Vitamin D, age, sex and skin pigmentation: An analysis of how recommendations and standards regarding vitamin D need more comprehensive research for policy

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Abstract

Vitamin D has long been implicated in health research with its etiology hypothesized in many diseases. As recently as 2011, the Institute of Medicine (IOM), appointed a committee of 14 scientists to re-evaluate the 1994 dietary reference intakes for calcium and vitamin D as ample new research had been conducted to warrant an evaluation of vitamin D supplementation. The efforts were supported by the United States and Canadian governments. Research was evaluated and new recommendations were established. However, the committee of scientists, supported by IOM staff, continues to use the same evaluation methods for vitamin D as they do for all vitamin dietary recommendations, but vitamin D is not a vitamin in the traditional sense. It is a pro-hormone. Vitamin D is not gained solely from diet. It is more readily produced via the conversion of cholesterol to vitamin D through sun exposure. Therefore, traditional methods of evaluation to deduce dietary intakes may not apply for a vitamin that is environmentally influenced. While many scientists are adamant that the recommendation levels for vitamin D should be higher and not all population sub-group dietary needs are being addressed, new methods of evaluation may be what are warranted. It is vital that researchers evaluate novel ways to understand vitamin D and the implications for nutritional policy in the form of dietary recommendations to create more comprehensive recommendation for vitamin D dietary needs. Currently, dietary recommendations are created for life-stage (age range) and sex, but more comprehensive listings by latitude, skin pigmentation, and adiposity might provide for the needs of more individuals.

Introduction

While research has long implicated vitamin D as a vital component of bone health, recent studies have increasingly indicated that vitamin D plays a crucial role in regulating multiple body systems, with decreased vitamin D levels hypothesized to be a contributing factor in several diseases including cancer, cardiovascular disease, Type 1 diabetes, multiple sclerosis, and respiratory illness (1–5). Populations in higher latitudes are more likely to have vitamin D deficiencies due to lack of sun exposure (2,4,6–8), however recent research indicates that vitamin D deficiency has become a global phenomenon even in countries near the equator (2,9,10). Historically, research on vitamin D has focused heavily on natural selection and the adaptive significance of both constitutive (basal) and facultative (tanning) skin pigmentation to generate vitamin D (11–16). In contrast, the socio-cultural factors that influence and, in some cases, dictate sun exposure and skin pigmentation, have received relatively little attention (17).

Evolutionary perspectives on vitamin D have focused on skin color as a prototypical example of natural selection, where darker skin color is understood as an adaptation to minimize the harmful effects of exposure to ultraviolet rays while maintaining vitamin D production (18,19). Most of the variation in skin color is determined by melanin in the epidermis (13,17), and dark skin, highly melanized, allowed for protection against UV radiation and the photolysis of folate, critical for embryonic spinal and brain development (20,21). As humans migrated further from the equator, lighter skin developed in indigenous peoples as a response to the need for vitamin D synthesis (13,19). This research has contributed to our understanding of skin color and sun exposure as determining factors in the production of vitamin D, (12,16), and to our understanding of the origins and adaptive significance of variation in skin color across populations. However, skincare media often represents sun exposure as an obstacle to avoid

altogether opting to promote heavy sunscreen usage instead, which leaves the general population ignorant of the health benefits of light or moderate sun exposure.

Furthermore, policy recommendations surrounding vitamin D requirements are all deeply embedded in the dietary/nutritional literature despite the fact that vitamin D is a pro-hormone that is not obtained exclusively from food. In fact, evolutionarily vitamin D was a driving force in human adaptation (18). With few foods naturally containing vitamin D, and supplements obviously not having been developed, humans derived all their vitamin D from the sun. However, vitamin D policy is written to only include dietary recommendations. In the modern era, skin color variation at any latitude is the norm creating a mismatch between skin color and current ultraviolet radiation exposure in many environments, subsequently leading to vitamin D deficiency. Other demographics that may be at risk for inadequate levels of vitamin D are females and those that have a high body fat percentage. Vitamin D deficiency may be attributed to the fact that women have greater fat deposition than men (22–25). Further complicating the issue is that the literature on vitamin D is fraught with debate on what should be considered adequate dietary levels, so vitamin D policy must be assessed with these particular groups in mind in order to generate a policy that serves every demographic. While the dietary references are useful in generating guidelines for health, there are concerns that further research is warranted to create a more comprehensive guide for some groups. Therefore, the objectives of the current policy analysis regarding vitamin D dietary intakes are threefold:

1) Describe groups that may require more specific dietary guidelines
2) Evaluate the IOM dietary reference intakes need further revision and why controversy for vitamin D intakes exist despite the 2011 revision

3) Describe methods to illustrate how further research can be conducted to determine vitamin D necessities for other populations

Background

Dietary recommendations in the United States are based upon periodic review by the Institute of Medicine. The recommendations have occurred since 1941 and are meant to assist in the understanding and planning of human nutrient requirements across the life course. The dietary recommendations for vitamin D were first created in 1997 and revised in 2011. While the revision provided a greater review on the state of research on vitamin D, there were many scientists who were unhappy, feeling that the new recommendations were set too low. The guidelines for vitamin recommendations are reviewed here to assess whether following a general guideline for vitamins can be attributed to vitamin D since it is both a vitamin and a prohormone.

A prohormone is substance the body utilizes to make a hormone. The vitamin D precursor, 7-dehydrocholesterol, is converted to D_3 by photochemical conversion in the skin., which is then released into circulation and binds to vitamin D-binding protein (26–29). After several hydroxylation events, the hormone binds to the vitamin D receptor initiating gene expression in various tissues (1,30,30,31). Hormones and vitamin differ in that the body cannot generate vitamins in sufficient quantities for the use in the body. General differences of between vitamins and hormones are listed in **Table 1**. Vitamin D is unique in its ability to be produced in the skin as no other known hormones are generated in this manner. Though institutions will acknowledge the unique circumstances regarding vitamin D, the institution often neglect to treat vitamin D as anything other a vitamin despite the possible need to derive new regulations for the

unique micronutrient. However, dismissing the body's capacity to generate our own vitamin D through sun exposure may be neglectful.

Vitamin D

The active form of vitamin D (D_2 and D_3) is known as calcitriol. The two major forms are D_2, ergocalciferol, and D_3, cholecalciferol. Traditionally, vitamin D_2 was human synthesized and added to foods or found in plants, while vitamin D_3 is synthesized in the skin from sun exposure or consumed from animal products such as fish or egg yolks; however, both D_2 and D_3 forms are now found in supplements and fortified foods. Therefore, vitamin D is most often used to refer to both forms. While a vitamin is a substance that must be acquired solely through diet, most vitamin D is actually generated in the body by the absorption of sunlight, specifically ultraviolet B radiation as few foods naturally contain vitamin D. While vitamin D is known for its role in calcium metabolism and bone health, research has determined that vitamin D receptors are pervasive throughout cells in the body, including intestinal epithelium, mammary epithelium, pancreas (beta islet cells), pituitary gland, skeleton (osteoblasts and chondrocytes), and immune system (monocytes, macrophages, and T-lymphocytes) (32–35).

The production of vitamin D is initiated by one of two methods, either through the epidermis (via UVB exposure from wavelengths measuring 290–315 nanometers) or through intestinal absorption (via food or vitamin consumption) (1,30,36). When human skin is exposed to sunlight, 7-dehydrocholesterol is converted to vitamin D_3 by ultraviolet B radiation in a heat dependent process (6,26,37). Toxicity as a result of cutaneous synthesis of vitamin D seems to be impossible because V_3 is subject to photodegradation once formed (38).

Both the dermis absorbed vitamin D_3 and the ingested vitamin D_2 binds to vitamin D-binding protein (39). In a sequence of hydroxylation events vitamin D is converted to its active form via catalyzation by one of several types of enzymes in the cytochrome (CYP) P450 family (30,40). After absorption, vitamin D is transferred to the liver via the bloodstream and is hydroxylated by CYP2R1 and CYP27A1 to produce the circulating 25-hydroxy vitamin D [25(OH) D] (3,6,40). Then, the vitamin D derivative travels to the kidneys where it is hydroxylated again by 25(OH) D-1-α-hydroxylase (CYP27B1) to form 1,25-dihydroxy vitamin D (1,25$(OH)_2$ D), also known as calcitriol (3,41). Biological functions are then performed through 1,25$(OH)_2$D binding to vitamin D receptor (VDR) sites to regulate gene expression (6). Vitamin D receptors are located throughout the body, and upon binding 1,25(OH)2, they up- or downregulate approximately 2000 different genes in the skeleton, skin, intestines, liver, thymus, spleen, lymph nodes, mammary glands, and testis, among other organs and tissue expressing the pleiotropic effects of vitamin D (3,6,31,42–44). **(Figure 1)**

Vitamin D status is measured in nanomoles per liter (nmol/L) but can also be measured in nanograms per milliliter (ng/mL). Vitamin D deficiency is categorized as ≤20 ng/mL (50 nmol/L) of 25(OH)D based upon averages seen in the United States (45). Deficiency is based on serum 25(OH)D values (3,39). Though 1,25$(OH)_2$D is the biologically active form of vitamin D, research has shown that the precursor 25(OH)D is a better indicator of vitamin D status for a few reasons. For example, half-life for calcitriol is a few hours (48), while the half-life for 25(OH)D is 2 weeks or more (47,48). Furthermore, the close link between vitamin D and calcium absorption means low serum calcium, hypocalcemia, causes a cascade effect wherein parathyroid hormone converts 25(OH)D to 1,25$(OH)_2$D (1,30,36). The effects causes serum 1,25$(OH)_2$D to appear normal or even elevated when an individual is severely vitamin D deficient due to the

upregulation by parathyroid hormone resulting in an inaccurate representation of vitamin D status if using calcitriol (3,45).

Demographic Differences

Vitamin D differences exist in race and ethnic groups as a result of skin pigmentation variation. Skin pigmentation is the result of melanin in skin caused by melanocyte number, size, and distribution within the keratinocytes (49). Melanin absorbs UVB rays and determines how much light is able to penetrate the skin and generate vitamin D (50,51). It has been found that individuals categorized by race show marked differences in serum 25(OH)D increases with a known dose of UVB radiation to their whole body (52). Participants in each race group were classified by skin type by the Pathak et al. (1976) method relating to increasing melanosome distribution (52,53). While serum 25(OH)D might be expected to differ by skin color due to latitude (17,54), a meta-analysis analyzing global skin pigmentation of native residents and serum vitamin D indicated that latitude had no effect on serum vitamin D with Caucasians having a significantly higher serum average than non-Caucasians (55). Serum 25(OH) D has been shown to have an inverse relationship with skin pigmentation during the winter (56), and pregnant women with darker skin were most vulnerable to vitamin D deficiency (57).

Sex differences in vitamin D have been consistently reported across a range of populations, with women often having lower vitamin D across the life course (58–63). Because of the negative correlation between vitamin D and autoimmune diseases, which affect women more than men (59,64–67), differences in vitamin D between the sexes are often assumed to be biological/genetic in origin(68–70). However, it is possible that these differences represent gendered exposures to experiences and environments that are more proximately related to

vitamin D production. For example, women living in urban environments have often been found to have greater rates of vitamin D deficiency than women living in rural areas(71).

Furthermore, play research indicates that children between the ages of 5 and 13, often see boys spending significantly more time in outdoor sports than girls at all ages(72). Girls were found to stay predominately indoors. The phenomenon of girls spending more time indoors is not just seen in the United States. A cross-cultural analysis by Larson and Verma of time spent at work and at play for children and adolescents showed that girls consistently spent more time conducting indoor chores, while boys were more likely to spend time outdoors assisting in outdoor agricultural practices or in general yard work (73). The results indicate that gendered expectations of children may play a role in the decrease in vitamin D for girls in childhood.

Obesity has also been closely linked to vitamin D deficiency, and like vitamin D deficiency, obesity is a global epidemic. Studies have shown that micronutrients such as vitamin D are often lower in people who are obese (74,75). A metanalysis of 23 research articles indicated that those who were obese or overweight were more likely to be vitamin D deficient than those within a normal body mass index regardless of age (76). In fact, research on subcutaneous (SAT) and visceral body fat has shown that both are inversely related to vitamin D status (or levels) after adjusting for physical activity and vitamin D dietary intake (77). Like the obesity epidemic, the vitamin D epidemic is rooted in the globalization process and is part of a much broader context of drastic change within populations. For instance, in a study on acculturation of non-Western immigrant groups in to Nordic countries, results revealed that immigrant groups were both more likely to be overweight or obese and vitamin D deficient indicating that changes in environment may lead to changes in diet leading to poorer health outcomes (78).

Because most research on vitamin D deficiency has been case-control studies, the causal link has yet to be determined. That is, research has not yet discerned whether vitamin D deficiency contributes to obesity of whether obesity causes vitamin D deficiency. However, that are some indications that obesity may reduce availability of vitamin D because it is diluted within adipose tissue (79–81). Additionally, one study examining the genetic polymorphisms in the vitamin D receptor (VDR) gene showed an inverse relationship between vitamin D metabolism and a genetic susceptibility to obesity which was affected by variants in the VDR (82). Taken together, it may be that individuals with certain VDR variants are genetically prone to metabolize vitamin FVD less efficiency leading to decreased levels of vitamin D which are then exacerbated by the uptake of circulating vitamin D by adipose tissue. Clearly, more research is required to discern the exact relationship between adipocyte receptors for vitamin D and circulating levels of vitamin D.

Measurement & Diet

Vitamin D dietary intake in the literature is often measured in International Units (IU) but can also be measured in micrograms (μg) with 1 μg being the equivalent of 40 international units (45,83). However, in the United States the Food and Drug Administration has amended the regulations for nutrition labeling on food and dietary supplements for vitamin D to be listed as micrograms in 2016 (83). The World Health Organization Expert Committee on Biological Standardization sets the international unit standards to create a consensus on biological standards to allow for comparison across research (84). The biological activity of 1 μg of vitamin D is equivalent to 40 IU with 1 IU being defined as the activity level of 0.025 μg of cholecalciferol

(D_3) in research with rat and chick bioassays (45). These measures are used to discuss units related to oral intake of vitamin D via food and supplements.

40 IU = 1 µg

Vitamin D intake is the sum total of vitamin D through food intake as well as supplements. While diet is a contributing factor to vitamin D, few foods naturally possess vitamin D (85), and most foods that do provide vitamin D, such as dairy products, meat, and egg yolks, contribute only small amounts of vitamin D to the daily intake (86). One food that does provide a significant amount of vitamin D is fatty fish (85–87), but consumption of fish ≥ 4 servings per week is required to raise circulating vitamin D an average of10 nmol/L over those that ate fish only 1-3 times per week (88). However, the consumption of fish positively correlating with an increase in circulating vitamin D level was only detected in the winter and not summer (88,89).

Other food sources of vitamin D are through fortified foods. In the United States, the most common fortified foods are dairy items and some cereals. Studies indicate that even in countries with heavily fortified foods, meeting the daily requirements for vitamin D through diet is unlikely (90). A popular item that is fortified is milk. In the United States, milk is voluntarily fortified (45). However, studies have shown that milk often does not contain the correct amount (400 IU per quart), being under- or over-fortified (91–93).

Dietary Reference Intakes & What it Does?

Dietary reference intakes (DRI) are useful in creating a set of recommendations for individuals in a population. However, they do have limitations. As referenced by RS Gibson in

Principles of Nutritional Assessment (2005), the underlying principles for nutrient references most often are guided by the following (94):

- Are set for a particular group of individuals with specified characteristics (Set for age group and sex)
- Refer to average daily need over a reasonably period of time (the period of time is rarely defined)
- Refer to levels of intake needed to maintain health in healthy individuals only
- Tend to ignore possible interactions with other nutrients/other dietary components
- Assume that other energy and nutrient requirements are being met

In order to create the dietary reference intake, we have to look at the aggregate of the population. Nutrient reference levels are based on individual level measurements established for a particular group based on life stage (specific age range) and sex (male or female) (45). A distribution of the nutrient requirements for a specific nutrient is derived from the defined nutrient adequacy of individuals in a population (45,94). Nutrient requirements vary from individual to individual and measurements of these requirements form the distribution of a population. This distribution is thought to approximate a symmetrical, normal distribution. The median of this requirement is the *Estimated Average Requirement* and is defined as the requirement level at which half the population needs are being met for an age and sex group (45,94). However, when data is unavailable for a particular sex and age group, the requirements are extrapolated for certain groups (45,94). **(Figure 2).**

A major principle of the DRI is nutritional adequacy, but there is no agreed upon definition of what nutritional adequacy means. Thus, the end-point consideration for what is necessary can lead to discrepancies for establishing the median. Examples of nutritional adequacy are the amount required to cure clinical signs of deficiency, observations used in nutrient intakes of breastfed infants, or intakes corresponding to chronic diseases. Each expert committee must decide what marker of nutritional adequacy will be used to assess dietary recommendations.

Dietary reference values have been have been published by the National Academy of Sciences since 1941 (95,96). The initial report *included recommended dietary allowances* (RDA) for protein, energy, and 8 vitamins and minerals (96). In 1994, the recommended dietary allowances were expanded upon to create the Dietary Reference Intakes (DRIs), nutrient reference values developed by the Academies of Sciences, Engineering, and Medicine for nutrient intake in the United States and Canada. The *recommended dietary allowances* are the average daily dietary nutrient intake levels sufficient enough to meet the nutrient requirements for most, healthy individuals in a particular age and gender group (e.g., 97.5%). These are set two standard deviations above the population mean, which are based upon estimated average requirements (EAR). **(Figure 3)**

The utilization of the *recommended dietary allowance* value is not robust enough to meet population and medical needs by itself. For example, the value at which deficiency occurs or the level at which biological needs are not being met cannot be surmised with only the *recommended dietary allowance*. Therefore, the DRIs were a systematic method that involved median requirements, intake for most of the populations, an upper level for adverse risk, chronic disease indicators, and a discussion of the probability for each intake level (45,95,96). These assessment

values were provided for various age categories between men and women (45,95,96). It should be noted that though males and females are differentiated and listed with age categories the life stage groupings are the same except that there is a separate category for pregnant and lactating women.

Vitamin D Reference History

In 2008, the United States and Canadian governments made the decision to re-evaluate the DRIs for vitamin D based upon the fact that there was significant new and relevant scientific research to warrant the funding of new DRIs on vitamin D (97). A major change from the original summary for vitamin D in the 1997 to the current recommendations was the use of *adequate intake*. *Adequate intake* is used when there is not enough data to form an *estimated average requirement* and therefore not enough data to estimate a *recommended dietary allowance*. The 1997 dietary reference intakes stated the following (95).

> The AI [adequate intake] is the intake value that appears to be needed to maintain, in a defined group of individuals with limited but uncertain sun exposure and stores, serum 25-hydroxyvitamin D concentrations above a defined amount. The latter is that concentration below which vitamin D deficiency rickets or osteomalacia occurs. The intake value was rounded to the nearest 50 IU, and then doubled as a safety factor to cover the needs of all, regardless of exposure to the sun.

The adequate intake value is based on observed or experimentally determined estimates of nutrient intake by a group of apparently healthy people and is assumed to be adequate, and the reference values are determined with the intent to decrease the risk of developing a condition related to a nutrient (45). More specifically, individuals without any skeletal issues are assumed to be healthy, and the individual's serum 25(OH)D, the best measure of total vitamin D as previously mentioned, is determined to assess what is expected in a given population. As with the adequate intake, nutritional adequacy or the outcome of interest for vitamin D is skeletal health. Thus, all vitamin D recommendations are solely based on the biological outcomes for the skeletal system, including calcium absorption, rickets, fracture risk, and osteomalacia (45).

Though research indicates correlations between vitamin D with other health outcomes, the IOM determined that there was not sufficient random-controlled trial data available to determine whether any other outcomes could definitively be linked to vitamin D. Normally, the *estimated average requirement* and the subsequent *recommended dietary allowances* for the population are calculated statistically from a normal curve distribution with the estimated average requirement falling at the half-way point and the *recommended dietary allowances* calculated as two standard deviations above the mean. However, this was not the case with vitamin D. Instead the IOM used 25(OH)D concentrations in a dose-response relationship for vitamin D intake and bone health because the intake response curve of vitamin D is non-linear (45).

Using randomized-controlled trial research from 10 studies, where sun-derived vitamin D was considered negligible, the IOM analyzed the data to assess the serum 25(OH)D level corresponding to the *estimated average requirement* (ERA-like) to be 40 nmol/L, an intake of 400 IU (per day), with a SD of 100 IU/day (45). The *recommended dietary allowances* (RDA-

like) serum 25(OH)D level corresponds to 600 IU (per day) for individuals 1-70 years of age is 50 nmol/L, meeting the needs of 97.5% of the population **(Table 2)** (45). *The recommended dietary allowance* for adults older than 70 years was set 800. The upper-level daily intake was set at: 1,000 IU for 0-6 month infants; 1,400 IU for 6-12 month infants; 2,500 IU for 1-3 years, 3,000 IU for 4-8 year; and 4,000 IU for all other ages (45). An adequate intake value is still used for infants (0-12 months) as there is not enough research to inform an estimated average requirement (45).

Correctly interpreting the *estimated average requirement* and the *recommended daily allowances* are vital to the utilization of the DRI. If an individual is taking 400 IUs, there is a 50% chance that the individual is meeting their requirements for vitamin D intake. If an individual is taking 600 IUs, there is a 97.5% chance that the individual is getting sufficient vitamin D. However, most people will not need to reach 600 IUs to meet their daily needs. The upper levels are the maximum levels at which research indicated that no adverse effects were seen from consuming that amount of vitamin D. However, individuals are not meant to meet that level of consumption of vitamin D, and prolonged effects of consumption of vitamin D at the upper level have not been thoroughly researched.

Endocrine Society Recommendations

The same year the IOM release their revised dietary recommendations the Endocrine Society wrote an article titled Evaluation, Treatment, and Prevention of Vitamin D Deficiency: an Endocrine Society Clinical Practice Guideline published in the *Journal of Clinical Endocrinology and Metabolism* written by the Endocrinology Task Force, part of the Endocrinology Society (27). The Endocrinology Society is an international organization of

physicians and scientists whose aim is to "advancing hormone research, excellence in the clinical practice of endocrinology, broadening understanding of the critical role hormones play in health, and advocating on behalf of the global endocrinology community (98)." The references are actually for different populations than the IOM DRI. While the IOM DRI is for a healthy population, the endocrine recommendations are geared towards those that might be vulnerable to deficiency. While the Endocrine Society agreed with the 20 ng/mL deficiency cut-off, they classified 21 to 29 ng/mL as "insufficient" and recommended that people aim for a level of 30 ng/mL or higher.

American Cancer Society

Because of the corollary research indicating a possible link between vitamin D deficiency and cancer risk and " staying out in the sun without protection exposes people to harmful UV rays, which is a strong risk factor for most skin cancers", the American Cancer Society has written a news article regarding their stance on vitamin D (99). The American Cancer Society posted a News Article on their website as recently as March 2019 titled Do not skip using sunscreen or try other ways to get vitamin D from the sun essentially stating that only food and supplement dietary resources should be utilized for vitamin D (99).

Issues with the determination of RDA

Almost immediately after the IOM released the 2011 vitamin D Dietary Recommendations Intakes, mathematical errors relating to risk calculations were presented in Nature by Amy Maxmen questioning the *recommended daily average* (100). Further mathematical questioning followed in an article by Veugelers and Ekwaru (101). The article

received support in the form of a letter published in *Nutrients* by Heaney, Garland, Baggerly, French, and Gorham (102). Each stated that the math used to establish the DRI by the IOM used study averages and standard deviations instead of individual values resulting in narrower lower and upper cutoff for IUs which would require a higher dietary intake to equate a 50 nmol/L serum level. After a National Academies presentation by Dr. Keith A. Baggerly, Professor of Bioinformatics and Computational Biology at M.D. Anderson Cancer Center, to the leadership of the National Academies of Sciences, Engineering, and Medicine (103), the IOM responded with a memorandum (104). The IOM admitted there were/are mathematical in calculations used to determine the DRI for vitamin D, but the final conclusion was that the errors were negligible and would not change the dietary recommendations.

Discussion

There are a few assumptions that must be made in order for the dietary reference intakes to apply to the total population. To be clear, these assumptions are made with the best research information to date. While this paper aims to be clear about aspects to be improved upon, the 2011 Institute of Medicine committee who made the recommendations acknowledged there were gaps in the research. However, the gaps in research often neglected to acknowledge the narrow demographics that were presented in the analysis for the DRI. An assumption about the research used for the DRI is that the research is representative of the population writ large. However, most of the research conducted was conducted with older, primarily white populations in Northernly locations resulting in data that may not be acceptable for all individuals.

As mentioned previously, women might be a group that requires more vitamin D. The data analysis report from the National Health and Nutrition Examination Surveys (NHANES) from

2001-2006 on vitamin D found that females were at a greater risk of vitamin D deficiency than males at almost every age group (105). Given that women are more likely to have greater fat deposition than men (22–25), it is also important to note that those with more adiposity may have a more difficulty raising their serum vitamin D. Some studies have indicated as much as a 40% higher vitamin D intake than non-obese individuals to the same serum 25(OH)D levels (106). Therefore, the current recommendations are not necessarily suitable for the demographic indicating that more intricate guidelines need to be set for certain populations.

The IOM recommendations are set between 400- 600 IU/day to maintain a serum 25(OH)D level of 20 ng/ml. However, a dose-response study conducted on the necessary vitamin D intake on children between the ages of 8 to 14 years to maintain the IOM recommended serum 25(OH)D level indicated that 2068 IU were required to reach a level of 20 ng/ml (107). To reach a serum level above deficiency, 12 ng/ml, a dose of 1137 IU was required for the children (107). Because children require vitamin D for growth, the study may indicate that children are a group that require greater random controlled trial research to gather the best vitamin D supplement dosage information.

Ironically, the answer to the discrepancies in what an adequate intake is and what serum value showed be aimed for in a population may lie in studies about sun exposure. Vitamin D intake studies have almost exclusively relied on random-controlled trials all pertaining to bone health. However, the pleotropic effects of vitamin D means that we should explore the evolutionary implications of vitamin D. While the American Cancer Society has determined that only dietary sources should contribute for vitamin D, vitamin D derived purely from sun exposure is where we should begin. Afterall, our evolutionary history indicates that skin color is an adaptive trait that contributes to the production of vitamin D (12,16).

One such study that may indicate adequate serum 25(OH)D predominately from sun exposure is a study on elderly women native to Thailand, a country near the equator (108). Because vitamin D deficiency results in elevation of parathyroid hormone (PTH) resulting in accelerated bone loss, the study used PTH elevation as a marker of vitamin D sufficiency (108). Parathyroid hormone began to rise below serum 25(OH)D below 70 nmol/L indicating that a normal range for the elderly women might be much higher than 50 nmol/L (109).

Recommendations

Vitamin D is recognized as unique in its attributes as a vitamin and a prohormone. However, the dietary recommendations are created for an entire population using the same approaches used for all micronutrients. While the IOM was tasked with creating a diet recommendation, the normal methods used for dietary recommendations may not apply to the unique circumstances surrounding vitamin D.

While there is no denying that overexposure to ultraviolet radiation can lead to cancer(110), there may be moderate benefits of sun exposure. To be clear, the recommendation is not advocating for extreme tanning, but studying the benefits of time spent outdoors should be advocated for instead of dismissed entirely. This is especially true in attempting to establish the optimal circulating serum 25(OH)D levels. Because of photo-degradation, toxicity of vitamin D by sun exposure is virtually impossible. Therefore, understanding serum 25(OH)D levels in groups near the equator and those working in the sun are vital to understanding where dietary recommendations should start.

Consequently, latitude is thought to have a major effect on serum vitamin D (37,111). Therefore, the data should be analyzed with latitude in mind when assessing skin color types and

the length of time required to generate vitamin D. Vitamin D recommendations currently cover the whole of the United States and Canada, but the data must be disaggregated by latitude and racial/ethnic groupings to better understand the needs of people of various skin colors. Dietary recommendations are already made by life-stage and sex groupings. There is no reason why latitude cannot be integrated into those recommendations along with skin pigmentation.

As previously stated, vitamin D receptors are all present in numerous cells in various tissues in the body. Despite knowing that vitamin D binds and helps regulate these tissues, there is not enough evidence to indicate how these cells utilize vitamin D and the physiological consequences of vitamin D. Thus, all vitamin D recommendations are solely based on the biological outcomes for the skeletal system, including calcium absorption, rickets, fracture risk, and osteomalacia (45). The DRI recommends more data on these subjects occur before a using any other biological outcomes to determine vitamin D intake values. More random-controlled trials and longitudinal data analysis is required to understand the dietary intake values necessary for the pleotropic effects of vitamin D. Perhaps, a good place to begin is the effect of vitamin D on immune function and T-cell output. While vitamin D deficiency is implicated in many chronic diseases (41,77,112), specific relationships with immune factors in random controlled trials are a good place to begin researching the connections with disease states later in life.

Figures

Table 1: Differences between vitamins and hormones

Vitamin	Hormone
• Not synthesized in organism or very small amounts made by organism • Consumed by food intake • Catalytic action • Deficiency causes specific disease	• Synthesized in body by endocrine glands • Continually generated by body • Acts as a signaling messenger • Causes gene expression

Figure 1: Vitamin D Metabolic Pathway

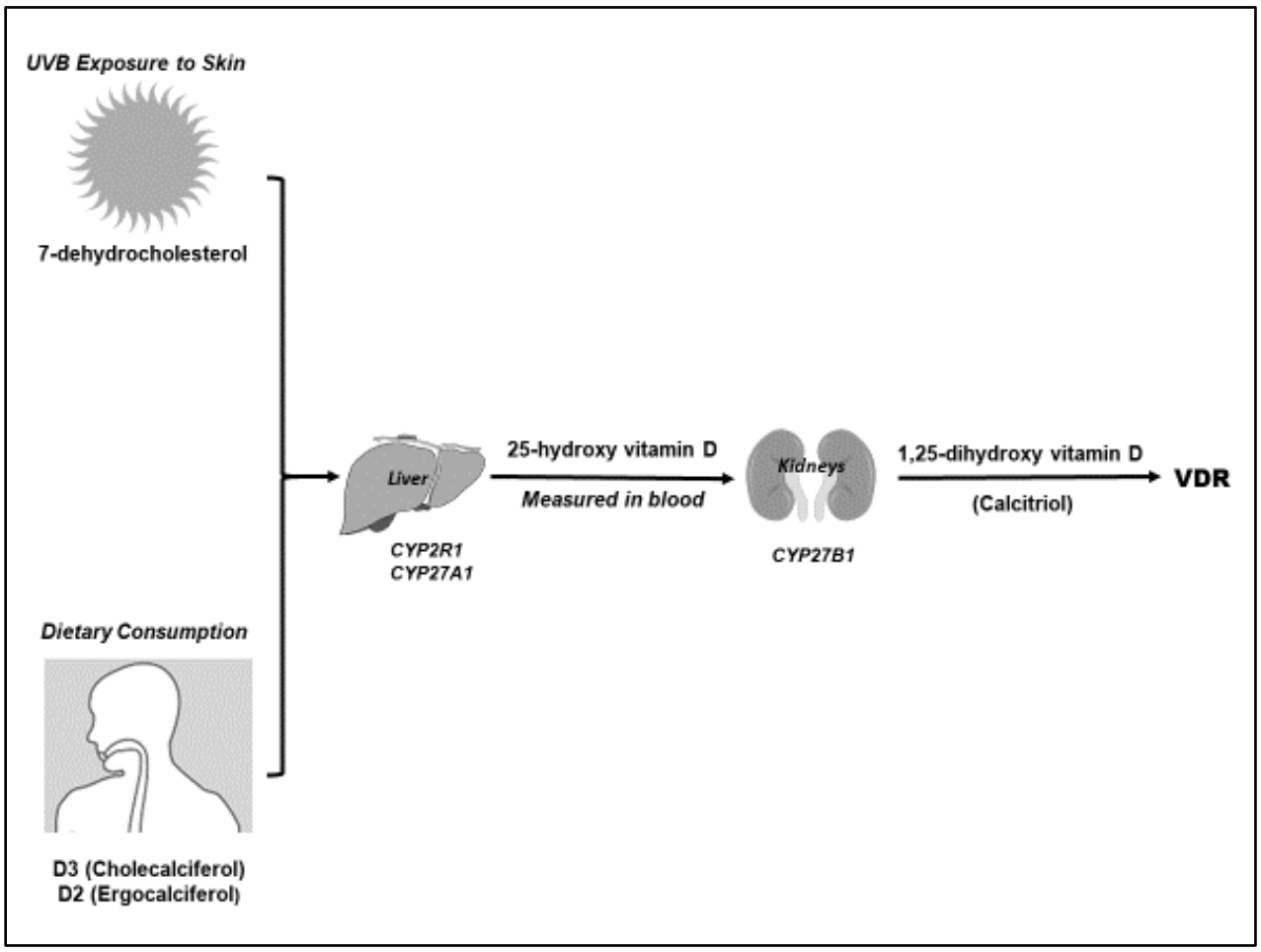

Figure 1. Vitamin D can be obtained via sun exposure and through dietary consumption. Both routes undergo hydroxylation events via Cytochrome P450 genes, CYP2R1 and CYP27A1, to produce 25-hydroxy vitamin D in the liver. After another hydroxylation event via CYP27B1 in the kidneys, 1, 25-dihydroxy vitamin D is formed, which is then regulated via the vitamin D receptor (VDR) genes. VDR sites are expressed in various tissues and organs all over the body.

Figure 2: Level of nutrient requirement for EAR

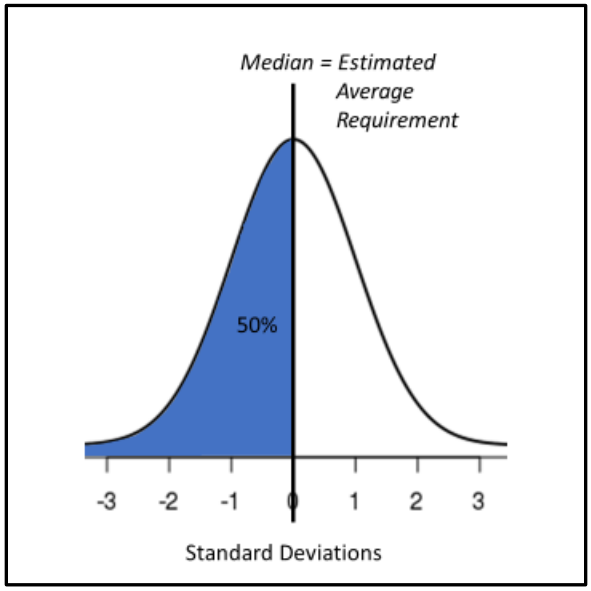

Figure 2. Fifty percent of the population is at or below the median of a normal distribution. The median determines the estimated average requirement.

Figure 3: Level of nutrient requirement for RDA

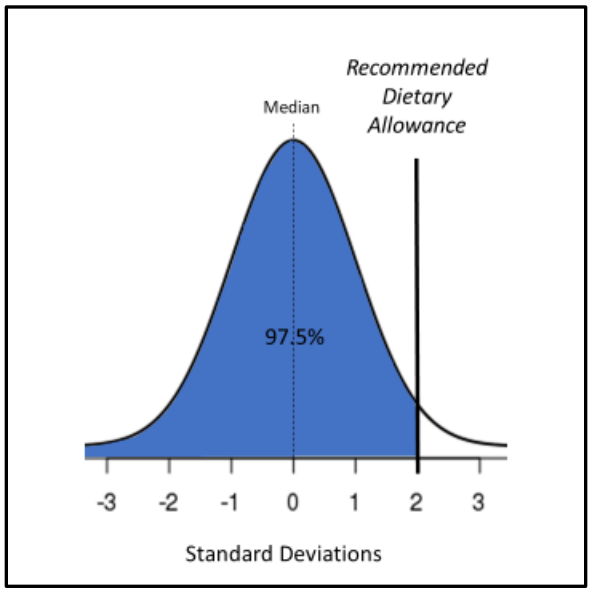

Figure 3. After determining the estimated average requirement, two standard distributions are calculated above the median. The recommended dietary allowance is set at this point indicating that at this dietary intake most of the population meets their required dietary needs.

Table 2: Dietary Reference Intakes for Vitamin D and the Corresponding Serum 25(OH)D Threshold Levels by Sex and Age Group

Life Stage Group		AI	25(OH)D	EAR	25(OH)D	RDA	25(OH)D
Infant	0-6 months	400 IU	16 ng/mL (40 nmol/L)	____		____	
	6-12 months	400 IU	16 ng/mL (40 nmol/L)	____		____	
Children	1-3 years	____		400 IU	16 ng/mL (40 nmol/L)	600 IU	20 ng/mL (50 nmol/L)
	4-8 years	____		400 IU	16 ng/mL (40 nmol/L)	600 IU	20 ng/mL (50 nmol/L)
Males	0-13 years	____		400 IU	16 ng/mL (40 nmol/L)	600 IU	20 ng/mL (50 nmol/L)
	14-18 years	____		400 IU	16 ng/mL (40 nmol/L)	600 IU	20 ng/mL (50 nmol/L)
	19-30 years	____		400 IU	16 ng/mL (40 nmol/L)	600 IU	20 ng/mL (50 nmol/L)
	31-50 years	____		400 IU	16 ng/mL (40 nmol/L)	600 IU	20 ng/mL (50 nmol/L)
	51-70 years	____		400 IU	16 ng/mL (40 nmol/L)	600 IU	20 ng/mL (50 nmol/L)
	> 70 years	____		400 IU	16 ng/mL (40 nmol/L)	800 IU	20 ng/mL (50 nmol/L)*
Females	0-13 years	____		400 IU	16 ng/mL (40 nmol/L)	600 IU	20 ng/mL (50 nmol/L)
	14-18 years	____		400 IU	16 ng/mL (40 nmol/L)	600 IU	20 ng/mL (50 nmol/L)
	19-30 years	____		400 IU	16 ng/mL (40 nmol/L)	600 IU	20 ng/mL (50 nmol/L)
	31-50 years	____		400 IU	16 ng/mL (40 nmol/L)	600 IU	20 ng/mL (50 nmol/L)
	51-70 years	____		400 IU	16 ng/mL (40 nmol/L)	600 IU	20 ng/mL (50 nmol/L)
	> 70 years	____		400 IU	16 ng/mL (40 nmol/L)	800 IU	20 ng/mL (50 nmol/L)*
Pregnancy	14-18 years	____		400 IU	16 ng/mL (40 nmol/L)	600 IU	20 ng/mL (50 nmol/L)
	19--30 years	____		400 IU	16 ng/mL (40 nmol/L)	600 IU	20 ng/mL (50 nmol/L)
	31-50 years	____		400 IU	16 ng/mL (40 nmol/L)	600 IU	20 ng/mL (50 nmol/L)
Lactation	14-18 years	____		400 IU	16 ng/mL (40 nmol/L)	600 IU	20 ng/mL (50 nmol/L)

	19-30 years	____	400 IU	16 ng/mL (40 nmol/L)	600 IU	20 ng/mL (50 nmol/L)
	31-50 years	____	400 IU	16 ng/mL (40 nmol/L)	600 IU	20 ng/mL (50 nmol/L)

*** For those older than 70 years, the recommended daily allowance was set to 800 IU to account for unknown factors that might affect normal aging and subsequently affect the estimating of the RDA for this age group. The RDA purpose is still meant to have a threshold of 20 ng/mL of 25(OH)D in serum.**

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