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 D_3 [1α,25$(OH)_2D_3$] 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$(OH)_2$D 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$(OH)_2D_3$ 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$(OH)_2D_3$, VDR, good health, bone, daily requirement, cardiovascular, immune system, muscle, diabetes, cancer

Experimental Biology and Medicine 2010; **235**: 1034–1045. DOI: 10.1258/ebm.2010.010014

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 D_3, 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

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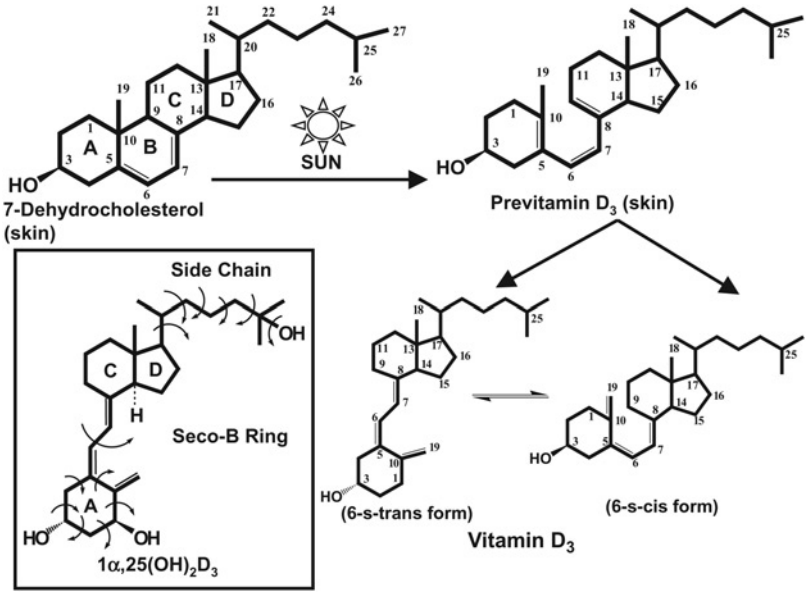

Figure 1 Chemistry and irradiation pathway present in the epidermis of man and higher animals for production of vitamin D_3. The provitamin, 7-dehydrocholesterol, which is characterized by the presence in the B ring of a Δ5-, Δ7-conjugated double bond system, upon exposure to ultraviolet light, is converted to a seco B previtamin steroid, where the 9,10 carbon–carbon bond has been broken. Then the previtamin D, in a process independent of ultraviolet light, thermally isomerizes over a short time interval to the 'vitamin' form, which is characterized by a Δ7,8, Δ5,6, Δ10,19 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 seco B 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 metabolite, $1\alpha,25(OH)_2$-vitamin D_3 ($1\alpha,25(OH)_2D_3$). Each of the arrows indicates carbon–carbon single bonds (in the side chain, the seco B ring and the A ring) that have complete 360° rotational freedom. This results for all the various vitamin D molecules (in solution and in biological systems) of a multitude of different shapes that are available for shape-selective interaction with the vitamin D receptor and the vitamin D binding protein (DBP)[66]

consequence of its sequential metabolism in the liver into 25-hydroxy-vitamin D (25(OH)D), and then in the kidney into the steroid hormone, 1α,25-dihydroxyvitamin D [$1\alpha,25(OH)_2D$].[5,7,8] The first formulation of the vitamin D endocrine system in 1971[9] linked the kidney functioning as an endocrine gland responsible for the regulated production of 1α,25-dihydroxyvitamin D_3 ($1\alpha,25(OH)_2D_3$), 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, $1\alpha,25(OH)_2D_3$, was found to be present in the intestine,[10] bone[11] and kidney,[12] 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 $1\alpha,25(OH)_2D_3$ as a steroid hormone was its ability to stimulate intestinal calcium absorption in severely uremic patients.[13]

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[14,15] (see Figure 2). A notable further expansion of the vitamin D endocrine system has been the clear demonstration that the enzyme which converts $25(OH)D_3$ to $1\alpha,25(OH)_2D_3$, namely the $25(OH)D_3$-1α-hydroxylase, is present in low concentrations in many tissues besides the kidney proximal tubule and generates $1\alpha,25(OH)_2D_3$ 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 $1\alpha,25(OH)_2D_3$;[14,16] (ii) experimental studies in the VDR-knockout (KO) mouse model;[17] (iii) several large observational epidemiological studies in subjects with variable nutritional vitamin D status;[18] 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 + $1\alpha,25(OH)_2D$ 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, $1\alpha,25(OH)_2D$ 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 + $1\alpha,25(OH)_2D_3$-responsive

Table 1 Tissues that express the VDR for the steroid hormone, $1\alpha,25(OH)_2D_3$*

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

VDR, vitamin D receptor; $1\alpha,25(OH)_2D_3$, $1\alpha,25$-dihydroxyvitamin D_3
*Reference citations for most of the VDR entries are available in reference[7]

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 $1\alpha,25(OH)_2D$ (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.

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 Medicine[1] 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.[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]

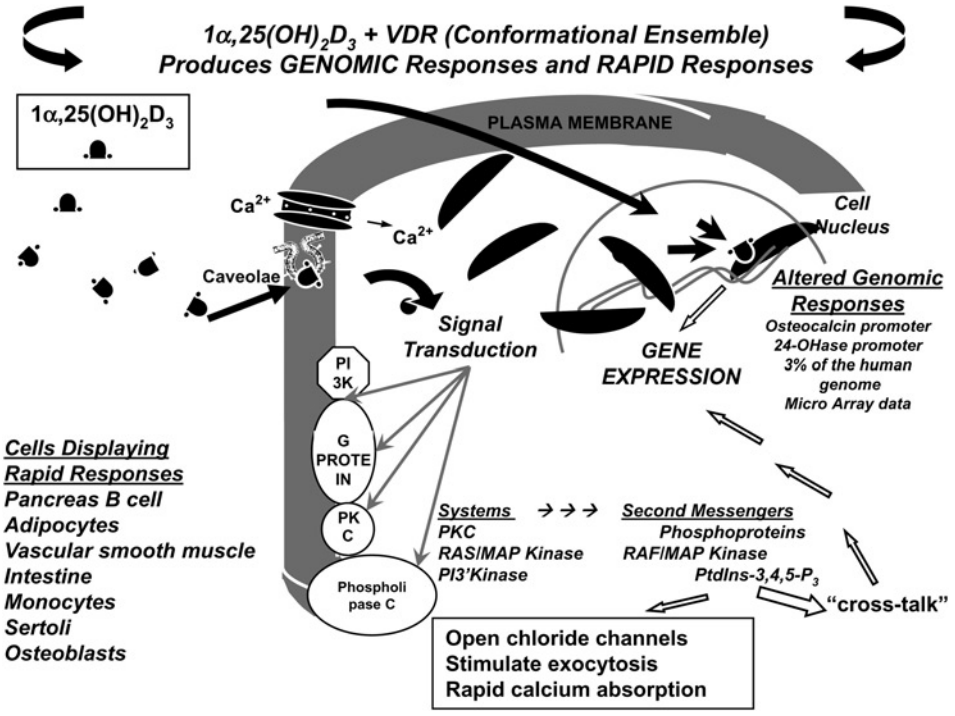

Figure 2 Functioning of vitamin D receptor (VDR) conformational ensemble (with two ligand pockets) can generate either genomic or rapid biological responses. In this model one shape (6-s-*trans*) of the conformationally flexible $1\alpha,25(OH)_2D_3$ can interact with the VDR localized in the cell nucleus to generate genomic responses via regulation of gene transcription, while a different shape (6-s-*cis*) of $1\alpha,25(OH)_2D_3$ binds to the second ligand pocket of the VDR associated with caveolae of the plasma membrane to generate rapid responses.[14,67] Binding of $1\alpha,25(OH)_2D_3$ to the caveolae-associated VDR may result in the activation of one or more second messenger systems, including phospholipase C (PKC), protein kinase C, G protein-coupled receptors or phosphatidylinositol-3_-kinase (PI3K). There are a number of possible outcomes including opening of the voltage-gated calcium or chloride channels, stimulation of exocytosis (osteoblasts) or generation of the indicated second messengers. Some of these second messengers, particularly RAF/MAPK, may engage in cross-talk with the nucleus to modulate gene expression. PtdIns-3,4,5-P3, phosphatidylinositol-3,4,5-trisphosphate. See reference[67] for details

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).

Table 2 Sites of extra-renal production of $1\alpha,25(OH)_2D_3$ in man as defined by the presence of the 25(OH)-D_3-1α-hydroxylase enzyme*

Tissue
Colon
Dendritic cells
Endothelial cells
Human brain (Schwann cells and oligodendrocytes)
Mammary, breast
Pancreatic islets
Parathyroid glands
Placenta, decidua
Prostate
Skin, keratinocytes

$1\alpha,25(OH)_2D_3$, $1\alpha,25$-dihydroxyvitamin D_3

*Reference citations for each site of extra-renal production of $1\alpha,25(OH)_2D_3$ are available in reference.[68] The tissue localization of extra-renal 25-(OH)D_3-1α-hydroxylase enzyme in man has been extensively studied by M Hewison and colleagues[69,70]

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.[31,32] The biological basis for intoxication resulting from the inappropriate intake of the parent vitamin D_3 is believed to occur from the unrestrained metabolism by the liver of the vitamin D_3 to 25(OH)D_3, 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 $1\alpha,25(OH)_2D_3$ levels.[33] 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,

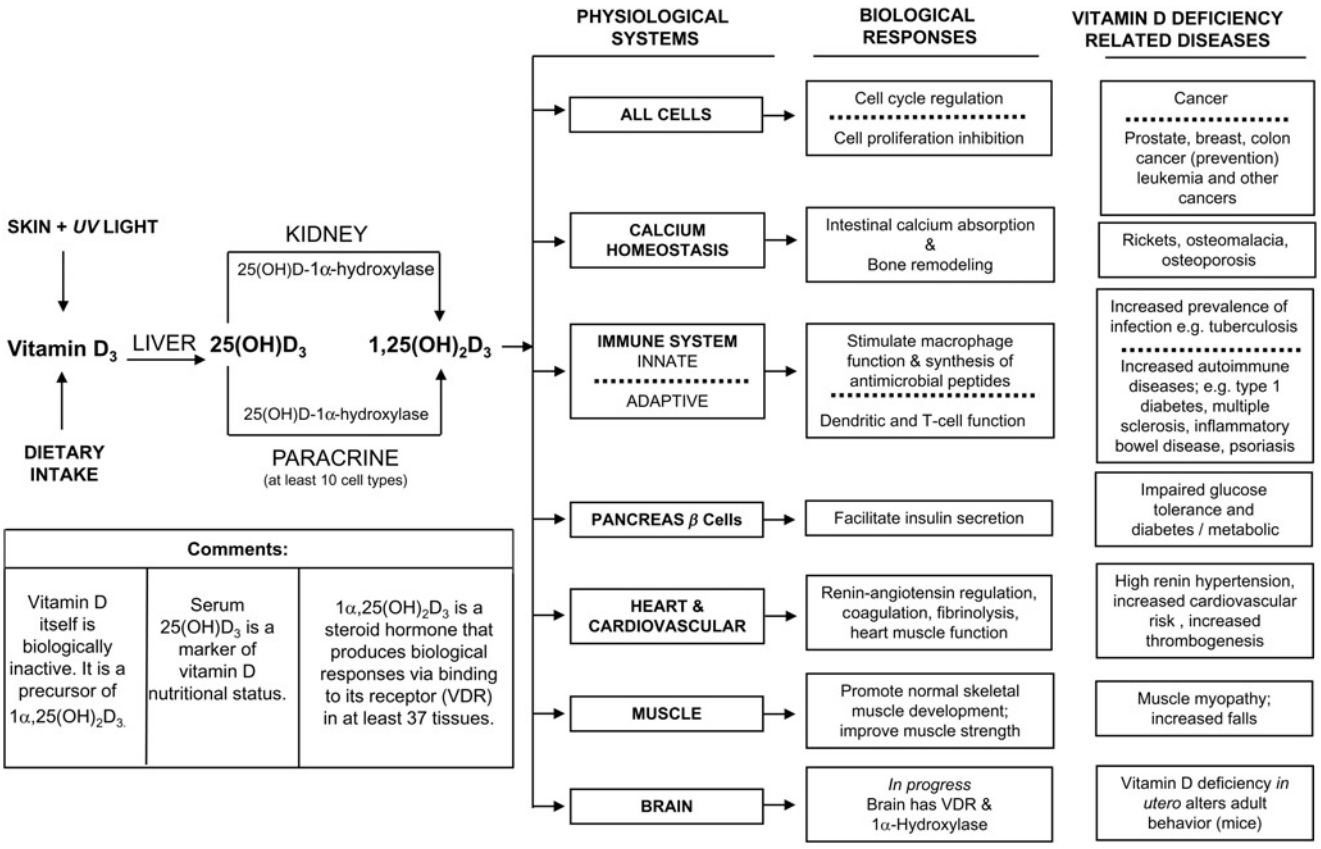

Figure 3 Contribution of vitamin D to good health. The three columns on the right side, respectively, indicate the following: physiological systems (the six physiological systems that the essential nutrient vitamin D_3 supports by its metabolism to 25(OH)D_3 and 1α,25(OH)$_2D_3$); biological responses (examples of biological responses generated by 1α,25(OH)$_2D_3$ in the six physiological systems); and vitamin D-deficient related diseases (identifies for each system some of the disease states that are associated with an inadequate vitamin D nutritional status)

tuberculosis, chronic inflammation). Also, transgenic animals with excessive endogenous 1α,25(OH)$_2D_3$ 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[34] and lifeguards[35,36] who had high daily exposure to UV and the consequent epidermal production of vitamin D_3, 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).[37] 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 D_3 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,[2,3] 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 D_3 or indirect supply by vitamin D_3 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

Table 3 VDR + 1α,25(OH)$_2$D$_3$-responsive physiological systems that in circumstances of human vitamin D nutritional deficiency or in VDR-KO mice result in the appearance of diseases

VDR + 1α,25(OH)$_2$D$_3$ physiological systems	Biological responses	Vitamin D deficiency-associated diseases in the human	Data from vitamin D deficiency (references)	VDR-KO mouse data (references)
All cells	Cell cycle regulation Cell proliferation inhibition	Cancer Prostate, colon and breast cancer (prevention) Leukemia and other cancers (treatment)	71–74 80–83	75–79
Intestine	Calcium absorption	Rickets, osteomalacia and osteoporosis	13, 84, 85	17*
Bone	Bone remodeling		86	
Immune system				
Innate	Stimulate phagocyte functions and synthesis of anti microbial peptides	Increased prevalence of infection, e.g. of tuberculosis	87, 88	89, 90†
Autoimmune	Dendritic and T-cell function	Increased autoimmune diseases: e.g. type-1 diabetes, multiple sclerosis, inflammatory bowel disease, psoriasis	45, 91	
Pancreas β-cells	Facilitate insulin secretion	Impaired glucose tolerance and type-II diabetes/metabolic syndrome	92, 93 56, 94, 95	75, 77, 89, 90
Heart and Cardiovascular	Renin–angiotensin regulation, coagulation, fibrinolysis, heart muscle functioning	High renin hypertension, increased cardiovascular risk, increased thrombogenesis	71, 96 51–53, 97, 98	48, 79‡ 49
Muscle	Promote normal skeletal muscle development; improve muscle strength	Muscle myopathy; increased risk of falls	99–101	99
Brain¶	In progress The brain has the VDR and 25(OH)D$_3$-1α-hydroxylase	Vitamin D deficiency *in utero* alters adult behavior in mice and man	102 103–106	75, 77, 107–109

VDR, vitamin D receptor; 1α,25(OH)$_2$D$_3$, 1α,25-dihydroxyvitamin D$_3$; 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 D$_3$ are lacking (due either to shortage of UVB exposure or adequate dietary intake). This condition will result in low levels of 25(OH)D$_3$ in the circulatory system. As a consequence, inadequate amounts of the steroid hormone 1α,25(OH)$_2$D$_3$ will be produced by the kidney 25(OH)D$_3$-1α-hydroxylases and the various paracrine 25(OH)D$_3$-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$_3$ 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)$_2$D$_3$-mediated biological responses, and generates unexpected physiological changes which occurred that would not have been predicted if vitamin D, acting through 1α,25(OH)$_2$D$_3$ and the VDR only, worked on the intestine and bone (calcium homeostasis). Some of the more surprising discoveries are described immediately below

*The VDR-KO mouse displays alopecia (no hair),[89,110] 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.[89,111] Also, the bone and cartilage growth plate abnormalities, as well as the skin phenotype (alopecia) of VDR-KO animals on a low calcium diet, are identical to the phenotype of children with either inactivating mutations of VDR[112,113] or the enzyme, which produces 1α,25(OH)$_2$D$_3$ (the 25(OH)D$_3$-1α-hydroxylase)[113–116]

†Vitamin D-deficient or VDR-KO mice are also more prone to autoimmune diseases such as inflammatory bowel disease[117] or type-1 diabetes,[77,89,118] and develop hypoinsulinemic hyperglycemia, increased thrombogenicity[49,117] and decreased fibrinolysis, delayed muscle maturation[99] and mild motoric and behavioral abnormalities[107,108]

‡VDR-KO mice display cardiac hypertrophy, which reflects the role of the systemic and cardiac renin–angiotensin systems[48,79]

¶It is the view of the authors that the understanding of the responsibilities and effects of 1α,25(OH)$_2$D$_3$ and the VDR in the brain are still not fully developed. There are no common themes and virtually no papers discussing effects at the molecular level. Clearly, the brain represents a complex and challenging system

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)$_2$D can induce cell differentiation, inhibit cell proliferation or activate cell apoptosis (cell death);[38] these actions are now known to be due to a coherent involvement of at least 50 genes involved in cell cycle regulation.[15] 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.[39] 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

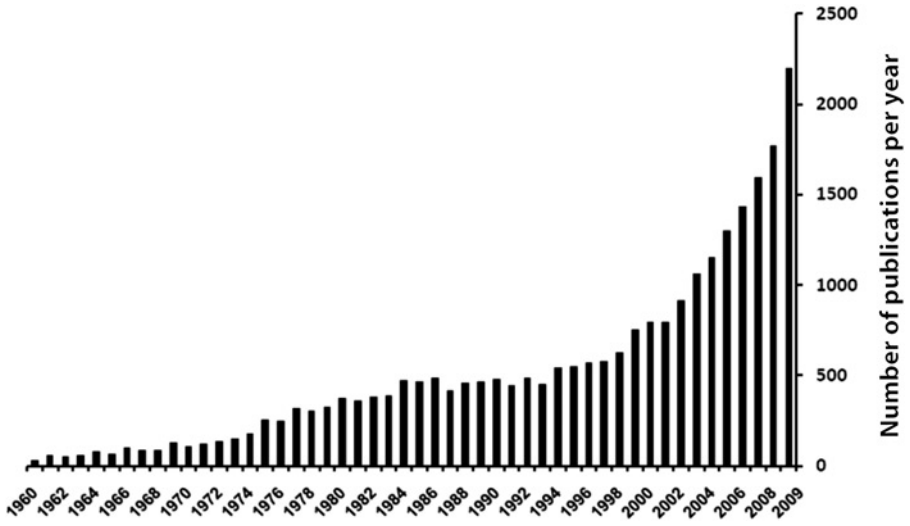

Figure 4 Rate of growth of the number of peer-reviewed publications published each year, which have the term 'vitamin D' in their 'title' or 'abstract' as reported by PubMed. PubMed currently lists over 25,000 publications that use the term 'vitamin D' in either the title or abstract from 1950 to the 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' (>1900), '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 1α,25(OH)$_2$D$_3$) 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 1α,25(OH)$_2$D. 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*

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

*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)D$_3$ and 25(OH)D$_2$ 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)D$_3$ and 25(OH)D$_2$ 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 D$_3$ into 25(OH)D$_3$ by the liver vitamin D-25-hydroxylase is not regulated and thus the serum concentration of 25(OH)D$_3$ is believed to be an accurate 'reporter' of both cutaneous UV-stimulated synthesis and dietary intake of vitamin D$_3$; 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$_3$ <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

‡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 deficiency' and the border-line level associated with 'vitamin D sufficiency (either >20 or >30 ng/mL as described in footnote ¶)

¶As described in the main text under 'Policy challenges', there are at least two quite distinct proposals as to what is the minimum serum level of 25(OH)D to be classified as 'vitamin D sufficient'; they are either >20 or >30 ng/mL

#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

**Three examples are given for 'safe' levels of 25(OH)D that are higher than the 'sufficient levels' of 25(OH)D of footnote ¶. The first report is a cohort of 26 healthy summer workers in Omaha, NB; their group mean 25(OH)D was 49 ng/mL.[34] The second entry is for beach life guards in the summer time in St Louis, MO and Israel, respectively.[62,121] In both the worker and lifeguard studies, their daily exposure to sunlight was such that their 25(OH)D levels were well above the physiological ranges of either >20 or >30 ng/mL defined in footnote ¶, and clearly below levels that were correlated with overt toxicity, footnote ††

††One example is provided for a flagrant instance of vitamin D toxicity[37] with extreme hypercalcemia that resulted from daily consumption of drinking milk that was inappropriately fortified with 5.7 mg of vitamin D$_3$ per liter or 230,000 IU/L

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.[38,40] Additional studies showed that individuals with low serum levels of 25(OH)D (<20 ng/mL) experienced a higher incidence of cancer.[41,42] 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.[42] 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.[43] A very extensive critical analysis of the epidemiological data on vitamin D and cancer by the World Health Organization[44] 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$(OH)_2$D 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$(OH)_2$D at sites of possible cancer development may be higher than expected from its serum concentration. Use of 1α,25$(OH)_2$D or its less calcemic analogs[7] to prevent or treat cancers is further substantiated by several animal models of cancer.[15]

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).[15] Several retrospective studies have shown that vitamin D supplementation early in life reduces the subsequent risk of autoimmune type-1 diabetes later in life.[45,46] 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.[47]

Metabolism, cardiovascular risk and vitamin D

Vitamin D-deficient or -resistant rodents develop high renin hypertension and eventually develop cardiac hypertrophy.[48] VDR null mice also have an increased risk for thrombosis and 1α,25$(OH)_2D_3$ has favorable effects on the endothelial cell function.[49] Observational studies in humans also link poor vitamin D status with hypertension in Caucasians, Hispanics and Afro-Americans,[50] and small-scale studies showed beneficial effects on blood pressure. Several recent reviews on vitamin D deficiency and cardiovascular disease have appeared[51–53] 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[54] and VDR null mice have decreased fat mass and are resistant to diet-induced obesity.[55] Even other aspects of the metabolic syndrome apart from hypertension and obesity are associated with a poor vitamin D status,[56] such as impaired insulin secretion and increased insulin resistance.[46,56,57]

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$(OH)_2D_3$-deficient adults can develop severe muscle weakness, which respond well to 1α,25$(OH)_2D_3$ 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%.[21]

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[18] and in patients with chronic renal failure.[58,59] 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.[60]

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.[1]

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 countries' 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 minimorum* 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 $25(OH)D_3$ 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/mL[63] would be increased so that most subjects would reach minimal values of 20 ng/mL. Thus, in this option, the vitamin D_3 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 RCTs[64] 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 supplement of 2000 IU of vitamin D_3 can increase mean $25(OH)D_3$ 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,[28] 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 supplement 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, $1\alpha,25(OH)_2D$, 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.

Author contributions: The vitamin D nutritional policies proposed in this paper were the outcome of several lengthy discussions by the two authors over ~18 months. Both authors contributed equally to preparing the original outline and in writing the first draft of the text, as well as in finalizing the manuscript for submission.

ACKNOWLEDGEMENTS

The authors thank Professor Helen Henry for extensive proofreading of the manuscript. AWN acknowledges

financial support from the National Institutes of Health, RO1-DK-09012, for 42 y.

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