond milk and milk substitutes (e.g. soy beverages, fortified orange juice) should be fortified with vitamin D so that those who do not drink milk can derive benefit. Drawbacks to fortification are in the implementation and in the political response. Mandatory food fortification is politically contentious because of perceived tampering of the food supply, and there might be an economic cost associated with food fortification. Increased fortification may also be of limited use for those with low energy intake. In the United States, fortification of milk with vitamin D by the manufacturer is voluntary, and most milk on store shelves is labeled as "Vitamin D Milk". This voluntary option, without a difference in the price of the product would eliminate political reticence about fortification. In practice, consumers respond well to voluntary fortification of food, and with the USA as the example, it is difficult to find milk on store-shelves there that is not fortified with vitamin D.

Fortification is not likely address recommended intakes of vitamin D totally, so it will always remain necessary for some subgroups of the population to consume supplements to reach the minimally desired S-25(OH)D. However, the margin of safety for vitamin D plays a substantial role in determining permissible levels of fortification, because the ratio of the targeted intake (likely to be the RDA) versus the upper level for the nutrient (presently 4,000 IU/day based on the IOM) determines the permissible excess consumption of the nutrient beyond the RDA. Figure 1B shows that in Canada, recent levels of vitamin D consumption from food and supplements exhibit 95th percentile values at 1,100 IU/day, which is 28 % of the current UL. This means that even in Canada, where the amount of food fortification and non-prescription supplementation with vitamin D is more than in most countries, there is still a at least a 3-fold margin of safety for fortification and supplementation levels.

Another point to consider is whether only foods that are rich in calcium, or fortified with calcium, should be the only targets for vitamin D fortification. Since the bone-health outcomes for vitamin D have generally been demonstrated with the combination of vitamin D and calcium, then if bone health is officially the only pertinent outcome, policy makers often consider it important to tie these two nutrients together. This is unfortunate, because the need for calcium along with vitamin D hinders efforts to improve vitamin D nutritional status. Calcium supplements are generally awkward to consume, and if vitamin D needs to be taken with them, the net effect is to diminish adherence to vitamin D along with the poor adherence to calcium supplements). This is a doubly unfortunate marriage, because it is increasingly clear that an inverse requirement exists for these two nutrients. With more vitamin D, there is a diminished need for calcium). Furthermore, the pharmacologic behavior of these two nutrients differs dramatically: calcium needs to be consumed daily, while vitamin D can be consumed in cumulatively equal doses at intervals of at least one month [34].

Perceived risks with higher S-25(OH)D

Risks of adverse health outcomes exist for almost all biologically active substances at doses that are either excessively low or excessively high. The IOM based its concern about the risks of high S-25(OH) D and the concentrations at which these risks occur

primarily on the clinical trial of Sanders et al. that gave exceptionally large doses of vitamin D all at once [19] and on epidemiologic data suggestive of U- or reverse J-shaped curves associating S-25(OH)D with all cause mortality. Higher S-25(OH)D have been related to increased risk of prostate cancer [35], pancreatic cancer], and other cancers [36] as well as all cause mortality [37]. However, supplementation with vitamin D in clinical trials of bolus doses below 200,000 IU has never been related to adverse effects. In fact, the interval of vitamin D consumption being discussed here (over 400 IU up to about 1,000 IU daily) has resulted in lower mortality than placebo] and no excess in adverse event reports [40]. A recent 1-year long randomized clinical trial comparing 800 IU per day versus 6,500 IU per day detected no difference in adverse events [41]. Further work will always be helpful to clarify the levels of S-25(OH)D at which both skeletal/mineral and extra-skeletal effects are deleterious at both the upper and the lower ranges of S-25(OH)D.

The information in the published literature about the safety of vitamin D is growing steadily, and to date, there is no clinical trial that has shown adversity related to the supervised consumption of vitamin D. The best of the longer-term studies is by Jorde et al. [11,42] but these extended to only one year and assessed only selected outcomes. Ideally, a longer-term trial e.g. a 5-year RCT using different doses of vitamin D up to 4,000 IU daily and with a defined calcium intake could be helpful to examine both indices of efficacy and of toxicity and potential interaction between vitamin D and calcium intake.

Conclusion: Implications for the clinical laboratory

Vitamin D has become a focus of attention for physicians dealing with patients in poor health. The tool for assessing vitamin D status is the S-25(OH)D. While the desirable interval of this analyte remains a subject of debate, it is safe to say that even the most conservative of commentators are advising a minimal concentration of 50 nmol/L [43,44]. Although the latest IOM dietary guidelines are intended to bring the S-25(OH)D to at least 50 nmol/L [3], the reality is that even the government mandated guideline advising the highest intake of vitamin D (800 IU/day; 20 μg/day) fails to deliver on its stated intent if adults are sun-deprived [43]. Even the older, lower guidelines for vitamin D were not consumed by the population of Canada, were food is fortified (Figure 1) [27]; consequently it is unrealistic to expect that the population of high-latitude countries will consume enough vitamin D to keep the lower tail of the distribution of S-25(OH)D is above 50 nmol/L. Therefore, physicians will continue to request measurements of S-25(OH)D on patients in poor health for many more years.

Questions and answers

I Young, UK

How may toxicity be mediated or influenced by calcium intake. You didn't refer to calcium intakes in the studies you referenced. What are your views on this issue?

R Vieth

Actually, in the study I showed with the high vitamin D and urine calcium concentrations, all the individuals were given 1,200 mg elemental calcium so it was an early phase study and we created a worst case scenario. These were healthy individuals, at least in terms of bone mineralisation, and the calcium didn't change anything. Within that interval, things are still relatively well regulated. I want to point out that in the Women's Health Initiative study in which it was suggested that the incidence of kidney stones went up by 17 %, those women were already on calcium supplements and many of them were above the upper level for calcium. The vitamin D intake was, I think, in the order of 200 U per day, because of poor compliance. The baseline serum 25(OH)D concentration was not reported and it has been suggested that because of this average low intake, the serum 25(OH)D concentrations did not change at all. This study is the only one in which vitamin D has been implicated as causing kidney stones, but it is likely that it was calcium which was the cause.

H Morris

I make a comment in relation to the Sanders project in that the 25(OH)D concentration of 125 nmol/L, the average achieved, has no relationship to the adverse effects because they only measured blood concentrations in a very small subgroup. Those who had had an adverse effect are likely to have been excluded from the subgroup.

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