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REVIEW ARTICLE

Targeted 25-hydroxyvitamin D concentration measurements and vitamin D_3 supplementation can have important patient and public health benefits

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Abstract

Over the past two decades, many studies reported the benefits of higher 25-hydroxyvitamin D [25(OH)D] concentrations for nonskeletal effects. Researchers found significant benefits in reducing risk of acute respiratory tract infections, many types of cancer, type 2 diabetes mellitus, premature death, and adverse pregnancy and birth outcomes. In addition, 25(OH)D concentrations are low for various reasons in several categories of people, including the obese, those with dark skin living at higher latitudes, the elderly, and those who do not eat much eggs, fish, meat, or vitamin D fortified milk. Measuring 25(OH)D concentrations is one way to both increase the awareness of vitamin D's importance in maintaining good health and to encourage vitamin D supplementation or increased solar ultraviolet-B exposure to sustain well-being throughout life by reducing disease incidence. Although 20 ng/ml seems adequate to reduce risk of skeletal problems and acute respiratory tract infections, concentrations above 30 ng/ml have been associated with reduced risk of cancer, type 2 diabetes mellitus, and adverse pregnancy and birth outcomes. Thus, judicious testing of 25(OH)D concentrations could reduce disease incidence and make treatment expenditures more cost-effective.

Introduction

The understanding of the health benefits of higher 25-hydroxyvitamin D [25(OH)D] concentrations has greatly expanded during the past two decades. Mounting evidence from observational studies and clinical trials indicates that vitamin D reduces risk of many adverse health outcomes. Although concentrations > 20 ng/ml may be adequate for bone health and acute respiratory tract infections (RTIs), concentrations above 30 ng/ml are needed for many other health outcomes [1]. Recently, high-dose (~4000 IU/day) vitamin D_3 supplementation studies, raising serum 25(OH)D concentration above 40 ng/ml, yielded evidence for reduced risk of cancer [2–4], type 2 diabetes mellitus (T2DM) [5], acute RTIs [6], hypertension [7], and preterm birth [8]. The physiology and mechanisms of vitamin D are generally well understood [9].

Debate is ongoing in the journal literature regarding the advisability of measuring serum 25(OH)D concentration. On one hand, testing everyone can be expensive and inefficient [10–12]. On the other hand, those tested are more likely to supplement with vitamin D and increase 25(OH)D concentrations [13].

A recent paper from the United States summarized the situation:

> Many vitamin D testing patterns reflected screening rather than targeted testing for individuals at high risk of vitamin D deficiency or insufficiency. Interventions aimed at managing inappropriate clinical practices related to LVD (low vitamin D) were effective in the short term. Variability and controversy were pervasive in many aspects of vitamin D management, shining a light on physicians' practices in the face of uncertainty. Future research is needed to inform better clinical guidelines and to assess implementation

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practices that encourage evidence-based management of LVD in adult populations [14].

By contrast, a recent paper from the UK concluded:

Testing for vitamin D deficiency increased over the past decade among adults in the UK. One-third of UK adults who had a vitamin D test performed in primary care were vitamin D deficient, and deficiency was much higher among ethnic minority patients. Future research should focus on strategies to ensure population intake of vitamin D, particularly in at-risk groups, meets recommendations to reduce the risk of deficiency and need for testing [15].

This paper's goal is to review the evidence for beneficial effects of vitamin D, identify who would be likely to benefit from increasing 25(OH)D concentrations, and determine whether measuring 25(OH)D concentrations is an appropriate approach to persuade people to increase 25(OH)D concentrations through supplementation.

Methods and materials

This paper is a narrative review of the benefits of vitamin D, leading to guidelines for measuring 25(OH)D concentrations. Literature searches were conducted at the PubMed database (https://www.ncbi.nlm.nih.gov/pubmed/) and Google Scholar (https://scholar.google.com/). Search terms included cancer, cardiovascular disease, respiratory tract infection, sepsis, vitamin D, 25-hydroxyvitamin D, obesity, testing, diet, and risk.

Results

The results section gives findings for various conditions and diseases and groups of people. For each category, evidence for a beneficial role of vitamin D is presented, along with whether testing is likely to be advantageous.

Pregnancy

Vitamin D status during pregnancy is important. 25(OH)D concentrations increase during pregnancy implying an important regulatory role for this hormone in fetal development [16].

Low 25(OH)D concentrations have been associated with preeclampsia. A meta-analysis of 20 studies involving 39,031 participants and 3305 preeclampsia cases showed that women with 25(OH)D concentrations < 20 ng/ml had a 65% higher risk of preeclampsia (95% CI, 1.02–2.69) than women with 25(OH)D concentrations of 20–30 ng/ml [17]. Another study reported that supplementing with vitamin D reduced risk of preeclampsia by 63% (OR, 0.37; 95% CI, 0.26–0.52) [18]. Low 25(OH)D concentrations also are a risk factor for gestational diabetes (OR, 1.85; 95% CI, 1.47–2.33) [19].

An open-label multiracial clinical trial in South Carolina examined how serum 25(OH)D concentration affects risk of preterm birth. Women were enrolled near the 13th week of pregnancy. Their 25(OH)D concentrations were measured, participants received bottles of 5000 IU vitamin D_3 capsules, and they were counseled on how to achieve concentrations > 40 ng/ml. Serum 25(OH)D concentration also was measured shortly before delivery. Women achieving > 40 ng/ml had a 59% reduced risk of preterm birth compared with women with <20 ng/ml (adjusted OR, 0.41 [95% CI, 0.24–0.72]) [8].

A recent meta-analysis reported that high versus low maternal 25(OH)D during pregnancy was associated with a 5% higher cognitive development or global IQ, 28% lower risk of attention deficit–hyperactivity disorder, and 58% lower risk of autism-related traits of babies/infants born to these mothers [20].

Measuring 25(OH)D concentration during pregnancy is important, because most women are unaware of vitamin D's importance during pregnancy and have little idea how much to take or what concentration to aim for. Of course, if individual pregnant women took 4000–6000 IU/day of vitamin D_3 without testing, that would be acceptable [21, 22].

The elderly

Serum 25(OH)D concentrations decline with age. For example, concentrations in Budapest in August 2009 decreased from 36 ng/ml for people aged 40–49 years to 29 ng/ml for those aged 50–59, 33 ng/ml for those aged 60–69, 25 ng/ml for those aged 70–79, and 21 ng/ml for those aged 80–89 [23]. That decline occurs for several reasons, including spending less time in the sun and having lower concentration of 7-dehydroxyvitamin D in the epidermis [24]. In addition, death rates rise dramatically as people age, with many deaths related to chronic diseases. For example, U.S. death rates per 100,000 standard population in 2017 in the five highest-rate states rose from 302 for those aged 35–44 years, to 598 for those aged 45–54, 1262 for those aged 55–64, 2371 for those aged 65–74, 5516 for those aged 75–84, and 14,847 for those 85 or older [25].

An important reason to achieve 25(OH)D concentrations > 40 ng/ml is increased life expectancy. According to a meta-analysis of 32 observational studies, mortality rates increased nearly linearly below 36 ng/ml by about 90% for people with 25(OH)D concentration <10 ng/ml [26].

Based on the understanding of serum 25(OH)D concentration–health outcome relationships in 2011, an analysis was made for a variety of diseases for increasing serum 25(OH)D concentrations from 54 to 110 nmol/l for the various continents [27]. That increase would reduce the vitamin D–sensitive disease mortality rate by an estimated 20%. The reduction in all-cause mortality rates ranges from 8% for African females to 17% for European females. The estimated increase in life expectancy is 2 years for all six regions.

Dark-skinned people living outside the tropics

Because solar UVB exposure is the most important natural source of vitamin D, dark-skinned people living poleward of their native lands tend to have lower 25(OH)D concentrations than neighboring light-skinned people. For example, mean U.S. 25(OH)D concentrations for 2001–2004 were 25–28, 18–23, and 14–17 ng/ml for whites, Mexican Americans, and African Americans (AAs), respectively, depending on age range [28]. AAs have denser bones than white Americans, because of accruing more calcium than whites during adolescence—a result of increased calcium absorption and superior renal calcium conservation [29]. Thus, many AAs think that they do not need much vitamin D. However, AAs have poorer health outcomes for many diseases than whites, due partly to low 25(OH)D concentrations. For example, AAs have 0–50% poorer survival following diagnosis from many cancers, and after adjustment for socioeconomic status, stage at diagnosis, and treatment [30]. Vitamin D's importance is further underscored by the fact that women of all ethnic groups have lighter skin pigmentation than males, likely due for increased vitamin D requirements during pregnancy and lactation [31].

Vegetarians and vegans

Because foods that vegetarians and vegans eat contain little or no vitamin D, these individuals tend to have low 25(OH)D concentrations. Only animal products contain vitamin D_3. A U.K. study reported that meat eaters had mean 25(OH)D concentrations 4 ng/ml higher than those of vegetarians and 8 ng/ml higher than those of vegans [32]. More recently, an ecological study of 25(OH)D concentration for elderly women in 19 countries in the Middle East and Europe reported that dietary ocean fish had the highest correlation with serum 25(OH)D concentrations [33]. Meat did not have the highest correlation with 25(OH)D, possibly because women eat less meat than men do.

Obesity

Obesity is a risk factor for several noncommunicable diseases, such as T2DM, hypertension, CVDs, and cancer. Increased adiposity promotes insulin resistance, dyslipidemia, and chronic inflammation [34]. Vitamin D supplementation can promote beneficial effects on various risk factors influencing cardiometabolic health outcomes [35].

Moreover, observational studies have reported an inverse relationship between obesity and serum 25(OH)D concentrations [36, 37]. Several factors could contribute to that effect, including sedentary indoor lifestyle, which reduces sun exposure, and increased adiposity and BMI. Adipose tissues actively store vitamin D, and ~65% of total vitamin D in the body is in the form of vitamin D_3, stored in adipose tissue and skeletal muscle [38].

According to a systematic review of 144 cohorts from 94 independent studies of adults, a logarithmic association existed between vitamin D dose per kilogram of body weight (BW) per day and increment in circulating 25(OH)D. In multivariate regression analysis, BW was one of the most significant predictors, explaining 34.5% of variation in circulating 25(OH)D [39]. Usually BW is relatively closely associated with fat mass and fat-free mass. With the increasing BW in obese patients, this finding is an indication to recommend higher dosing for obese individuals.

Increase in serum 25(OH)D was compared in postmenopausal white women of normal to obese BMI in an RCT in which women were supplemented with seven doses of vitamin D (400–4800 IU/day). Low doses were 400–800 IU/day; medium doses, 1600–2400 IU/day; and high doses, 3200–4800 IU/day [40]. At baseline, an inverse correlation existed between body fat mass in all women and serum 25(OH)D ($r = 0.19$; $p < 0.0001$) and baseline serum $1,25(OH)_2D$ ($r = 0.09$; $p = 0.03$). Upon supplementation, the higher-BMI group showed a lower response than the low-BMI group. The increase in serum 25(OH)D after vitamin D was significantly less on lower doses than in the medium- and higher-dose groups ($p < 0.0001$). The highest increase in serum 25(OH)D after vitamin D occurred in thinner women with BMI < 25 kg/m^2. No significant differences were found in the serum 25(OH)D response to medium and high doses in BMI groups ≥ 30 kg/m^2. Total body fat in all those women did not change upon vitamin D supplementation. Vitamin D supplementation in 110 healthy AA women also achieved significant elevation in serum 25(OH)D concentrations, similar to white women, when administered in an RCT by the same group [41]. Those findings collectively indicate that body size, BMI, and adiposity need to be considered when recommending vitamin D supplementation, especially in women.

Imga et al. showed that vitamin D supplementation in overweight and obese premenopausal women increased serum 25(OH)D significantly (~5.6- and 5.2-fold, respectively). Supplementation significantly reduced insulin resistance (HOMA-IR), low-density lipoproteins, and intact

parathyroid hormone. A 1-ng/ml increase in circulating serum 25(OH)D resulted in a 0.30-fold reduction in HOMA-IR ($p = 0.002$) [42].

A recent study in Pakistan on 109 hospital patients (average age, 44 ± 16 years) showed that vitamin D status was inversely proportional to T2DM status (as per American Diabetes Association 2016 international criteria) and increasing adiposity concentrations, but not sex. Overall, 76% of patients were vitamin D deficient or insufficient, with a statistical difference observed between type 2 diabetic versus nondiabetic patients ($p = 0.015$). With regard to BMI and increasing adiposity, vitamin D status worsened with increasing BMI. Deficiency was 88% in obese subjects, 57% in overweight subjects, and 51% in nonobese subjects; $p = 0.02$. Vitamin D deficiency increased with increasing age but was not statistically significant with that sample size (90% in participants ≥65 years old, 66% in 41- to 65-year-olds, and 47% in 18- to 40-year-olds; $p = 0.06$) [43]. Some Iranian studies showed that sex differences could be noted, with a higher prevalence of vitamin D deficiency among females than males [44]. Several other studies in neighboring regional countries—the United Arab Emirates, Kuwait, and Saudi Arabia, which share some dietary influences—showed that vitamin D deficiency was associated with high prevalence of obesity, type 2 diabetes mellitus, and hypertension [45, 46].

To set the stage for discussing the benefits of 25(OH)D testing, we first present data on mortality rates for disease states for representative countries. The data are for 2015, obtained from the World Health Organization [47] (see Table 1) Rates for cardiovascular disease (CVD) are highest, followed by malignant neoplasms (cancer), with rates of Alzheimer's disease and other dementias, chronic obstructive pulmonary disease (COPD), T2DM, and RTIs varying by country. Those variations relate to, for example, dietary factors, smoking and air pollution rates, health system quality, and per capita income. As will be discussed, vitamin D status has played a role for all those outcomes, though the concentrations at which the effect of 25(OH)D plateaus for each outcome varies.

Type 2 diabetes mellitus

An RCT recently investigated vitamin D's role in reducing risk of progression from prediabetes to T2DM [5]. A total of 2423 prediabetic participants were enrolled, with half in the treatment group (4000 IU/day of vitamin D_3) and half in the control group. At baseline, mean 25(OH)D concentrations were near 28 ng/ml, which in the treatment group increased to 54 ng/ml. The risk of progressing to T2DM was not significantly different between treatment and control groups overall, although it was for several subgroups. For participants with BMI < 30 kg/m^2, HR = 0.71 (95% CI, 0.53–0.95). For males, HR = 0.82 (95% CI, 0.66–1.01), but for females, HR = 0.98 (95% CI, 0.77–1.26). For participants not taking calcium supplements, HR = 0.81 (95% CI, 0.66–0.98). For those older than 60.9 years, HR = 0.80 (95% CI, 0.64–1.01). For non-Hispanics, HR = 0.86 (95% CI, 0.72–1.02). However, some of these results, such as those based on BMI, indicate that 4000 IU/day of vitamin D_3 was not enough, suggesting that higher vitamin D doses would have yielded greater benefits.

Cardiovascular disease

The most important risk factors for CVD are diet, hypertension, obesity and smoking. For both CVD and T2DM, evidence-informed dietary priorities include increased

Table 1 Mortality rates for representative countries for 2015 from the World Health Organization [47].

Outcome	Finland	France	Hungary	India	Saudi Arabia	Poland	UAE	UK	US
All causes	389.6	345.0	666.6	923.4	707.6	548.7	582.5	401.0	487.7
Respiratory tract infections	1.9	8.1	7.9	64.2	44.3	20.5	22.2	20.8	11.4
Malignant neoplasms	99.7	126.4	177.5	75.3	59.5	156.3	55.1	123.3	113.4
Type 2 Diabetes mellitus	4.1	6.9	13.5	32.4	28.1	11.1	40.5	4.3	15.0
Alzheimer's disease, other dementias	48.6	19.1	16.1	16.5	44.5	3.1	36.6	34.7	32.4
Cardiovascular disease	128.6	73.2	295.6	261.8	303.4	231.2	273.1	98.4	132.4
Ischemic heart disease	71.8	32.1	188.5	161.2	192.1	155.1	174.0	50.6	79.3
Stroke	28.1	17.2	57.7	72.8	83.9	41.5	72.5	23.5	22.3
COPD	9.4	10.3	32.3	89.8	13.5	20.4	20.3	24.2	30.8
Data quality as defined by the WHO	G	G	G	P	P	Y	T	G	G

COPD chronic obstructive pulmonary disease, *G* high quality, *P* low, *T* intermediate minus, *UAE* United Arab Emirates, *UK* United Kingdom, *US* United States, *WHO* World Health Organization, *Y* intermediate plus.

fruits, non-starchy vegetables, nuts, legumes, fish, vegetable oils, yogurt, and minimally processed whole grains; and fewer red meats, processed (e.g., sodium-preserved) meats, and foods rich in refined grains, starch, added sugars, salt, and *trans*-fat [48]. The role of smoking is at least partly related to increased inflammation [49]. An open-label study conducted in Canada found that raising 25(OH)D concentrations above 40 ng/ml lowered blood pressure sufficiently for hypertensive participants that they were no longer hypertensive [7].

Observational studies associate 25(OH)D concentrations below 15–20 ng/ml with risk of CVD [50] and stroke [51]. In a meta-analysis of 16 prospective observational studies, low versus high 25(OH)D concentration was associated with a 32% increased risk of ischemic stroke (relative risk [RR] = 1.32 [95% confidence interval (CI), 1.19–1.48]) [52]. However, clinical trials have not reported a reduction in risk of CVD with vitamin D supplementation [53]. There are three possible reasons for this finding: (1) that few people with low 25(OH)D concentrations are enrolled in vitamin D randomized controlled trials (RCTs) [54]; (2) that vitamin D does not affect risk of CVD; and (3) that the role of vitamin D is cumulative over many years and CVD events may occur during periods of stress, such as during cold weather when blood pressure rises. In the United States, all-cause mortality rates are about 25% higher in winter than in summer, with CVD a major contributor to the seasonality [55]. Mean U.S. serum 25(OH)D concentrations are 21 ng/ml in March and 28 ng/ml in August [56]. Although testing 25(OH)D concentrations may identify some individuals who should take vitamin D supplements to reduce risk of CVD, an easier approach might be to recommend that everyone take at least 1000–2000 IU/day of vitamin D_3 in winter.

Cancer

A large body of evidence now indicates that higher 25(OH)D concentrations are linked causally to lower risk of cancer incidence and death. Researchers conducting single-country ecological studies found that higher UVB doses are inversely correlated with mortality rates for about 20 cancers [57]. Prospective observational studies show that colorectal cancer incidence is inversely correlated with serum 25(OH)D concentration. A meta-analysis reported that for women, 25(OH)D > 29 ng/ml versus <15 ng/ml was associated with a relative risk of 0.55, $P_{trend} < 0.001$, and >30 ng/ml versus <16 ng/ml was associated with a relative risk of 0.83, whereas for men, $P_{trend} = 0.20$ [58]. More recently, a pooled analysis of results for 5038 women from two vitamin D RCTs and one volunteer cohort with a mean follow-up time of 4 years showed that 25(OH)D concentrations >60 ng/ml versus <20 ng/ml were associated with a hazard ratio for breast cancer incidence of 0.20 (95% CI, 0.05 to 0.82), $P_{trend} = 0.04$ [3].

Higher 25(OH)D concentrations have been associated with higher cancer survival rates. A meta-analysis of 11 prospective studies regarding colorectal cancer survival with respect to high versus low serum 25(OH)D concentration reported a relative risk of 0.67 (95% CI, 0.57–0.78) for cancer-specific survival and 0.68 (95% CI, 0.55 to 0.78) for overall survival [59]. An observational study in Ireland reported "a 20% reduction in breast cancer-specific mortality in de novo vitamin D users (modelled as a time-varying variable) compared to non-users ([hazard ratio] HR 0.80; 95% CI 0.64–0.99, $p = 0.048$) and the reduction was greater at 49% (HR 0.51; 95% CI 0.34–0.74, $p < 0.001$), if vitamin D was initiated soon after the breast cancer diagnosis (within 6 months)" [60].

A major vitamin D RCT showed reduced risk of cancer incidence and mortality rates in the secondary analyses of several groups. The VITamin D and OmegA-3 TriaL (VITAL) for cancer, in which participants in the treatment arm received 2000 IU/day of vitamin D_3, reported that for those with body mass index (BMI) < 25 kg/m^2 of body surface area, the all-cancer HR = 0.76 (95% CI, 0.63–0.90) [4]. For blacks, HR = 0.77 (95% CI, 0.50–1.01). For cancer death, omitting the first year of data, HR = 0.79 (95% CI, 0.63–0.99). Had higher vitamin D doses been used, the reductions in cancer incidence and death would have been expected to be greater. Unfortunately, the secondary analyses of that RCT were not included in the abstract or discussed in the media [61].

Thus, both individuals wishing to reduce the risk of cancer and cancer patients would be well advised to have serum 25(OH)D concentrations measured to see whether they are above 30 ng/ml and, if not, supplement with vitamin D and retest after a few months.

Chronic obstructive pulmonary disease

A meta-analysis of 21 studies including 4818 COPD patients and 7175 controls reported that vitamin D deficiency was associated with increased risk of COPD (odds ratio [OR], 1.77; 95% CI, 1.18–2.64; $p = 0.006$) and with COPD severity (OR, 2.83; 95% CI, 2.00–4.00; $p < 0.001$) but not with COPD exacerbation (OR, 1.17; 95% CI, 0.86–1.59; $p = 0.33$) [62]. Thus, 25(OH)D concentration below 20 ng/ml is apparently a significant risk factor for COPD.

Acute respiratory tract infections

Acute RTIs such as seasonal influenza are much more common in winter than in summer. That fact led John Cannell to propose that vitamin D could reduce the risk of

epidemic influenza [63]. That hypothesis has been confirmed in vitamin D RCTs, such as Urashima and colleagues [64]. A meta-analysis of vitamin D RCTs and acute RTIs reported that for "those receiving daily or weekly vitamin D, protective effects were stronger in those with baseline 25(OH)D concentrations <25 nmol/L (adjusted odds ratio 0.30, 0.17–0.53) than in those with baseline 25 (OH)D concentrations ≥25 nmol/L (adjusted odds ratio 0.75, 0.60–0.95; P for interaction = 0.006)" [6]. Thus, supplementing with 1000–2000 IU/day of vitamin D_3 during the influenza season is advisable.

Admission to critical-care and intensive-care units

Several observational and clinical studies have shown the prevalence of vitamin D deficiency among patients with critical illnesses and its strong association with morbidity and mortality [65–70]. The prevalence of vitamin D deficiency among patients admitted to intensive-care units (ICUs) ranges between 40% and 70% [65]. Moreover, vitamin D deficiency is associated with negative health outcomes, including a higher illness severity score, higher risk of death, and increased incidence of organ malfunction and pneumonia. The hospital cost of ICU admission and care is remarkably higher among patients who are vitamin D deficient upon admission [71]. According to a systematic review of 14 observational studies involving 9715 ICU patients, vitamin D deficiency was associated with higher risk of death and vulnerability to life-threatening infections. The review concluded that vitamin D deficiency could predict adverse health outcomes among those critically ill patients [66].

Few vitamin D interventional clinical trials on vitamin D–deficient individuals in ICUs have been completed [72]. Most trials used megadose supplementation strategies for first loading to normalize vitamin D status among patients. One such study was the VITdAL-ICU trial initiated by Amrein and colleagues [73]. The interventional RCT involved 475 ICU patients with vitamin D deficiency (<20 ng/mL), randomly assigned to either high-dose vitamin D_3 supplementation (single dose of 540,000 IU followed by a 90,000-IU monthly maintenance dose for 5 months) or placebo. Vitamin D sufficiency (>30 ng/mL) was reached after 1 week in 52.2% of patients who received the intervention. The results showed no difference in hospital length of stay and no significant overall mortality benefit. However, for severe vitamin D deficiency subgroup [25(OH)D < 12 ng/ml], a large, significant mortality benefit was observed [73]. Another RCT on 30 critically ill septic patients and admitted to the ICU in Boston used a single dose of either 40,000 or 200,000 IU of vitamin D_3, enteral versus placebo. The results showed an abrupt normalization of 25(OH)D concentrations and increased concentrations of LL-37, the cathelicidin member with antimicrobial activity, among patients who received vitamin D_3 [74]. A similar interventional study in Atlanta on 30 mechanically ventilated ICU patients reported shorter hospital stay and a dose-dependent increase for 25(OH)D concentrations among those who received $5 \times 50{,}000$ IU of vitamin D_3, or 100,000 IU of vitamin D_3 enteral compared with those assigned to placebo [75].

Alzheimer's disease and other dementia

"Observational studies have pointed to vitamin D deficiency as a genetic risk factor for AD, Parkinson's disease (PD), vascular dementia, and multiple sclerosis (MS), as well as other neurological disorders, brought about by alterations in genes involved in metabolism, transportation, and actions of vitamin D. Molecular studies have demonstrated that vitamin D treatments prevent amyloid production while also increasing its clearance from the brain in AD. Finally, recent vitamin D intervention studies have reported significant improvement in cognitive performance in subjects with senile dementia, mild cognitive impairment, and AD [76]. In addition, people with dementia often have comorbid conditions such as hypertension and T2DM, resulting in a lower quality of life and health status [77]. These are conditions that vitamin D helps ameliorate. Furthermore, since people with dementia generally stay indoors, their 25(OH)D concentrations tend to be low. Thus, it appears that they should be supplemented with vitamin D, and that measuring 25(OH)D concentrations of a representative sample of demented people in care facilities or under physician supervision would lead to vitamin D supplementation guidelines that would improve the quality of life and health of these people.

Demonstrated economic benefits of 25(OH)D measurements

An analysis of vitamin D deficiency and vitamin D testing for 15,340 veterans at six southwestern U.S. Veterans Administration Medical Centers indicated that total inpatient cost per patient was approximately twice as high for vitamin D–deficient patients as for nondeficient patients [78]. In addition, per-patient costs decreased as the number of vitamin D tests increased from none to one and two. Also, average total per-patient cost decreased by 15–70% for patients with one or more vitamin D tests versus none.

Physicians associated with the Veterans Administration Medical Center in Mountain Home, Tennessee, reported "that veterans who were initially vitamin D deficient were significantly less likely to survive than those who were not initially deficient, and that both initial and follow-up

vitamin D deficiency were associated with decreased likelihood of survival after prostate cancer diagnosis" [79].

More recently, a study in Germany involving 4014 patients reported, "In cross-sectional analysis of "Study of Health in Pomerania-Trend", non-linear associations between the 25(OH)D concentration and inpatient costs and hospitalization were detected: participants with 25(OH)D concentrations of 5, 10, and 15 ng/ml had 226.1, 51.5, and 14.1%, respectively, higher inpatient costs than those with 25(OH)D concentrations of 20 ng/ml (overall p-value = 0.001) in multivariable models" [80]. However, a in a previous study involving 3193 patients from 'Study of Health in Pomerania-1" in 2002–2006 found inpatients costs 204, 27, and 7% higher, respectively (overall p-value = 0.12).

Public awareness and the need for assaying 25(OH)D

A self-questionnaire was developed for elderly people living in France. It was "composed of 17 items exploring age, gender, general condition, nutrition, vision, mood, cognition, gait and falls, and osteoporosis. All participants subsequently underwent a full clinical examination by a physician exploring the same areas (rater-VDSP). The agreement between the self-VDSP and the rater-VDSP was almost perfect for the probability of having low vitamin D concentrations, regardless of the definition used (i.e., ≤25, ≤50, or ≤75 nmol/L)" [81].

Later, another approach to 25(OH)D screening, a classification tree analysis, was developed. Individuals are evaluated for several parameters to determine whether they might have hypovitaminosis D. Use of that approach in France employed "various combinations of the following characteristics: polymorbidity, obesity, sadness, and gait disorders" [82]. For a data set of 1991 older French community-dwelling volunteers, "the probability of hypovitaminosis D was 1.42-fold higher [95% CI: 1.27–1.59] for those with polymorbidity and gait disorders compared to those with no polymorbidity, no obesity, and no sadness."

Many people think that if they live in a sunny climate and spend a reasonable amount of time in the sun, they have good vitamin D status. One problem with that assumption is that they do not account for solar elevation (or zenith) angle, which varies throughout the day and by season. Above 35° N, one cannot make much vitamin D during the darker months of the year [83]. The other problem is that the time in the sun could vary markedly. A study in Milan using serum 25(OH)D concentrations evaluated on 30,400 individuals from May 2006 and December 2018 reported that the R^2 value for monthly 25(OH)D concentrations versus cloud-free UV determined from satellite data was 0.54, increasing to 0.63 when cloud cover was included [84]. Of course, many people had values different from the mean.

Vitamin D fortification of food

To reduce the burden of 25(OH)D screening, countries might adopt measures to fortify food with vitamin D as well as promote vitamin D supplementation for the population at large. A recent review outlined the rationale and described a plan for achieving adequate vitamin D food fortification. It recommended aiming for intakes of 10–20 µg (400–800 IU) for the population to achieve serum 25(OH)D concentrations of at least 20 ng/ml [85]. Among the evidence presented was that Finland introduced food fortification in fluid milk and fat spreads in 2003 and that doubling the amounts added in 2010 virtually abolished vitamin D deficiency. As a result of that voluntary measure by manufacturers, plus a trend for increased vitamin D self-supplementation, mean serum 25(OH)D concentrations rose from 19 ng/ml in 2000 to 26 ng/ml in 2011 [86], with the prevalence of vitamin D supplement users increasing from 11 to 41%. Another recent paper presented a road map for food fortification and/or targeted vitamin D supplementation policies that can be implemented to reduce the burden of vitamin D deficiency–related conditions in vulnerable populations in low- and middle-income countries [87].

However, fortifying food with vitamin D does not eliminate the need to measure 25(OH)D concentrations. Some people will not consume adequate amount of fortified food or have an adequate variety of supplemented foods in their diet for many reasons including socioeconomic reasons. For example, people of African descent are generally lactose intolerant and do not drink much milk. In addition, fortification might supply 400 IU/day of vitamin D_3, which can raise 25(OH)D concentrations of adults by about 3 ng/ml [88]. That paper also reported that the daily amount of vitamin D to sustain an increase from 28 to 48 ng/ml was 3800 IU/day. Thus, fortification can be expected to only modestly increase 25(OH)D concentration.

Summary and conclusion

Evidence is mounting that higher 25(OH)D concentrations are associated with lower disease incidence and mortality rates. For some diseases, such as cancer and acute RTIs, RCTs offer evidence that vitamin D supplementation reduces both risk of incidence and perhaps death. However, for others, such evidence has not yet been reported. For some diseases, such as acute RTIs, the greatest risk is apparently for people with 25(OH)D concentrations below 20 ng/ml. For such diseases, risk can be reduced by taking 1000–2000 IU/day, especially in the darker half of the year. For other outcomes, such as cancer and diabetes mellitus, risk continues to decrease as 25(OH)D concentration

increases above 30 ng/ml. For that, measuring 25(OH)D concentrations gives people the information they need to adjust their vitamin D supplementation to achieve the desired 25(OH)D concentration. People with chronic health conditions, pregnant and nursing women, the elderly, and those who are obese would probably benefit from knowing their 25(OH)D concentrations and supplement to achieve a concentration greater than 30 ng/ml [89]. Physicians too would be better informed which patients have low 25(OH)D concentrations and be able to advocate/prescribe supplementation to improve patient health outcomes

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Compliance with ethical standards

Conflict of interest WBG receives funding from Bio-Tech Pharmacal, Inc. (Fayetteville, AR, USA). The other authors have no conflicts of interest to declare.

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