Mitigating epidemic vitamin D deficiency

The agony of evidence

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For unless they see the sky
But they can't and that is why
They know not if it's dark outside or light
Bernie Taupin, Elton John, 1972

If we define a vitamin as a required substance that is not endogenously produced, vitamin D does not meet the criteria. It is produced in skin upon UVB exposure, acting on 7-dehydrocholesterol and undergoing hydroxylation in the liver and kidneys. It behaves, in fact, more like a steroid hormone, binding to vitamin D receptors throughout the body.[1] As humankind becomes increasingly urban and specialized, life choices have consequences, including reduced exposure of skin to sunlight and so, reduced ability of skin to synthesize vitamin D.[2] Predicted future environmental changes could have unpredictable consequences. If weather becomes excessively wet or hot, people might be driven indoors. Should the behavioural response to warmer temperatures be increased time in the sun, use of sunscreens or sunblocks might be mandated to protect skin from the strengthened UVB rays from atmospheric ozone depletion, minimizing exposure necessary to vitamin D production. With the passage of time, it could be that vitamin D will become a true vitamin after all. Optimal health might, therefore, require an exogenous source, as there are few natural food sources apart from fatty fish.

Life choices and risk factors

The genesis of mankind was almost certainly in sub-Saharan Africa, and these people were probably deeply pigmented. As some of them migrated northward some 60 000 years ago, they experienced less direct UVB radiation from the sun, and there were periods of time when no radiation was available during winter months.[2,3] As they moved north and adapted to these conditions, their skin became increasingly depigmented, providing a survival advantage over more deeply pigmented subgroups whose vitamin D deficiency produced problems with mobility and reproduction.[4] The possible exceptions were the Inuit in the far north, who consumed a diet of fat and oily fish, one of the few food sources high in vitamin D.

Adaptation occurred gradually over generations and is reflected in such features as skin colour, clothing, rituals, and diet. These days there can be rapid changes in location and environment that cause new stresses, advantages, and deprivations without time for adaptation. A variety of these changes and life choices strongly affect vitamin D levels, and some, such as advancing age, reduced exercise, obesity, and lack of sun exposure, act in synergy. **Table 1** identifies risk factors, which can act individually or in concert to produce low levels of vitamin D.[4-19]

Prevalence of vitamin D deficiency

Hepatic hydroxylation of vitamin D3 produced in skin or taken orally produces 25-hydroxyvitamin D (25[OH]D), a major metabolite, which has a long half-life, allowing measurement of serum vitamin D levels. There is no complete consensus on optimum serum levels of 25(OH)D needed for prevention of disease. There is some support, however, for using the following benchmarks[20]:

- Deficiency: less than 25 nmol/L; leads to short-latency disease seen in rickets in children and osteomalacia in adults.
- Insufficiency: 25 to 75 nmol/L; leads to long-latency disease such as osteoporosis, fractures, and falls.
- Optimal: 75 to 110 nmol/L or more.[7,21]

Even in the sunniest places, such as Saudi Arabia and Australia, 30% to 50% of adults and children have deficient or insufficient levels of vitamin D.[5] At the latitude of Edmonton, Alta, 90% of children have deficient or insufficient levels.[6] There were 104 confirmed cases of rickets in Canada between 2002 and 2004.[22] The frail elderly have particularly low levels, with one study showing an average decrease of 6 nmol/L over a 2-year period.[23]

Average 25(OH)D levels are also tending to fall over time. A US nutrition survey done in an interval between 1988 and 2004 showed prevalence increases in levels of marked deficiency from 2% to 6%, while prevalence of adequate levels fell from 45% to 23%.[24]

The evidence conundrum

The development of evidence demonstrating the health effects of vitamin D deficiency has been delayed and confused owing to a combination of multiple factors:

- The marketplace drives much research. There are low profit margins in vitamin D manufacturing. Some statins, for example, are thought to increase levels of vitamin D.[25] Both statin administration[26] and vitamin D levels[27] correlate inversely with the prevalence of multiple

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Table 1. Risk factors for vitamin D deficiency

RISK FACTOR	MECHANISM
Lack of sun exposure[5]	Reduced skin synthesis
Latitude of residence[6]	No skin synthesis November to March at 52° north (eg, Edmonton, Alta)
Sunscreen use[7]	SPF of 15 blocks 99% of skin synthesis
Urbanization[8]	Increasing time indoors and increased automobile use
Aging[9]	75% reduction in skin production by age 70; increased institutionalization as a greater percent of the population ages
Increased chronic disease prevalence[10]	Reduced sun exposure due to increased time indoors; some chronic conditions contribute physiologically to reduced vitamin D production (eg, chronic renal disease); as the population ages, prevalence of chronic disease will rise
Increased medication use[11]	Anticonvulsants, glucocorticoids, HIV medications, and some antirejection drugs reduce levels of vitamin D
Limited dietary choices[12]	Fatty fish and fish oils are the only ample food source, and are becoming increasingly unavailable
Reliance on food fortification[13]	Food sources are inadequate; in Canada, cow and soy milks and margarines are fortified
Migration of populations[5]	Rapid migration of people with pigmented skin toward polar areas can reduce skin synthesis as much as 99%
Traditional clothing[14]	All clothing impairs synthesis; Muslim women wearing traditional clothing have a 2.3 odds ratio of developing osteoporosis
Obesity[15]	A 2006 survey found that two-thirds of the US population was overweight or obese; vitamin D is sequestered in body fat, and levels are inversely related to BMI
Reduced exercise opportunities[16]	Vehicle prioritization, poor urban planning, and poor air quality force many to exercise indoors
Skin pigmentation[4]	Melanin is a very efficient blocker of UVB radiation
Season[5]	Very little vitamin D synthesis can occur from sun exposure in northern latitudes in winter months
Sex[17,18]	Women are at increased risk of deficiency because of reduced peak bone mass, increased pregnancy demands, and traditional attire in some areas
Metabolic demand[19]	Rapid skeletal growth in utero and in early infancy increases demand for calcium and vitamin D; breast milk is a poor source
Malabsorption[5]	Vitamin D is fat-soluble; therefore, those with fat malabsorption syndromes such as Crohn disease or celiac disease are at risk

BMI—body mass index, SPF—skin protection factor.

sclerosis. Several prospective dosing studies treating multiple sclerosis with statins have now been done, with both negative[28] and positive[29] results; however, to date, no dosing studies have been done with vitamin D.

- Dosage is clearly important. Early, larger randomized trials used dosages that were probably too low to show statistically significant benefits.[30-32] Subsequent smaller trials using higher dosages have had positive results, but have had less influence on outcomes when meta-analyses were done. Subgroup analysis to control dose heterogeneity has demonstrated the benefits of higher dosing.[33]
- Control subjects in larger studies were not prevented from taking vitamin D on their own, potentially masking differences between groups.[34]
- Food supplementation led to the assumption that deficiency was prevented and that no further studies were needed.[35] It took some time to recognize the effects of insufficiency leading to long-latency disease.
- Calcium was often administered concurrently, which could have independently influenced end points.[36,37]
- Despite a multitude of epidemiologic studies showing the association between low vitamin D levels and common diseases (**Table 2**),[27,38-45] few follow-up, randomized, prospective dosing studies have been done, despite suggestions such studies are needed.[27,46,47] Evidence frequently has never gone beyond hypothesis generation.

Proven and potential benefits

Consequences of vitamin D deficiency were comprehensively outlined in this journal in 2007,[48] and have been further addressed in recent reviews and meta-analyses. The more established benefits are summarized in **Table 3**.[49-57]

Potential benefits from epidemiologic studies or those for which level I and II studies provide conflicting evidence appear in **Table 2**.[27,38-45] While these conditions can only be said to be associated with low levels of 25(OH)D, there are compelling data to prompt larger-scale randomized trials.

Supplementation to achieve adequate levels

Available higher-level evidence provides some guidance on vitamin D intakes for health maintenance:

- 400 IU daily is sufficient to prevent rickets in children and osteomalacia in adults, but is insufficient to achieve adequate serum levels of 25(OH)D.[1]
- 700 to 1000 IU daily is the minimum required to reduce risk of falling in the elderly.[53]
- 400 to 800 IU daily is the minimum required to reduce risk of fracture in the elderly.[51]
- 500 to 1500 IU daily reduced cancer mortality and all-cause mortality in various studies.[49,50,58]
- 2000 IU daily reduced the incidence of type 1 diabetes in young children.[56]
- 1000 IU daily is required to bring 50% of adults to 25(OH)D levels above 75 nmol/L (considered adequate).[59]
- 2000 IU daily is required to bring 85% to 90% of the adult population to 25(OH)D levels above 75 nmol/L.[59]

The Canadian Paediatric Society[22] has expressed concerns about insufficient vitamin D intake in children,

Table 2. Epidemiologic association or conflicting studies suggesting potential benefits of vitamin D supplementation

CONDITION	BEST EVIDENCE	LEVEL OF EVIDENCE	COMMENTS
Chronic unexplained pain	Straube et al,[38] 2009	Meta-analysis	Insufficient epidemiologic or RCT evidence for link between pain and insufficiency or deficiency
MS	Munger et al,[27] 2006	Prospective nested case-control	Solid association between high 25(OH)D and low risk of MS; no available dosing studies
Deterioration of cognition	Annweiler et al,[39] 2009	Systematic review	No clear association between cognitive function and 25(OH)D, but considerable heterogeneity; intervention studies inconsistent
Some infectious diseases	Yamshchikov et al,[40] 2009	Systematic review	Strongest evidence for tuberculosis, influenza, and viral upper respiratory tract illness; considerable heterogeneity
CVD	Pittas et al,[41] 2010 Wang et al,[42] 2010	Systematic reviews	Possible association of 25(OH)D with hypertension and CVD (not diabetes[41]); prospective dosing trials suggest benefit at moderate to high doses—more studies needed
Type 2 diabetes	Pittas et al,[41] 2010	Systematic review	Insufficient evidence for association of 25(OH)D levels with incident diabetes; no good evidence on dosing studies benefiting glycemic control
Periodontal disease	Dietrich et al,[43] 2004	Cross sectional	Low 25(OH)D levels might be associated with periodontal disease independent of effects on bone mineral density
Breast cancer	Garland et al,[44] 2007	Pooled analysis of longitudinal studies	Estimated 50% reduction in breast cancer incidence with use of 2000 IU vitamin D daily; no available dosing studies
Prostate cancer	Yin et al,[45] 2009	Meta-analysis of longitudinal studies	Serum 25(OH)D not found to be associated with incident prostate cancer

25(OH)D—25-hydroxyvitamin D, CVD—cardiovascular disease, MS—multiple sclerosis, RCT—randomized controlled trial.

Table 3. Currently established benefits of vitamin D

CONDITION	BEST EVIDENCE	LEVEL OF EVIDENCE	COMMENTS
All-cause mortality	Autier et al,[49] 2007	Meta-analysis	300-833 IU/d; mortality a secondary end point in all but 1 study
Cancer mortality	Lappe et al,[50] 2007	RCT	1000 IU/d; 1179 postmenopausal women; included calcium supplement
Fracture	Bischoff-Ferrari et al,[51] 2009	Meta-analysis	400-800 IU/d; dose dependent; 20 RCTs; independent of calcium
Muscle strength	Moreira-Pfrimer et al,[52] 2009	RCT	3000-5000 IU/d for 6 mo; elderly population
Falls	Bischoff-Ferrari et al,[53] 2009	Meta-analysis	700-1000 IU needed; elderly population; 8 trials
Colon cancer	Zhou et al,[54] 2009	Evidentiary review	1000 IU/d recommended; 25 studies included
Hypertension	Witham et al,[55] 2009	Meta-analysis	11 studies; weak evidence for reduction in BP
Type 1 diabetes	Hyppönen et al,[56] 2001	Prospective case control	2000 IU/d; 10 821 children; relative risk reduction of 0.22 in first year of life
Psoriasis	Kreuter et al,[57] 2006	RCT	Topical calcipotriol equivalent to topical steroid; 80 patients for 4 wk

BP—blood pressure, RCT—randomized controlled trial.

particularly at northern latitudes, where rickets continues to be reported. They also suggest higher doses than currently recommended might be required in adolescents and adults to achieve and maintain adequate bone mass, particularly during pregnancy. Recent recommendations by the Food and Nutrition Board of the US Institute of Medicine appear in **Table 4**.[60] These doses do not seem adequate in view of current evidence.[61]

Clearly, any decision made that increases dosing must take potential toxicity into consideration. Fortunately there seems to be a wide margin of safety, with trials of supplementation from 4000 to 10 000 IU daily causing no rise in serum or urinary calcium and no adverse events.3,62,63 An increase in urinary tract stones was reported as 5.7 per 10 000 participants in the Women's Health Initiative study, despite

Table 4. Adequate intakes of vitamin D

AGE, Y	RECOMMENDED ADEQUATE INTAKE
Birth to 13	600 IU
14-18	600 IU
• Pregnant or lactating	600 IU
19-50	600 IU
• Pregnant or lactating	600 IU
51-70	600 IU
≥ 71	800 IU

Data from the Office of Dietary Supplements, National Institutes of Health.[60]

the low-dose supplementation. This might reflect the relatively high calcium intakes of the study population.34,64 We might, however, expect a slightly increased incidence of stones in a vitamin D–replete population. Maintaining vitamin D deficiency seems a poor strategy for preventing renal colic.

Given the favourable risk-to-benefit ratio, it seems reasonable, and quite conservative, to recommend a supplemental intake of 1000 to 2000 IU daily to patients older than 1 year of age (**Table 5**). Higher-risk patients, such as the obese, those with chronic disease, or the elderly could take 2000 IU daily.[65,66]

Table 5. Suggested update to adequate intakes for vitamin D based on best evidence

AGE	SUGGESTED ADEQUATE INTAKE
0-12 mo	400-800 IU
• Below 55th parallel	400 IU
• Above 55th parallel	800 IU
1-13 y	1000-2000 IU
14-18 y	1000-2000 IU
• Pregnant or lactating	2000 IU
19-50 y	1000-2000 IU
• Pregnant or lactating	2000 IU
51-70 y	1000-2000 IU
≥ 71 y	1000-2000 IU

Patients with deficiency or insufficiency will require larger doses to raise 25(OH)D levels to normal. Increased doses are necessary for repletion, although it does not matter whether these doses are given daily, weekly, or monthly.[67,68] The best-studied regimen is to give 600 000 IU of vitamin D2 (which is 60% less available than vitamin D3 at high doses)[5,67,69] over a period of 8 weeks. Vitamin D2 is available in 50 000-IU capsules. Administration could then be 3 capsules of 50 000 IU every 2 weeks 4 times before reducing intake to maintenance levels. As D3 is now available in 50 000-IU capsules as well, a similar strategy could be employed using a lower dose. Serum levels can then be tracked. Other strategies are obviously possible, including intramuscular administration.

Options for health care providers

There are 2 approaches to prevention of disease: individual- or population-based strategies.[70] Population-based programs, such as adding vitamin D to foodstuffs or increasing daily dosage recommendations, are of minimal benefit to individuals, and are very sensitive to slim risk-benefit ratios.[70] With this scenario, as with vaccination, success is often a nonevent. Population-based programs do, however, speak to the etiology of the illness in the population, and are of great public health importance.

Recent guidelines reflect a gradually increasing acceptance of enhanced supplementation. The US Institute of Medicine's recently released recommendations for vitamin D intake[60] suggested that most Americans and Canadians up to age 70 needed no more than 600 IU of vitamin D daily to maintain health, and those 71 years of age and older might need 800 IU. These doses are still very conservative. In their review of more than 1000 studies, they found that considerable evidence confirmed the role of vitamin D in bone health, and that while numerous studies point to other possibilities that warrant further investigation, those studies have yielded conflicting and mixed results and do not offer the evidence needed to confirm that vitamin D has other health effects. New 2010 Canadian guidelines for management of osteoporosis[71] recommend higher intakes, with routine supplementation at 400 to 1000 IU daily for those at low risk and up to 2000 IU daily for high-risk individuals.

Until further research is done and more appropriate population strategies are made available, the office practitioner can make use of the individual or case-finding approach, identifying patients most likely to be vitamin D deficient by history. These individuals might need repletion therapy, while the remainder should probably consider maintenance supplementation. Screening serum levels would seldom be necessary unless used for treatment follow-up or patient motivation. The intervention of supplementation at 1000 to 2000 IU daily has a wide margin of safety, and the potential for individual health improvement is likely to be substantial.[21,59,66] This measure would be an interim expedient to protect our patients until a more adequate population-level strategy is crafted.

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Competing interests
None declared

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