Minireview

Vitamin D nutritional policy needs a vision for the future

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Abstract
Historically vitamin D is known to be essential for normal bone growth and quality, and thus appropriate dietary vitamin D supplementation can eliminate vitamin D deficiency childhood rickets and adult osteomalacia. In spite of many government and medical associations worldwide guidelines for the reference daily intake (RDI) of vitamin D, scientists and nutritionists from many countries agree that at present about half of elderly North Americans and Western Europeans and probably also of the rest of the world are not receiving enough vitamin D to maintain healthy bone. In addition, over the past decade there has been a dramatic increase in our understanding of the many biological actions that result from vitamin D acting through its daughter steroid hormone, 1α,25-dihydroxyvitamin D3 [1α,25(OH)2D3] in collaboration with its cognate vitamin D receptor (VDR). Consequently, evidence has accumulated that beside intestine and bone, there are five additional physiological systems where the VDR with 1α,25(OH)2D generates biological responses. These include the immune system (both the innate and adaptive), pancreas and metabolic homeostasis, heart-cardiovascular, muscle and brain systems as well as the control of the cell cycle, and thus of the disease process of cancer. Acting through the VDR, 1α,25(OH)2D3 can produce a wide array of favorable biological effects that collectively are projected to contribute to the improvement of human health. Responsible medicine demands that worldwide vitamin D nutritional guidelines reflect current scientific knowledge about vitamin D’s spectrum of activities. Thus, worldwide vitamin D nutritional policy is now at a crossroads. This paper presents several proposed policy changes with regard to the amount of vitamin D daily intake that if implemented will maximize vitamin D’s contribution to reducing the frequency of many diseases, which would then increase the quality and longevity of life and significantly reduce the cost of medical care worldwide.

Keywords: vitamin D, 1α,25(OH)2D, VDR, good health, bone, daily requirement, cardiovascular, immune system, muscle, diabetes, cancer


Introduction

Vitamin D is essential for both normal growth and bone quality. Appropriate vitamin D supplementation can eliminate vitamin D deficiency childhood rickets and adult osteomalacia. Many government and medical associations worldwide have guidelines for reference daily intake (RDI) of vitamin D necessary to ensure good calcium homeostasis and to prevent classic bone-related vitamin D deficiency.1 Yet, scientists and nutritionists from many countries agree that about half of elderly North Americans and probably also of the rest of the world are not receiving enough vitamin D to maintain healthy bone.2–4 Also, the recent identification of many new biological actions of vitamin D make it appropriate to reconsider vitamin D guidelines and propose worldwide policy changes that will maximize vitamin D’s contribution to a higher level of lifelong good health.

Fundamentals of vitamin D biology

The substance now known as vitamin D was discovered 90 y ago as a dietary agent that prevented the bone disease rickets.5 Soon it was found that ultraviolet B (UVB) irradiation of the skin of vitamin D-deficient animals resulted in protection against rickets (see Figure 1). Thus, the dictum that ‘light equals vitamin D’ was coined. Cod-liver oil, rich in vitamin D3, through an empirical approach to determine safe doses, was found to be an excellent antirachitic agent, and became widely used in the Western world to treat and prevent rickets in humans.6 The essentiality of vitamin D throughout life in higher animals is the result of its indispensable contributions by maintaining calcium homeostasis and good bone health.

Since 1970 we have known that vitamin D itself is biologically inert and that its biological effects result only as a
Figure 1 Chemistry and irradiation pathway present in the epidermis of man and higher animals for production of vitamin D₃. The provitamin, 7-dehydrocholesterol, which is characterized by the presence in the B ring of a 7α, 7β-conjugated double bond system, upon exposure to ultraviolet light, is converted to a secosteroid provitamin steroid, where the 9,10 carbon–carbon bond has been broken. Then the previtamin D₃, in a process independent of ultraviolet light, thermally isomerizes over a short time interval to the ‘vitamin’ form, which is characterized by a 7α, 7β, 10α, 10β conjugated double bond system. The main portion of the figure also illustrates the two principal conformations or shapes of the molecule that results as a consequence of rotation about the 6,7 carbon single bond of the secosteroid ring. These are the 6-s-cis conformer (the steroid-like shape) and the 6-s-trans conformer (the extended shape). The interconversion of the two conformers occurs millions of times per second. The extreme conformational flexibility potential of all vitamin D metabolites is illustrated in the inset box for the principal seco B ring. These are the 6-s-cis shapes that are available for shape-selective interaction with the vitamin D receptor and the vitamin D binding protein (DBP).

The consequence of its sequential metabolism in the liver into 25-hydroxy-vitamin D (25(OH)D₃), and then in the kidney into the steroid hormone, 1α,25-dihydroxyvitamin D₃ [1α,25(OH)₂D₃]. The first formulation of the vitamin D endocrine system in 1971 linked the kidney functioning as an endocrine gland responsible for the regulated production of 1α,25-dihydroxyvitamin D₃ (1α,25(OH)₂D₃), with the functioning of the vitamin D receptor (VDR) in three target organs key to calcium homeostasis. Thus, the VDR with its cognate bound ligand, 1α,25(OH)₂D₃, was found to be present in the intestine, bone, and kidney, which, in turn, were linked with the generation of the physiological responses of intestinal calcium absorption and bone mineralization. The first clinical demonstration of the essential role of 1α,25(OH)₂D₃ as a steroid hormone was its ability to stimulate intestinal calcium absorption in severely uremic patients.

Over the last four decades it has been learned that the vitamin D endocrine system, as defined by the presence of the VDR, is operational in at least 38 tissues of the body (see Table 1). In these target tissues, the VDR functions both in the cell nucleus as a transcriptional factor to influence about 3% of the human genome, and in the plasma membrane caveolae as a modulator of signal transduction pathways (see Figure 2). A notable further expansion of the vitamin D endocrine system has been the clear demonstration that the enzyme which converts 25(OH)D₃ to 1α,25(OH)₂D₃, namely the 25(OH)D₃-1α-hydroxylase, is present in low concentrations in many tissues besides the kidney proximal tubule and generates 1α,25(OH)₂D₃ for paracrine action; these tissues are summarized in Table 2.

Over the past decade, four lines of investigation have collectively yielded striking new insights into the many newly appreciated actions of vitamin D. These include the following: (i) a broad range of molecular and cellular effects of 1α,25(OH)₂D₃, (ii) experimental studies in the VDR-knockout (KO) mouse model, (iii) several large observational epidemiological studies in subjects with variable nutritional vitamin D status, and (iv) prospective randomized intervention studies with vitamin D. Consequently, evidence has accumulated that besides the calcium homeostasis system (intestine, kidney, bone and the parathyroid gland), there are five additional physiological systems where VDR + 1α,25(OH)₂D₃ generate essential biological responses. These include the immune system (both innate and adaptive), pancreas and glucose and fat metabolism, heart-cardiovascular, muscle and brain systems, as well as the control of the cell cycle in virtually all cells, and thus of the disease process of cancer.

Acting through the VDR, 1α,25(OH)₂D₃ can produce a wide array of favorable biological effects that collectively are projected to contribute to the improvement of human health. Figure 3 highlights these five physiological systems, their respective biological responses and identifies for each system some of the disease states that are associated with an inadequate vitamin D nutritional status. The supporting information for Figure 3 are introduced in Table 3; its extensive legend summarizes evidence for the existence of VDR + 1α,25(OH)₂D₃-responsive
physiological systems that in circumstances of human vitamin D nutritional deficiency or in VDR-KO mice result in the appearance of diseases. The bulk of the scientific citations of Table 3 were published between 2002 and 2009. Please see Figure 4 and its legend which summarizes the extraordinary increase in publication rate of peer-reviewed papers on the topic of vitamin D over the last 40 y.

The causal link between severe vitamin D deficiency and rickets or osteomalacia bone is overwhelming,19 while the link between vitamin D insufficiency and osteoporosis with associated decreased muscle strength and increased risk of falls in osteoporotic humans is well documented by evidence-based intervention studies.20,21 In contrast, the causal link between vitamin D insufficiency and the many other diseases linked to the non-calcemic actions of 1α,25(OH)2D (e.g. tuberculosis, psoriasis, multiple sclerosis, inflammatory bowel disease, type-1 diabetes, high blood pressure, increased heart failure and muscle myopathy) has not yet been proven by appropriate vitamin D intervention studies.

Table 1  Tissues that express the VDR for the steroid hormone, 1α,25(OH)2D3

<table>
<thead>
<tr>
<th>Tissues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adipose</td>
</tr>
<tr>
<td>Adrenal</td>
</tr>
<tr>
<td>Bone, osteoblasts</td>
</tr>
<tr>
<td>Brain, general</td>
</tr>
<tr>
<td>Brain, amygdala</td>
</tr>
<tr>
<td>Brain, hypothalamus</td>
</tr>
<tr>
<td>Brain, glial cells</td>
</tr>
<tr>
<td>Breast</td>
</tr>
<tr>
<td>Cartilage</td>
</tr>
<tr>
<td>Colon</td>
</tr>
<tr>
<td>Eggshell gland</td>
</tr>
<tr>
<td>Epididymus, seminiferous tubules</td>
</tr>
<tr>
<td>Gillis (fish)</td>
</tr>
<tr>
<td>Hair follicle</td>
</tr>
<tr>
<td>Intestine</td>
</tr>
<tr>
<td>Kidney</td>
</tr>
<tr>
<td>Liver</td>
</tr>
<tr>
<td>Lung</td>
</tr>
<tr>
<td>Lymphocytes (B&amp;T)</td>
</tr>
<tr>
<td>Muscle, cardiac</td>
</tr>
<tr>
<td>Muscle, embryonic</td>
</tr>
<tr>
<td>Muscle, smooth</td>
</tr>
<tr>
<td>Ovary</td>
</tr>
<tr>
<td>Pancreas β-cell</td>
</tr>
<tr>
<td>Parathyroid</td>
</tr>
<tr>
<td>Parotid</td>
</tr>
<tr>
<td>Pituitary</td>
</tr>
<tr>
<td>Placenta</td>
</tr>
<tr>
<td>Prostate</td>
</tr>
<tr>
<td>Retina</td>
</tr>
<tr>
<td>Skin</td>
</tr>
<tr>
<td>Sperm</td>
</tr>
<tr>
<td>Stomach</td>
</tr>
<tr>
<td>Testis</td>
</tr>
<tr>
<td>Thymus</td>
</tr>
<tr>
<td>Thyroid</td>
</tr>
<tr>
<td>Tonsils, dendritic cells</td>
</tr>
<tr>
<td>Uterus</td>
</tr>
<tr>
<td>Yolk sac (bird)</td>
</tr>
</tbody>
</table>

VDR, vitamin D receptor; 1α,25(OH)2D3, 1α,25-dihydroxyvitamin D3

‘Reference citations for most of the VDR entries are available in reference7

Current vitamin D recommendations

The Dietary Reference Intake (DRI) allowance of vitamin D recommended in 1998 by the United States Food and Nutrition Board of the Institute of Medicine6 is 200 IU/d (5 µg/d) for infants, children and adult male and female subjects up to age 51. For men and women aged 51–70 or aged over 70, the adequate indicated level is set at 400 IU/d (10 µg/d) or 600 IU (15 µg/d), respectively. The adequate allowance during pregnancy and lactation is set at 200 IU/d (5 µg/d). The nutritional guidelines set forward by the EU commission are very similar.22–24 These recommendations focused only on vitamin D’s actions on calcium and bone issues and can successfully eliminate simple vitamin D deficiency rickets.

Sources of vitamin D

Unfortified foods naturally containing vitamin D are limited. The best sources are animal products and more particularly fatty fish and liver extracts, like salmon or sardines and cod liver oil.5,6,25 Vitamin D-fortified food sources in the US include only the following food categories (as mandated by the Food and Drug Administration): milk and milk products, orange juice, breakfast cereals and bars, grain products, and pastas, infant formulas and margarines. In most second- and third-world countries, there is no reliable nutritional source of vitamin D-enriched food.

In addition to being an essential nutrient, vitamin D is also known as the sunshine vitamin. Skin exposed to solar UVB radiation (wavelengths of 290–315 nm) can produce significant quantities of vitamin D that can easily exceed the DRI guidelines.26 However, this vitamin D synthesis is only reliably available year-round at latitudes between 40°N and 40°S. Given the present 2009 world population of 6.8 billion,27 approximately one-third of the world’s citizens (2.3 billion) live between 90°N and 40°N where levels of UVB are low or non-existent for a significant portion of the year; thus, they will require access to either dietary or supplemental vitamin D. In dark-skinned individuals, because of the presence of melatonin which absorbs the UVB, little or no vitamin D is produced photochemically at northerly latitudes in the winter, making vitamin D supplementation even more important.28

Unfortunately, the UVB wavelengths that photochemically produce vitamin D in the skin are also a proven carcinogen resulting in skin cancer (malignant melanoma), which can result in death,29 UV tanning booths also cause the same problem.30 Thus, a challenging question is to address the health benefits and risks involving the link between vitamin D and cancer that may result from increased sun exposure.

Current issues

Determination of vitamin D status

It is generally agreed that the serum concentration of 25(OH)D in normal subjects is the best indicator for judging the vitamin D status in patients with vitamin D-related disease states.1
Table 4 classifies circulating levels of 25(OH)D as a marker for describing vitamin D nutritional status; this includes three gradations of prevalent deficiency categories, two proposed normal ranges for 25(OH)D and examples of a higher safe level and a toxic level. Since these data were largely obtained from human studies relating to calcium homeostasis in white populations, it is therefore crucial to conduct appropriate intervention studies in large ethnically diverse population groups to identify the vitamin D adequate intake (AI) levels and correlated 25(OH)D levels necessary to prevent the diseases listed in Figure 3 (column 3).

**Safety and vitamin D intake**

Excessive amounts of vitamin D are not normally available from usual dietary sources and thus reports of vitamin D intoxication are rare. However, vitamin D excess from UVB or vitamin D-rich food is exceptional, but iatrogenic vitamin D excess can cause catastrophic problems as shown in animals and occasionally in children and adults, causing hypercalcemia, vomiting, thirst and polyuria, ectopic calcifications and widespread tissue damage and lethality. In fact, vitamin D excess is used as a rat toxin. The biological basis for intoxication resulting from the inappropriate intake of the parent vitamin D3 is believed to occur from the unrestrained metabolism by the liver of the vitamin D3 to 25(OH)D3, which is a largely unregulated metabolic step. Most cases of vitamin D intoxication are thought to occur as a result of high plasma levels of 25(OH)D rather than high plasma 1α,25(OH)2D3 levels. Excess sensitivity to high normal vitamin D/25(OH)D levels also occurs when the normal feedback system by (renal) 1α-hydroxylase is compromised. This is especially the case in patients with chronic inflammation and ectopic activation of monocytic 1α-hydroxylase (e.g. sarcoidosis,
tuberculosis, chronic inflammation). Also, transgenic animals with excessive endogenous 1α,25(OH)2D3 production such as mice with 24-hydroxylase, FGF-23 or Klotho deficiency, all display life-threatening hypercalcemia and a short life span. So there is clearly an upper limit for vitamin D or its metabolites that, once exceeded, can cause major health problems. The precise upper threshold for 25(OH)D before such problems may occur is not well defined and may vary according to the endogenous renal and extra-renal 1α-hydroxylase activity, so that on a population level a broad security level should be respected.

Table 4 presents examples of 25(OH)D levels present in summer workers and lifeguards who had high daily exposure to UV and the consequent epidermal production of vitamin D3, but who had no symptoms at all of toxicity (25D levels of 50–60 ng/mL or 125–150 nmol/L). For comparison, a flagrant example of toxicity resulting from daily intake of milk contaminated with high concentrations of vitamin D is presented in Table 4 (25D levels of 300 ng/mL or 750 nmol/L). The authors are of the conservative view that in large population cohorts (>1000 individuals), some individuals may be at risk for ‘toxicity’ when their 25(OH)D levels are in the range of 100–150 ng/mL or 250–300 nmol/L or greater. Clearly, much more 25(OH)D blood level data are needed from very large cohorts where it is known with certainty for each individual what has been their daily vitamin D3 intake.

**Supplementation or fortification of vitamin D**

A major challenge to each of the world countries’ nutrition and health agencies, given the emerging data supporting a worldwide epidemic of some level of vitamin D deficiency, is to document the severity of the vitamin D deficiency for each resident racial and ethnic group and their dietary practices and to consider whether to use food fortification or individual supplementation as a means to improve the health status of their citizens. This is a complex political and public health policy issue, and it is beyond the scope of this presentation to provide a detailed set of recommendations. To improve the vitamin D status of the world population, greater exposure to sunlight or UVB is not a viable option for most of the population because of the phototoxicity of UVB. There is no sufficient naturally vitamin D-rich food around the world to correct the worldwide insufficiency either. Therefore, the options are direct supplementation with vitamin D3 or indirect supply by vitamin D3 enrichment of natural food. Both options are valid and will have to be used with variable focus in different parts of the world or for specific target groups. Simple vitamin D supplementation facilitates correct dosage and allows adjustments for specific needs of problematic target...
The disease process of cancer in two ways: in cancer patients, Vitamin D and its endocrine system could be involved with the development of cancer and vitamin D insufficiency. Therefore, no universal worldwide strategy is possible and fine tuning is needed.

**Table 3** VDR + 1α,25(OH)2D3-responsive physiological systems that in circumstances of human vitamin D nutritional deficiency or in VDR-KO mice result in the appearance of diseases

<table>
<thead>
<tr>
<th>VDR + 1α,25(OH)2D3 physiological systems</th>
<th>Biological responses</th>
<th>Vitamin D deficiency-associated diseases in the human</th>
<th>Data from vitamin D deficiency (references)</th>
<th>VDR-KO mouse data (references)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cells</td>
<td>Cell cycle regulation</td>
<td>Cancer</td>
<td>71–74, 80–83</td>
<td>75–79</td>
</tr>
<tr>
<td></td>
<td>Cell proliferation inhibition</td>
<td>Prostate, colon and breast cancer (prevention)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Leukemia and other cancers (treatment)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intestine</td>
<td>Calcium absorption</td>
<td>Rickets, osteomalacia and osteoporosis</td>
<td>13, 84, 85</td>
<td>17†</td>
</tr>
<tr>
<td>Bone</td>
<td>Bone remodeling</td>
<td></td>
<td>86</td>
<td></td>
</tr>
<tr>
<td>Immune system</td>
<td>Innate</td>
<td>Stimulate phagocyte functions and synthesis of anti microbial peptides</td>
<td>Increased prevalence of infection, e.g. of tuberculosis</td>
<td>87, 88</td>
</tr>
<tr>
<td></td>
<td>Autoimmune</td>
<td>Dendritic and T-cell function</td>
<td>Increased autoimmune diseases: e.g. type-1 diabetes, multiple sclerosis, inflammatory bowel disease, psoriasis</td>
<td>45, 91</td>
</tr>
<tr>
<td>Pancreas β-cells</td>
<td>Innate</td>
<td>Facilitate insulin secretion</td>
<td>Impaired glucose tolerance and type-II diabetes/metabolic syndrome</td>
<td>92, 93</td>
</tr>
<tr>
<td>Heart and Cardiac</td>
<td>Innate</td>
<td>Renin–angiotensin regulation, coagulation, fibrinolysis, heart muscle functioning</td>
<td>High renin hypertension, increased cardiovascular risk, increased thrombogenesis</td>
<td>71, 96</td>
</tr>
<tr>
<td>Muscle</td>
<td>Innate</td>
<td>Promote normal skeletal muscle development; improve muscle strength</td>
<td>Muscle myopathy; increased risk of falls strength</td>
<td>99–101</td>
</tr>
<tr>
<td>Brain†</td>
<td>Innate</td>
<td>The brain has the VDR and 25(OH)D3-1α-hydroxylase</td>
<td>Vitamin D deficiency in utero alters adult behavior in mice and man</td>
<td>102</td>
</tr>
</tbody>
</table>

VDR, vitamin D receptor; 1α,25(OH)2D3, 1α,25-dihydroxyvitamin D3; KO, knock out

This Table 3 is linked to Figure 3. Both Figure 3 and Table 3 list the six physiological systems that are now known to be integral components of the vitamin D endocrine system; these physiological systems are defined by the presence of the VDR. For each physiological system listed in Column 1 of Table 3, the succeeding columns to the right provide the following information. Column 2: The principal biological responses for that system are identified. Column 3: Human vitamin D deficiency-associated diseases may result if adequate amounts of vitamin D3 are lacking (due either to shortage of UVB exposure or inadequate dietary intake). This condition will result in low levels of 25(OH)D3 in the circulatory system. As a consequence, inadequate amounts of the steroid hormone 1α,25(OH)2D3 will be produced by the kidney 25(OH)D3-1α-hydroxylases and the various paracrine 25(OH)D3-1α-hydroxylases (see Table 2). Human diseases, like rickets or osteomalacia, are known to be caused by vitamin D deficiency, whereas numerous other human diseases have been found to be associated with poor vitamin D nutritional status where a definite causality relationship has not yet been proven. Often an identifiable human disease may be diagnosed. Column 4: This column lists selected reference citations relevant to the human disease(s) described in the companion column 3 that occur because of an inadequate vitamin D nutritional status. Column 5: This column provides selected reference citations for the companion columns for experimental studies conducted using a mouse VDR-KO. In this system, the absence of the VDR imposes a shortage of 1α,25(OH)2D3, which occurs because the VDR in the wild-type mouse is located in the hair follicle. However, normalization of mineral ion homeostasis in the VDR-KO mouse, by dietary means, while preventing hyperparathyroidism, rickets and osteomalacia, does not prevent alopecia.

The correlation between ‘potential’ UVB exposure according to latitude and actual vitamin D status is however poor. Subsequently, a link or association between true nutritional vitamin D status as evaluated by dietary vitamin D and groups, but requires voluntary and consistent lifelong cooperation. Food fortification can reach a much larger target group of the population and circumvents inadequate compliance. However, the choice of food-to-be-fortified and the dosage are problematic as food preferences vary widely and therefore the problem of not reaching the most vulnerable target groups as well as overdosing can hardly be avoided. Therefore, no universal worldwide strategy is possible and fine tuning is needed.

**Cancer and vitamin D**

Vitamin D and its endocrine system could be involved with the disease process of cancer in two ways: in cancer chemoprevention and in treatment of active cancer. There is ample evidence that 1α,25(OH)2D3 can induce cell differentiation, inhibit cell proliferation or activate cell apoptosis (cell death), these actions are now known to be due to a coherent involvement of at least 50 genes involved in cell cycle regulation. The first clinical indication of possible vitamin D involvement in cancer chemoprevention came from epidemiological studies, suggesting a link between increased sunlight UVB exposure of populations living in lower latitudes with lower incidences of colon cancer. The correlation between ‘potential’ UVB exposure according to latitude and actual vitamin D status is however poor. Subsequently, a link or association between true nutritional vitamin D status as evaluated by dietary vitamin D and
Tokyo, Japan; and Leo Pharma, Ballerup, Denmark) of over 4000 analogs of the chemical synthesis, by academic chemists as well as three pharmaceutical companies (Hoffmann-La Roche, Nutley, NJ, USA; Chugai Pharmaceuticals, ‘cancer’ (≏1000), ‘renal failure’ (≏800), ‘intestine’ (≏800), ‘cardiovascular/heart’ (≏900), ‘diabetes’ (≏700), ‘insulin’ (≏600) or ‘brain’ (≏300). Finally, PubMed lists more than 1200 papers with ‘calcitriol’ (a synonym for 1a,25(OH)2D3) in the ‘title’ or ‘abstract’. In 1975 there were only ~250 papers published per year that met the criterion of the term ‘vitamin D’ in the paper title or its abstract, while 30 y later, in 2007, this number had grown by ~6- to >1600 papers published per year. From 2000 through the end of 2009, the rate of publication increased even more rapidly, so that at the beginning of 2010 there will have been a ~3 ×-fold increase, from 700 papers/y to about 2100 papers/y. Another driving factor contributing to this increased vitamin D publication rate from 1975 to 2010 was the chemical synthesis, by academic chemists as well as three pharmaceutical companies (Hoffmann-La Roche, Nutley, NJ, USA; Chugai Pharmaceuticals, Tokyo, Japan; and Leo Pharma, Ballerup, Denmark) of over 4000 analogs of 1a,25(OH)2D3. Most of these analogs were targeted at giving selective responses in disease states such as osteoporosis, renal osteodystrophy, psoriasis, etc. and their biological properties were reported in a multitude of peer-reviewed publications.

Figure 4  Rate of growth of the number of peer-reviewed publications published each year, which have the term ‘vitamin D’ in their ‘title’ or ‘abstract’ as reported by PubMed. PubMed currently lists over 25,000 publications that use the term ‘vitamin D’ in either the title or abstract from 1950 to the present (vitamin D3 ~5500 and vitamin D2 ~900). This total includes papers that combine the use of ‘vitamin D’ with one of the following terms: ‘bone’ (>7000 papers), ‘deficiency’ (>3800), ‘cancer’ (>1000), ‘renal failure’ (>800), ‘intestine’ (>800), ‘cardiovascular/heart’ (>900), ‘diabetes’ (>700), ‘insulin’ (>600) or ‘brain’ (>300). Finally, PubMed lists more than 1200 papers with ‘calcitriol’ (a synonym for 1a,25(OH)2D3) in the ‘title’ or ‘abstract’. In 1975 there were only ~250 papers published per year that met the criterion of the term ‘vitamin D’ in the paper title or its abstract, while 30 y later, in 2007, this number had grown by ~6- to >1600 papers published per year. From 2000 through the end of 2009, the rate of publication increased even more rapidly, so that at the beginning of 2010 there will have been a ~3 ×-fold increase, from 700 papers/y to about 2100 papers/y. Another driving factor contributing to this increased vitamin D publication rate from 1975 to 2010 was the chemical synthesis, by academic chemists as well as three pharmaceutical companies (Hoffmann-La Roche, Nutley, NJ, USA; Chugai Pharmaceuticals, Tokyo, Japan; and Leo Pharma, Ballerup, Denmark) of over 4000 analogs of 1a,25(OH)2D3. Most of these analogs were targeted at giving selective responses in disease states such as osteoporosis, renal osteodystrophy, psoriasis, etc. and their biological properties were reported in a multitude of peer-reviewed publications.

Table 4  Vitamin D nutritional status is described by circulating levels of 25(OH)D

<table>
<thead>
<tr>
<th>Serum 25(OH)D</th>
<th>ng/mL</th>
<th>mmol/L</th>
<th>Nutritional description</th>
<th>Reference citation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5†</td>
<td>&lt;12</td>
<td></td>
<td>Severe vitamin D deficiency</td>
<td>1</td>
</tr>
<tr>
<td>&lt;10†</td>
<td>&lt;25</td>
<td></td>
<td>Vitamin D deficiency</td>
<td>119</td>
</tr>
<tr>
<td>(Option 1)†</td>
<td>10−20</td>
<td>25−50</td>
<td>Vitamin D insufficiency</td>
<td>119</td>
</tr>
<tr>
<td>(Option 2)†</td>
<td>10−30</td>
<td>25−75</td>
<td>Vitamin D insufficiency</td>
<td>119</td>
</tr>
<tr>
<td>(Option 1)†</td>
<td>&gt;20</td>
<td>&gt;50</td>
<td>Vitamin D sufficiency</td>
<td>3, 61</td>
</tr>
<tr>
<td>(Option 2)†</td>
<td>&gt;30</td>
<td>&gt;75</td>
<td>Vitamin D sufficiency</td>
<td>3, 61</td>
</tr>
<tr>
<td>(Risk of toxicity)†</td>
<td>100−150</td>
<td>250−375</td>
<td>Possible toxicity</td>
<td></td>
</tr>
<tr>
<td>Examples 51†, 58 and 65††, 300‡‡</td>
<td>126†, 148 and 162††, 750‡‡</td>
<td>(Outdoor workers in summer) (life guard studies)</td>
<td>Flagrant toxicity (contaminated milk)</td>
<td>34, 35, 36, 37</td>
</tr>
</tbody>
</table>

The Food and Nutrition Board of the Institute of Medicine in 1997 defined serum 25(OH)D levels as a surrogate marker for describing vitamin D nutritional status.1 Serum 25(OH)D levels entered in Table 4 describe the ‘total’ concentration of 25(OH)D, i.e. the sum of the concentration of 25(OH)D2 and 25(OH)D3 present in a serum sample. Depending upon the methodology for the assessment of the serum 25(OH)D being evaluated, the detecting signal would measure both 25(OH)D3 and 25(OH)D2 without distinction, or if a mass spectrometry method was employed, discrete values for each form of 25(OH)D would be obtained. The use of total serum levels of 25(OH)D as a marker for vitamin D nutritional status is justified by the following three points: (i) there is no clinical assay for the parent vitamin D; (ii) the metabolism of vitamin D3 into 25(OH)D3 by the liver vitamin D-25-hydroxylase is not regulated and thus the serum concentration of 25(OH)D3 is believed to be an accurate ‘reporter’ of both cutaneous UV-stimulated synthesis and dietary intake of vitamin D3; and (iii) the plasma levels of 25(OH)D correlate with many clinical disease states.29,120

In the ‘severe vitamin D deficiency’ group, individuals with a 25(OH)D <5 ng/mL that exists over an extended interval (1–2 y) would be at risk for developing clinically diagnosable rickets or osteomalacia.1 Individuals classified as ‘vitamin D deficient’ have a high risk of developing rickets or osteomalacia.2 Vitamin D insufficiency is used to describe serum 25(OH)D levels that are higher than those associated with either ‘severe vitamin D deficiency’ or ‘vitamin D insufficiency’ and the borderline level associated with ‘vitamin D sufficiency’ (either >20 or >30 ng/mL, as described in footnote †) is 25(OH)D levels that were correlated with overt toxicity, footnote ††.

The authors are of the view that in a large population cohort (>1000 individuals) some individuals may be at a risk for ‘toxicity’ when their 25(OH)D levels are in the range of 100−150 ng/mL or greater.

Examples 51†, 58 and 65††, 300‡‡. One example is provided for a flagrant instance of vitamin D toxicity27 with extreme hypercalcaemia that resulted from daily consumption of drinking milk that was inappropriately fortified with 5.7 mg of vitamin D3 per liter or 230,000 IU/L.

Vitamin D sufficiency 3, 61
Severe vitamin D deficiency 1
Vitamin D sufficiency 3, 61
Vitamin D deficiency 119
Vitamin D insufficiency 119
Vitamin D insufficiency 119
Vitamin D sufficiency 3, 61
Vitamin D sufficiency 3, 61
Possible toxicity
Flagrant toxicity (contaminated milk)
especially serum 25(OH)D levels was confirmed in many but not all observational studies, especially when dealing with colon and breast cancer and less convincingly with regards to prostate cancer. Additional studies showed that individuals with low serum levels of 25(OH)D (<20 ng/mL) experienced a higher incidence of cancer. It was found in one study that a 10 ng/mL or 25 nmol/L increase in serum 25(OH)D level was associated with a 17% reduction in total cancer incidence. This could be achieved by vitamin D supplementation of at least 1500 IU/d. The overall cancer mortality in the US population was, however, not directly associated with 25(OH)D levels in the NHANES III study, but such an association was clearly present for colorectal cancer. A very extensive critical analysis of the epidemiological data on vitamin D and cancer by the World Health Organization concluded that: (a) observational studies link low 25(OH)D levels with colorectal adenoma and cancer; (b) two intervention studies did however not change the risk of cancer; (c) so that the causal relationship between vitamin D and cancer is still open and randomized clinical trials (RCTs) are therefore needed; and (d) pending such studies a restrictive attitude should be applied with regard to aggressive vitamin D supplementation or increased UVB exposure.

A physiological explanation for the healthful benefit of increased serum 25(OH)D levels is given in Figure 3. Indeed, in addition to its presence in the kidney, the 1α-hydroxylase enzyme that converts 25(OH)D into 1α,25(OH)2D has a paracrine presence in at least 10 other tissues, including the prostate, breast and colon (see Table 2). Therefore, the local concentration of 1α,25(OH)2D at sites of possible cancer development may be higher than expected from its serum concentration. Use of 1α,25(OH)2D or its less calcemic analogs to prevent or treat cancers is further substantiated by several animal models of cancer.

**Immune system and vitamin D**

In vitro and animal data have convincingly demonstrated that the vitamin D endocrine system regulates a large number of immune genes resulting in an activation of the innate immune system (and thus increased defense against infections) and a tapering down of the T helper-1 arm of the acquired immune system (and thus decreasing the risk of autoimmune diseases). Several retrospective studies have shown that vitamin D supplementation early in life reduces the subsequent risk of autoimmune type-1 diabetes later in life. A large prospective study in US military recruits concluded that vitamin D insufficiency at the time of recruitment conveys a two-fold increased risk of later onset of multiple sclerosis.

**Metabolism, cardiovascular risk and vitamin D**

Vitamin D-deficient or -resistant rodents develop high renin hypertension and eventually develop cardiac hypertrophy. VDR null mice also have an increased risk for thrombosis and 1α,25(OH)2D3 has favorable effects on the endothelial cell function. Observational studies in humans also link poor vitamin D status with hypertension in Caucasians, Hispanics and Afro-Americans, and small-scale studies showed beneficial effects on blood pressure. Several recent reviews on vitamin D deficiency and cardiovascular disease have appeared and support that low vitamin D status is associated with increased cardiovascular diseases. Obesity is also clearly associated with lower vitamin D status in humans and VDR null mice have decreased fat mass and are resistant to diet-induced obesity. Even other aspects of the metabolic syndrome apart from hypertension and obesity are associated with a poor vitamin D status, such as impaired insulin secretion and increased insulin resistance.

**Muscle and vitamin D**

The muscle of VDR-KO mice display a delayed development as genes and proteins of stunted muscle maintain genes and proteins of their early developmental stage and show delayed expression of adult muscle genes. Also vitamin D- or 1α,25(OH)2D3-deficient adults can develop severe muscle weakness, which respond well to 1α,25(OH)2D3 treatment of patients with chronic renal failure or inborn CYP27B1 deficiency. Several randomized intervention studies also demonstrated that supplements of vitamin D or 1α-hydroxylated metabolites can improve muscle function of elderly subjects and reduce the risk of falls by about 20%.

**Mortality and vitamin D**

If the vitamin D status would indeed be causally linked to all major human diseases, such as infections, cancer and metabolic and cardiovascular diseases, then it would be no surprise that a poor vitamin D status would be linked to increased mortality. Some large-scale observational studies indeed confirmed this conclusion in both normal subjects and in patients with chronic renal failure. A meta-analysis of an RCT of vitamin D supplements with fractures as the primary endpoint revealed a modest decrease (7%) in mortality in elderly subjects.

**Policy challenges**

The authors believe that the evidence summarized above shows that worldwide public health is best served by a recommendation of higher daily intakes of vitamin D. Safety must be the first priority in formulating any changes in vitamin D intake. Our starting point is that the present DRI recommendations largely meet only the important vitamin D calcium interdependencies, as summarized in the Institute of Medicine report in 1997.

**Goals**

It is crucial to agree upon an appropriate range of normal 25(OH)D serum levels to support all 37 VDR-containing target organs and the five physiological systems over a complete life span. Further, revised recommendations must identify appropriate functional measures for the multiple physiological systems and disease risks.
Other important questions include the following. Will the optimal vitamin D status for each of the five vitamin D-responsive physiological systems be derived from evidence-based medicine (RCTs in the appropriate target populations) or via observational approaches? What is the frequency and severity of vitamin D toxicity when vitamin D supplementation is implemented in a very large population of many millions of people over a life time? There are currently no adequate answers to these questions. Thus, there is a need for evidence-based clinical research on large populations in different ethnic groups living at different latitudes to evaluate efficacy and safety concerns.

Dilemma

What nutritional advice should be given until results are available from evidence-based studies or until public opinion demands change? There are at least four options as follows:

(i) No change in present situation: If the current nutritional guidelines in North America and Europe do not reach some of their country’s ethnic groups that are frequently vitamin D-deficient, or if appropriate DRI guidelines are not introduced throughout the world, then rickets and osteomalacia that could be easily prevented will continue to occur. Most experts and certainly lay people underestimate the true frequency of rickets around the world even today.4

(ii) Strict implementation of present guidelines for vitamin D intake: If there is no change in US public policy, then the current vitamin D DRI recommendations, if carefully implemented, could eliminate the number of individuals with serum 25(OH)D levels in the vitamin D-deficient range (<5–12 ng/mL or <12–30 nmol/L). If such a minimum minimum approach of adopting the present US and EU recommendations were applied worldwide to pregnant or lactating women, newborns and children, then the present guidelines could effectively eradicate the occurrence of rickets in infants.

(iii) Implementation of an intermediate approach: Optimal bone health in postmenopausal women and the elderly population requires that the minimal 25(OH)D serum levels be >20 ng/mL (>50 nmol/L). To reliably obtain such 25(OH)D levels in >97% of the target world population above 50 y of age would require additional supplementation of vitamin D. The vitamin D dose required could be 400 IU/d for populations with an already adequate baseline 25(OH)D level. But for most of the world, at least an extra 800 IU/d would be required to achieve 25(OH)D3 levels of >20 ng/mL (>50 nmol/L) in all adults, particularly for individuals living above 40°N or below 40°S latitude.61 Indeed, if serum 25(OH)D increased by a median level of 8 ng/mL during prolonged intake of 800 IU/d,62 then the mean world level of 21 ng/mL63 would be increased so that most subjects would reach minimal values of 20 ng/mL. Thus, in this option, the vitamin D3 daily dietary intake would have to be increased by 600–1000 IU/d in all adults above the present supply from their skin synthesis and/or nutritional intake. Such an approach has beneficial effects on bone health in the elderly as based on an evaluation of several meta-analyses of RCTs64 and has a good safety profile in more than 50,000 subjects over a several year treatment period. Such therapy might also be beneficial for all major human diseases (cancer, cardiovascular, metabolic and immune diseases) as in most observational studies, 25(OH)D levels below 20 ng/mL were associated with the greatest risk for the morbidity and mortality due to these diseases.

(iv) Implementation of an interventionist policy: If the vitamin D dietary intake were increased to 2000 IU/d and even more for the subgroups of the world population with the poorest vitamin D status, this should ensure that their 25(OH)D levels achieve a minimum of >30/40 ng/mL (>75/100 nmol/L) throughout life.3 Indeed, a daily supplementation of 2000 IU of vitamin D3 can increase mean 25(OH)D3 levels by 20 ng/mL and, starting from the world mean level of 21 ng/mL, this would imply that nearly all subjects would reach the 30 ng/mL threshold. This dose level of vitamin D could favorably impact the disease states associated with vitamin D deficiency, such as autoimmune diseases (multiple sclerosis [MS]), type-1 diabetes (especially perinatal vitamin D status), tuberculosis, particularly in blacks,26 metabolic syndrome, cardiovascular risk factors and most cancers (see Figure 3). Indeed, association studies showed a clear trend for the lowest risk of these diseases in subjects with the highest 25(OH)D status. There are however no reliable RCTs that have demonstrated the efficacy of such policy. Moreover, the use of such doses for a lifetime has neither prospectively nor even retrospectively been evaluated. While short-term, six-month supplementation studies in ~100 subjects are reassuring,65 these results should not be extrapolated to a lifetime supplementation regimen for millions of people of all ages.

Summary

In summary, worldwide vitamin D nutritional policy needs a vision for the future. Responsible medicine demands that vitamin D nutritional guidelines reflect current scientific knowledge that vitamin D and its daughter steroid hormone, 1α,25(OH)2D3, produce important biological effects that extend well beyond calcium and bone in at least five new physiological systems. Lifetime exposure to age-appropriate, sex-appropriate and ethnically appropriate adequate vitamin D nutritional intakes would result in a far-reaching collective impact in reducing the frequency of many diseases. This achievement would increase the quality and longevity of life and significantly reduce the cost of medical care worldwide.

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