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Vitamin D: Implications of the Institute of Medicine Report for Clinical Practice

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In November 2010, the Institute of Medicine (IOM) released* Dietary Reference Intakes for Calcium and Vitamin D, *a radical departure from previous advice given regarding these two nutrients that have been reported in respected health journals. The 14-member expert committee found clear and convincing evidence to support the association between adequate levels of vitamin D and bone health. The IOM committee did not find enough evidence to support claims that inadequate levels of vitamin D are linked to increased risks for cancer, cardiovascular disease, or diabetes. In this article, the authors discuss the controversy surrounding vitamin D and provide guidance for primary care nurse practitioners.

Over the past 15 years, scientists have produced an impressive body of evidence highlighting vitamin D's central role in maintaining health.[1,2] As these dramatic benefits were reported both in health journals and the popular press, many clinicians embraced the findings by monitoring patients' vitamin D serum levels, encouraging safe sun exposure, and prescribing supplementation with vitamin D as needed.[2,3] But other clinicians remained skeptical.[4]

The purpose of the Institute of Medicine's (IOM's) *Dietary Reference Intakes for Calcium and Vitamin D* report[5] was to re-evaluate Dietary Reference Intakes (DRIs) for vitamin D in light of thousands of studies published since the last report in 1997. The IOM report's

authors investigated the relationship between calcium and vitamin D intake and bone health.[5] In addition, they ascertained whether low vitamin D levels might be related to increased risk for a wide variety of diseases and conditions, including cancer, cardiovascular disease, hypertension, diabetes, metabolic syndrome, falls, asthma, inflammatory bowel disease, Crohn's disease, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, tuberculosis, influenza, upper respiratory infections, autism, cognitive function, depression, and preeclampsia. Some studies showed that low vitamin D levels were related to increased risk for disease, but others did not show this relationship.

Overall, the evidence was inconclusive in confirming the many promising hypotheses regarding the efficacy of vitamin D in preventing a host of health problems.[5] In the view of the 14-member expert panel, evidence from randomized controlled trials (RCTs) was scant. The report increased the Recommended Dietary Allowance (RDA) for vitamin D, set the tolerable Upper Intake Levels, highlighted emerging data pointing to risks posed by high-dose vitamin D supplements, and called for standardization of laboratory cut-points for vitamin D deficiency. To understand how the IOM reached its conclusions, it is helpful to look more closely at the history of research into the health effects of vitamin D.

History of Vitamin D Research

Vitamin D and bone health have attracted scientific interest for decades.[1] Researchers have long known that vitamin D is essential to calcium and phosphorus regulation, and that severe deficiencies result in rickets and osteomalacia. In the 1980s, epidemiologists noticed an ominous trend, wherein persons living at higher latitudes with less sun exposure seemed to have higher rates of cancer. As is well known, exposure to the sun helps the body produce vitamin D, which is actually a hormone.[6] Might there be a cause-and-effect relationship between reduced vitamin D levels and cancer risk?

Several long-term observational studies, known collectively as the Harvard cohort studies, were used to investigate the role of vitamin D in this regard.[6] These studies included the Nurses' Health Study I and II, the Health Professional Follow-Up Study, and the Physicians' Health Study. These studies have amassed information about diet, lifestyle, and incidence of disease over the course of each participant's lifetime. Blood samples were collected, enabling investigators to analyze participants' vitamin D levels and the incidence of various illnesses. These studies generated a treasure trove of information, among which vitamin D's efficacy was but one key discovery. The strongest evidence from the Harvard cohort studies was the relationship between decreasing vitamin D levels and increasing cancer risk. The Health Professional Follow-Up Study showed that men with deficient vitamin D levels were at increased risk for a myocardial infarction.[7] *In toto*, data from these and other studies focused major attention on vitamin D.

Two extensive reports, *Effectiveness and Safety of Vitamin D in Relation to Bone Health*[8] and *Vitamin D and Calcium: Systematic Review of Health Outcomes*,[9] provided a critical analysis of the vitamin D scientific literature and laid the groundwork for the 2010 IOM report. Regarded by many experts as overly conservative, the thousand-page IOM report has sparked intense debate.[10-12] The Harvard School of Public Health published *Comment on IOM Vitamin D and Calcium Recommendations: For Adult Bone Health, Too Low on Vitamin D—and Too Generous on Calcium*[13] on the school's website, challenging the IOM's findings. According to the Harvard website, the lack of RCTs did not equate to lack of benefit. The Endocrine Society released its own set of clinical guidelines on the evaluation, treatment, and prevention of vitamin D deficiency.[14] The Endocrine Society task force, comprised of vitamin D experts, acknowledged the overall low-quality of evidence but expressed hope that the science would soon advance and that recommendations would soon be revised upward.

Incidence of Vitamin D Deficiency in the US Population

Few patients present with evidence of severe vitamin D deficiency such as rickets or hypercalcemia.[15] According to the IOM, the cut-point for identifying vitamin D deficiency is a serum 25-hydroxyvitamin D (25OHD) level below 30 nmol/L (<12 ng/mL).[5] A 25OHD level of 50 nmol/L (20 ng/mL) is sufficient to maintain bone health for most Americans. The IOM's cut-points are much lower than the advice of other experts, however. The Endocrine Society guidelines defined vitamin D deficiency as a serum 25OHD level below 50 nmol/L (20 ng/mL) and suggested a minimum 25OHD level of 75 nmol/L (30 ng/mL) to obtain extra-skeletal benefits.[14] According to Holick,[16] an expert in the field and lead author of the Endocrine Society guidelines, 25OHD levels of 52-72 nmol/L (21-29 ng/mL) represent insufficiency.

By these estimates, nearly 1 billion persons worldwide are vitamin D deficient.[16] According to Ginde et al,[17] who used data from two National Health and Nutrition Examination Surveys, the mean serum 25OHD level in the U.S. decreased from 30 to 24 ng in a 10-year period correlating with campaigns to use sunscreens and avoid sun exposure.

Older adults, obese individuals, pregnant or lactating women, persons with pigmented skin, and persons with little or no sun exposure are at high risk for vitamin D deficiency.[15,18] Dark-skinned persons, as compared with fair-skinned persons, require 5 times as much sun exposure to produce the same amount of vitamin D.[19] African Americans, compared with light-skinned populations, have lower serum 25OHD levels.[5] Obesity is associated with decreased vitamin D levels because excess fat absorbs and retains vitamin D, preventing it from reaching cells and bones.[2] Because the ability to synthesize vitamin D decreases with age, persons older than 60 years require 3-4 times more sun exposure than their younger counterparts.[1,19] Persons using anticonvulsants, rifampicin, or highly active antiretroviral drugs are at high risk for vitamin D deficiency because these drugs induce the cytochrome P450 enzymes that metabolize vitamin D.[15]

Dietary Reference Intakes

The Food and Nutrition Board of the IOM sets the DRI standard for nutritional requirements. Components of the DRI include the estimated average requirement, RDAs, adequate intake levels, and tolerable upper intake levels.[5] RDAs are used to develop clinical practice guidelines and to select doses used in multivitamins and fortified foods. New DRI values for vitamin D were released in IOM report, and are listed in Table 1.[5] The increased RDA levels for vitamin D are 600 IU/day for persons aged 1-70 years and 800 IU/day for those aged >70 years. The Endocrine Society guidelines regarding vitamin D adequate intake levels and upper intake levels differ from those of the 2010 IOM report (see references 5 and 14).[5,14]

Monitoring Vitamin D Levels

Signs and symptoms of vitamin D deficiency are insidious or nonspecific. As a result, they often go unrecognized unless blood testing is done.

Laboratory Testing—According to the National Institutes of Health (NIH),[18] wide variability in measuring vitamin D existed until July 2009, when a standard reference of measurement became available. Vitamin D levels are best represented by serum 25OHD,[5] which is measured by radioimmunoassay, enzyme-linked assays, or liquid chromatography with mass spectrometry.[20]

Routine Patient Screening—According to the 2010 IOM report,[5] routine blood screening for vitamin D deficiency is not necessary because most Americans have adequate vitamin D levels. The Endocrine Society recommends screening for vitamin D only in persons at risk for vitamin D deficiency.[14] For primary care practitioners who added assessment of patients' vitamin D status to their list of preventive health topics years ago, the new guidelines have been cause for confusion. Insurance companies have reacted by stopping payment or reimbursement for vitamin D blood testing. On the strength of

TABLE 1 VITAMIN D DIETARY REFERENCE INTAKES BY LIFE STAGE[5]

Age	Estimated Average Requirement (IU/day)	VITAMIN D Recommended Dietary Allowance (IU/day)	Upper Intake Level (IU/day)
0-6 months	*	*	1000
6-12 months	*	*	1500
1-3 years	400	600	2500
4-8 years	400	600	3000
9-13 years	400	600	4000
14-18 years	400	600	4000
19-30 years	400	600	4000
31-50 years	400	600	4000
51-70 years (males)	400	600	4000
51-70 years (females)	400	600	4000
>70 years	400	800	4000
14-18 years (pregnant/lactating)	400	600	4000
19-50 years (pregnant/lactating)	400	600	4000

*For infants, Adequate Intake is 400 IU/day for those aged 0-6 months and 400 IU/day for those aged 6-12 months.

the IOM report, some clinicians have suspended routine vitamin D screening and recommendations for vitamin D supplementation.[20]

Treating and Preventing Vitamin D Deficiency

The scientific community has not achieved consensus regarding the optimal measures needed to treat or prevent vitamin D deficiency, which include dietary intake of vitamin D, sun exposure, and vitamin D supplementation. Table 2 summarizes current guidelines for serum 25OHD cut-points, sun exposure, and supplementation from a number of prominent academic, professional, and governmental groups.

Diet—The IOM has acknowledged the difficulty of meeting vitamin D requirements by diet alone. Few foods naturally contain vitamin D. Dietary sources of vitamin D include fatty fish (eg, tuna, salmon, mackerel), egg yolk, mushrooms, and fish liver oil.[18] Most dietary vitamin D in the United States comes from fortified foods such as breakfast cereals, milk, and fruit juices and fruit drinks. Fortified foods have enough vitamin D to protect against rickets and osteomalacia, the most severe forms of vitamin D deficiency.

Persons with lactose intolerance cannot digest dairy products and may be at increased risk for vitamin D deficiency. These individuals can ingest lactose-reduced dairy products, non-dairy calcium-rich foods, calcium supplements, or lactase pills or drops to meet calcium and vitamin D requirements.

TABLE 2 SUMMARY OF GUIDANCE ON VITAMIN D

Guide	Serum 25OHD Cut-points	Sun Exposure	Vitamin D Supplementation
Institute of Medicine (IOM)[5]	**Deficiency** 30 nmol/L (12 ng/mL) **Inadequacy** 30-50 nmol/L (12-20 ng/mL) **Sufficiency** 50 nmol/L (20 ng/mL) is all that is required to maintain bone health **Reason for concern** 125 nmol/L (50 ng/mL)*	Calls for investigation of a "minimal-risk UVB exposure." The IOM asks, "Is it possible to create vitamin D synthesis and avoid skin cancer risk?" The IOM considered incidental sun exposure but wants more research on what is a safe exposure of sun where people could reap benefits without adverse effects. The IOM assumed "incidental" sun exposure in its deliberations.	Report states that most Americans are not vitamin D deficient and do not require supplements. Persons who are deficient and some with inadequacy require treatment. Supplements recommended for persons with 25OHD levels <50 nmol/L (<20 ng/mL).
Endocrine Society[14]	**Deficiency** Less than 50 nmol/L (20 ng/mL)		Suggests raising blood levels to more than 75 nmol/L (30 ng/mL) to obtain possible extra-skeletal benefits.
Harvard School of Public Health[10]	**Adequate level** 75 nmol/L (30 ng/mL)	Does not recommend unprotected sun exposure.	800-1000 IU/day; some persons may need 2000 IU/day or more (eg, those with dark skin, obesity, or little sun exposure).
American Academy of Dermatology and AAD Association[21]	N/A	Recommends protection at all times.	N/A
Holick[2,16]	**Deficiency** Less than 50 nmol/L (20 ng/mL) **Insufficiency** 52-72 nmol/L (21-29 ng/mL) **Sufficiency** More than 75 nmol/L (30 ng/mL) **To obtain full benefit for health** 100 nmol/L (40 ng/mL)	Recommends sensible sun exposure: formula based on skin type, latitude, and season (eg, 10-15 min for a fair-skinned person between 12 noon and 2 pm during summertime); see reference 2 for more details.	Determined by blood level. 1000 IU/day recommended for non-deficient persons; total daily intake target is 1500-2000 IU through all sources (diet, multivitamin, supplements); see reference 2 for more details.
International Osteoporosis Foundation[22]	**Target** 75 nmol/L (30 ng/mL) for older individuals	N/A	Based on blood test results, sun exposure, body mass index; 2000 IU/day for persons with obesity, osteoporosis, limited sun exposure (eg, institutionalized, homebound).

This table refers to recommendations for adults. It does not cover recommendations for newborns, children, pregnant woman, or persons with other health problems.
*The IOM found good evidence of adverse effects of very high doses of vitamin D.

Of note, calcium and vitamin D work effectively only in tandem, making adequate levels of both substances essential. Unlike vitamin D, calcium is easily obtained through dietary sources, although caffeine intake and medications such as proton pump inhibitors can have a negative effect on calcium levels.[2]

Sun Exposure—Sensible sun exposure is the most efficient way to obtain adequate levels of vitamin D.[23,24] A few minutes a day of unprotected sun exposure in the summer can help maintain adequate levels of vitamin D throughout the year.[2] Sunlight includes ultraviolet A (UVA) light and ultraviolet B (UVB) light, the latter of which is needed for production of vitamin D. The degree of success in obtaining vitamin D from UVB rays depends on a variety of factors, including the season, geography, latitude, time of day, cloud cover, smog level, amount of melanin and sunscreen, and mobility and access to the outdoors. Experts maintain that generating adequate levels of vitamin D through sun exposure is impossible during the winter months in cities located in northern latitudes (eg, New York City, Chicago). In addition, air pollution and glass filter out UVB rays that urban dwellers depend on for vitamin D.[24]

Sensible sun exposure in a fair-skinned person can be obtained by sunbathing without sunscreen for 10-15 minutes between noon and 2 PM during the summer.[2] Exposing the face may not even be necessary or desirable if one's arms and legs—25% of the body area—receive sunlight. Moderation is key. Any sun exposure causing erythema (sunburn) is avoided because the risk for melanoma increases. Many office workers have schedules that preclude them from spending any time in the sun. Increasing their sun exposure may mean walking down the sunny side of the street, eating lunch outside, or making phone calls from a park bench.

Sun exposure has several advantages over supplementation as a source of vitamin D. First, one cannot "overdose" on vitamin D through too much exposure to the sun.[2] The body has a natural mechanism to cut off production of vitamin D when a sufficient supply has been generated. Even severe sunburn will not result in vitamin D toxicity. Second, the body stores excess vitamin D in fat and then releases it during the winter months when it is needed. Spending the summer in the sun stores up vitamin D for gray and sunless winters that effectively halt vitamin D production.

Experts disagree about sun exposure. The American Academy of Dermatology issued a strong policy statement in 2009 advising patients to protect themselves against the sun at all times.[21] For years, the public heeded the advice of dermatologists to avoid all sun exposure by using sunscreen and wearing protective clothing. Companies manufacturing sun-protection products used advertising to reinforce the medical advice. Anxious mothers dutifully covered their children. Persons at risk for skin cancer (eg, those with a history of skin cancer, fair-skinned persons with multiple nevi) conscientiously avoided all sun exposure until new research regarding the health benefits of the sun came to light.[2] Some experts have acknowledged that rates of skin cancer, including melanoma, rise even with "sensible" sun exposure, but they argue that the risk is worth taking because of the overwhelming health benefits of vitamin D.[19] Increased skin cancer screenings are offered as a possible solution to cope with the risks of increased sun exposure. The IOM has identified the need to research the issue of safe sun exposure to produce vitamin D.

Supplementation—Getting sufficient vitamin D from the sun is not always possible. Vitamin D supplements come in two forms, ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3). The efficacy of supplementation is well documented.[2] The Endocrine Society endorses supplementation with vitamin D_2 or vitamin D_3.[14] Both the Nutrition Source at the Harvard School of Public Health and the International Osteoporosis Foundation endorse using D_3 for supplementation.[10,22]

However, consensus regarding the recommended daily dose, or even the need for vitamin D supplementation, does not exist.[2,5,20] The IOM does not recommend the high levels of supplementation endorsed by many vitamin D experts.[5] In fact, the IOM set 4000 IU/day as the upper tolerable limit for safety. If a person exceeds a daily dose of 4000 IU, the possibility of harm increases. The IOM was clear that "more is not better," citing emerging evidence that excess intake of vitamin D is linked to all-cause mortality, cancer, cardiovascular risk, falls, and fractures.

Vitamin D supplements are available over the counter (OTC) at health food stores, pharmacies, and grocery stores in strengths ranging from 400 to 5000 IU. Multivitamins are another source of vitamin D. Holick recommends vitamin D supplements of 1000-2000 IU/day for most individuals.[2] The Nutrition Source at the Harvard School of Public Health recommends higher daily doses

(≥2000 IU) for persons who have darker skin, spend winters in the northern U.S., or have little exposure to direct sunlight.[10] For persons with severe vitamin D deficiency, much higher doses are available by prescription. Vitamin D toxicity, albeit quite rare, is manifested by nausea, vomiting, poor appetite, constipation, increased thirst, depression, increased urination, and/or weight loss.[16]

Conclusion

The IOM report concluded that the available current evidence base was not sufficient to establish causal links between vitamin D and a host of diseases and that too much vitamin D can be harmful.[5] The IOM has outlined a blueprint for further research to explore the promising hypotheses that exist regarding the efficacy of vitamin D. RCTs with the potential to answer questions posed by the IOM report are already in progress. The Vitamin D and Omega-3 Trial (VITAL), an RCT, began enrolling patients in January 2010.[25] This study, funded by the NIH, is investigating the role of dietary vitamin D supplements or fish oil in reducing risks for cancer, heart disease, and stroke. Vitamin D has received much attention because of its numerous anticancer properties, including reduced proliferation, invasiveness, angiogenesis, and metastasis, and increased differentiation and apoptosis.[6,26] Laboratory animal experiments involving the anticancer properties of vitamin D have provided encouraging results.[5]

The public health implications of the vitamin D debates are profound, because inexpensive measures such as sensible sun exposure, supplementation, and diet can prevent disease worldwide by maintaining and restoring adequate levels of vitamin D. Practices relating to sun avoidance and sun protection appear to have spread, and have had the unintended consequences with respect to vitamin D levels, which have plummeted over the past 30 years.[27] Until strict "no sun" policies were promulgated by dermatologists starting in the 1970s, most of the public co-existed happily with the sun. From an evolutionary perspective, the sun has been and will continue to be central to human existence.

Nurse practitioners need to keep pace with the rapid advances in knowledge of vitamin D. Much of the data being amassed is encouraging and useful for engaging patients in a culturally sensitive dialogue. The outcome of this dialogue must be informed decisions by patients regarding safe sun exposure, dietary sources of calcium and vitamin D, and safe supplementation. ■

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