The importance of assessing and supplementing vitamin D has bombarded the medical literature and lay press, greatly affecting the practice of most clinicians. Concern has been raised that there is inadequate data to support the cost of ubiquitous testing, and without the benefit of randomized controlled trials, there may be unanticipated consequences to aggressive repletion. The Institute of Medicine (IOM) recently proffered recommendations for daily intake and optimal levels of vitamin D based on an extensive review of the existing literature.1 Their recommendations for vitamin D intake are higher than prior dietary reference levels for intake, but considerably lower than levels proposed by many in the field.2,3 This commentary will attempt to clarify the controversy and present evidence to inform practice decisions.

VITAMIN D SOURCES AND METABOLISM

Vitamin D is not commonly consumed in the diet of the general population. Most plants and meats contain little vitamin D except for oily fish. Most vitamin D is derived through action of solar ultraviolet B radiation acting on 7-dehydrocholesterol in the skin to form previtamin D3, which is quickly converted to vitamin D3. Vitamin D2 is similarly produced by solar irradiation of marine plankton or yeast and molds.4,5 Given its endocrine functions, its limited supply in food sources, and the ability of mammals to synthesize it, vitamin D is not truly a vitamin, but rather a prehormone.4

Ingested or skin-derived vitamin D enters the bloodstream and is hydroxylated to 25-hydroxyvitamin D2 (or D3) (25-vit D) in the liver by the activating cytochromes, CYP2R1 and CYP27A1.6 Although having little metabolic activity, 25-vit D has high affinity for vitamin D binding protein, rendering it very stable in circulation with a half-life of 2 weeks.6,7 The relatively long half-life and high concentration in blood makes 25-vit D the optimal form to measure and assess vitamin D sufficiency.5,6

In the kidney, 25-vit D is converted to its most active form, 1,25-dihydroxyvitamin D2 or D3 (1,25-vit D) by the enzyme 25-hydroxyvitamin D-1α-hydroxylase, also known as CYP27B1. Although the kidney is the major site of 1,25-vit D production, there is clear evidence that CYP27B1 is present and functioning in other cells, leading to local, extrarenal 1,25-vit D production.8 The formation of 1,25-vit D is greatly influenced by serum levels of other hormones and ions, such as parathyroid hormone (PTH), fibroblast growth factor 23, calcium, and phosphorus. Because of its very short circulating half-life, and the minute quantities present in the blood (approximately 1000 times less than 25-vit D), 1,25-vit D is an inferior measure of vitamin D adequacy.2,5,6

Circulating 1,25-vit D induces the cytochrome P 450 enzyme, CYP24, which catabolizes both 25-vit D and 1,25-vit D into 24,25(OH)2 vitamin D and other metabolites.4,6 Elevated levels of 1,25-vit D inhibit CYP27B1, further downregulating its own production.

MEASUREMENT OF 25-VITAMIN D

Levels of 25-vit D are generally measured either by competitive immunoassays or chromatographic extraction followed by direct nonimmunologic measurement. All are quite precise, but the chromatographic methods, liquid chromatography-
tandem mass spectrometry and high-pressure liquid chromatography (HPLC), have the advantage of increased sensitivity, improved detection of very low vitamin D levels and the ability to independently measure both 25-vit D$_2$ and 25-vit D$_3$. Liquid chromatography-tandem mass spectrometry is more precise than HPLC and has recently been utilized for large clinical trials.

**PREFERRED VITAMIN D MEASUREMENTS FOR HYPOCALCEMIA AND HYPERCALCEMIA**

25-vit D is the measurement of choice when assessing adequacy of body stores of vitamin D. With sufficient 25-vit D, 1,25-vit D levels should be adequate in the absence of chronic kidney disease (CKD). Hypocalcemia is generally due to a deficiency in PTH or vitamin D and thus measurement of PTH and 25-vit D are generally the tests of choice for this disorder. The two most common causes of hypercalcemia are primary hyperparathyroidism and malignancy. Although it is less common for excessive 1,25-vit D to cause hypercalcemia, it may occur as a consequence of excessive ingestion or increased production, such as with sarcoidosis or other granulomatous diseases. 1,25-vit D levels should generally be ordered in hypercalcemic patients when the more common causes of hypercalcemia are excluded.

**WHAT IS AN ADEQUATE LEVEL OF 25-VITAMIN D?**

In an effort to determine optimal vitamin D and calcium intake and levels for the general population, the Canadian and United States governments appealed to the IOM to conduct a review of the existing literature. An ad hoc committee gathered and reviewed data and heard from others in the field. In addition, they commissioned the Agency for Healthcare Research and Quality (AHRQ) to perform evidence-based systematic reviews of the extensive literature on calcium and vitamin D, and to rate the quality of the data. The IOM used a risk assessment process to determine a dose of vitamin D and goal 25-vit D level that would be optimal for the majority of the population.

Vitamin D insufficiency was initially determined by the vitamin D level at which PTH began to rise. 1,25-vit D induces intestinal calcium absorption and low levels of blood-ionized calcium stimulate PTH secretion. 1,25-vit D also inhibits PTH secretion. Thus, elevated levels of PTH indicate an insufficient vitamin D and in this setting vitamin D supplementation will reduce PTH levels. In various populations, PTH levels begin to nadir as 25-vit D levels rise to $\geq15$ to 20 ng/ml (37.5 to 50 nmol/L) and are maximally suppressed at 25-vit D levels of 30 to 40 ng/ml (75 to 100 nmol/L). This initially led to designation of vitamin D insufficiency at 25-vit D levels less than approximately 15 to 20 ng/ml. However, PTH levels vary with age, kidney function, race, ethnicity, calcium and phosphorus intake, physical activity, time of day, and the accuracy of the assay.

Further investigation sought more clinically significant outcomes associated with vitamin D levels. Heaney et al. determined that supplementation with either vitamin D$_3$ or 25-vit D that raised levels of 25-vit D resulted in a significant increase in intestinal calcium absorption. Pooling the results of three studies on vitamin D and calcium absorption revealed a significant increase in the fraction of calcium absorbed as 25-vit D levels were increased from 20 to 30 ng/ml (50 to 75 nmol/L), suggesting that the minimum level of vitamin D necessary to maintain optimal calcium absorption should be $>30$ ng/ml rather than $\geq20$. The IOM, however, noted in some of the studies that calcium was not directly measured and the methodology used was suboptimal. Other studies also did not reveal a significant increase in calcium absorption with an elevation in 25-vit D levels above 20 to 25 ng/ml (50 to 60 nmol/L).

Perhaps the strongest reason to supplement vitamin D and increase levels of 25-vit D would be if fractures were reduced. Bischoff-Ferrari et al. reviewed several randomized control trials (RCTs) and cross-sectional studies that examined health outcomes associated with vitamin D status. These included bone mineral density (BMD), fracture prevention, and lower extremity function, all measures of bone and skeletal muscle health. In the third National Health and Nutrition Examination Survey (NHANES), they noted a significant increase in hip BMD as 25-vit D levels increased in Caucasian and Mexican American persons of all ages. The increase in BMD continued to rise throughout the range of 25-vit D concentrations between 8.8 and 37.6 ng/ml (22.5 to 94 nmol/L). Review of RCTs of hip and nonvertebral fracture rates also revealed a significant association between adequate levels of 25-vit D and reduced fracture risk. Significant fracture prevention was noted only in trials that supplemented patients with 700 to 800 IU of vitamin D$_3$, achieving a mean 25-vit D concentration of 40 ng/ml (100 nmol/L).

One of the largest RCTs was the Women’s Health Initiative (WHI) Trial which included over 36,000 women randomized to 400 IU of vitamin D with 1000 mg of calcium daily versus placebo. Although this treatment offered no fracture prevention, it did increase the incidence of kidney stones. The achieved 25-vit D levels in the WHI trial treatment group, however, did not rise above 25 ng/ml (62.5 nmol/L). Baseline calcium intake in participants was approximately 1150 mg daily before calcium supplementation, perhaps contributing more to the increased stone occurrence than the vitamin D. Given the NHANES and WHI data for bone health and fracture prevention, the minimal optimal vitamin D level recommended by many became 40 ng/ml (100 nmol/L) with a minimal vitamin D dose required to achieve this of $\geq$700 IU.

The AHRQ, however, found results relating to vitamin D levels and bone mineral density or fractures to be inconsistent and found no significant advantage to any minimum level of 25-vit D. There was benefit noted to a combina-
tion of vitamin D₃ (<800 IU daily) with calcium (500 mg daily) in promoting small increases in bone mineral density in postmenopausal women and in reducing fractures in institutionalized elderly women (800 IU vitamin D with 1.2 g of elemental calcium).¹¹,⁴,⁴⁵

The committee’s task was further complicated by many study designs that grouped calcium with vitamin D, rendering it difficult to determine the independent contribution of the ion and the prehormone. In addition, 25-vit D levels are influenced by sun exposure, which is seasonal and difficult to quantify, and variations in assay sensitivity and specificity. Nonetheless, they reviewed the many purported benefits of vitamin D, including a positive effect on cardiovascular disease, type 2 diabetes mellitus, immune function, malignancy, and bone health.¹ Ultimately, other than for skeletal health, the IOM found a paucity of data demonstrating any causal benefit to vitamin D for most health outcomes. With the critical appraisal of the bone health literature by the AHRQ, the data supporting higher goal levels of 25-vit D became less impressive.

**SHOULD ANYONE BE SUPPLEMENTED AND, IF SO, AT WHAT DOSE?**

Little ultraviolet B radiation is absorbed through the skin between November and March at latitudes >35° N and S (United States, north of Atlanta and Las Vegas; all of Europe and New Zealand; and South America, south of Buenos Aires).³⁵,³⁶ Given the ubiquitous use of sunscreen, even less ultraviolet B radiation is received. People at particularly high risk for vitamin D deficiency include African Americans (increased skin pigmentation reduces vitamin D production), the obese (fat sequestration of vitamin D), and patients with fat malabsorption due to reduced absorption of ingested vitamin D.²,³⁶

In general, 100 IU of vitamin D is thought to raise serum levels of 25-vit D by 1 ng/ml, although the increase may only be 0.7 ng/ml.³⁷ However, vitamin D may not be absorbed in a linear dose-dependent manner, with doses of <1000 IU daily increasing 25-vit D levels to a greater degree than doses ≥1000 IU daily.³⁸–⁴⁰ The IOM wrote that, in most children and adults, total vitamin D intakes of 600 IU were adequate to raise the 25-vit D level to levels of at least 20 ng/ml (50 mmol/L).¹

**VITAMIN D SUPPLEMENTATION IN CKD PATIENTS**

Patients with advanced CKD often have inadequate kidney function to convert 25-vit D to 1,25-vit D.² This insufficiency of 1,25-vit D results in excess PTH production and elevated PTH levels. In patients with advanced CKD, it has been assumed that PTH suppression can be achieved only with activated vitamin D (1,25-vit D) or an analog. Observational studies note that PTH suppression can be achieved with vitamin D₂ or D₃, especially with GFR >30 (stage 3).⁴¹ A recent review of observational studies and randomized controlled trials reveal that vitamin D (not activated) not only increases 25-vit D levels in patients with advanced CKD, including those on dialysis, but also significantly reduces PTH levels. Vitamin D supplementation did not result in hypercalcemia or hyperphosphatemia.⁴²

**POTENTIAL FOR VITAMIN D TOXICITY**

Vitamin D intoxication, as manifest by hypercalcemia, is rare in adults who are supplemented with 1000 to 2000 IU of vitamin D daily and is generally not observed unless 25-vit D levels exceed 115 to 200 ng/ml (375 to 500 nmol/L).⁶,⁴³ Increasing 25-vit D levels reduce 1,25-vit D production and increase breakdown of both 25-vit D and 1,25-vit D. Elevated 25-vit D levels are uncommon unless ingestion (usually accidental) of extremely large amounts of vitamin D occurs. Vieth reviewed studies of vitamin D supplementation and toxicity and noted that hypercalcemia was not evident unless ingestion rose above 40,000 IU for prolonged periods in healthy adults, or 25-vit D levels rose above 214 ng/ml (>535 nM/L).⁴³

In developing the guidelines for vitamin D intake, the IOM sought to determine the tolerable upper intake level; that is, the highest intake level at which there would be no risk of adverse effects for the majority of the population. They recognized that most people would not develop acute toxicity unless extremely large amounts of vitamin D are ingested; however, there was concern for possible adverse effects with a more moderate intake for longer periods of time.

Several investigators have shown an association of increased mortality with low vitamin D levels. Nutritional studies report the highest mortality in persons in the lowest quintile of 25-vit D (<20 or 30 ng/ml), but also increased mortality in persons in the highest quintiles, with 25-vit D levels >30 ng/ml (>75 nmol/L).¹⁴–⁴⁶ An analysis that pooled several large studies with >2000 persons found a twofold increased risk for pancreatic cancer in participants with 25-vit D levels ≥40 ng/ml (100 mmol/L) compared with those with levels in the 25 to 30 ng/ml range.⁴⁷,⁴⁸ In smaller studies of Scandinavian men, a higher risk of prostate cancer was noted in those with 25-vit D levels >32 ng/ml (>80 nmol/L);⁴⁹ however, this was not consistent in all studies.⁵⁰ In the IOM report, studies purporting harm were correctly held to less rigorous standards than those claiming benefit.

**FINAL RECOMMENDATIONS**

Given the limited available data, physicians are still left in a quandary as to the optimal dose, if any, of supplemental vitamin D. Most of us reside in communities where sun exposure is not adequate to provide sufficient vitamin D for many months of the year and, more importantly, we do not want to suggest therapy with clear carcinogenic potential.⁵¹–⁵³ The IOM recommendation of 600 IU of vitamin D daily to anyone above the age of 1 and 800 IU to those greater than
age 70, while aiming for a level ≥20 ng/ml, appears reasonable. As physicians and health care providers, however, we must be aware that population guidelines may not be adequate for every individual and must use our best judgment for each of our patients. Hopefully, future large controlled trials will not only define any benefits of vitamin D supplementation but also determine if supplementation causes harm.

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DISCLOSURES

None.

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