Vitamin D and inflammation

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ABSTRACT

The discovery that most body cells and tissues have vitamin D receptors and that some of them have the enzymatic machinery to convert the circulating form of vitamin D (25-hydroxyvitamin D) into the active form (1,25- dihydroxyvitamin D/1,25$(OH)_2D_3$) gave a new insight about the function of this vitamin. In the course of time, more and more evidences showed that a low vitamin D level leads to the occurrence or recurrence of cardiovascular diseases, type II diabetes mellitus (DM), cell dedifferentiation (oncogenesis), and immune derangement (autoimmune diseases such as lupus, type I DM, rheumatoid arthritis, and multiple sclerosis). Most researchers have agreed that a minimum 25$(OH)D_3$ serum level of about 30 ng/ml or more is necessary for favorable calcium absorption and good health. Until proven otherwise, the balance of the research clearly indicates that oral supplementation in the range of 1,000 IU/day for infants, 2,000 IU/day for children, and 4,000 IU/day for adults is safe and reasonable to meet physiologic requirements, to promote optimal health, and to reduce the risk of several serious diseases.

Most people assume that once food is already enriched with vitamin D and rickets is already managed, the main health problems resulting from vitamin D deficiency is solved. However, rickets can be considered the tip of the iceberg for vitamin D deficiency. The discovery that most body cells and tissues have vitamin D receptors (VDR) and that some of them have the enzymatic machinery to convert the circulating form of vitamin D (25-hydroxyvitamin D) into the active form (1,25-dihydroxyvitamin D/1,25$(OH)_2D_3$) gave a new insight about the function of this vitamin. What is most interesting is the role it can play in reducing the risk of many chronic illnesses such as cancer, autoimmune diseases, infectious diseases, and cardiovascular diseases.[1]

Vitamin D deficiency can cause metabolic disorder of the bones (osteoporosis and osteomalacia) and muscle weakness (resulting in increased risk of falling).[1,2] Prevention against the two above is known as the traditional function of vitamin D. In the course of time, more and more evidences showed that a low vitamin D level leads to the occurrence or recurrence of cardiovascular diseases, type II diabetes mellitus (DM), cell dedifferentiation (oncogenesis), and immune derangement (autoimmune diseases such as lupus, type I DM, rheumatoid arthritis (RA), and multiple sclerosis (MS)).[1,3,4] Many studies have revealed the non-traditional function of vitamin D. The significance of this non- traditional function was revealed when it was known that besides kidney cells, other cells can produce the active form of vitamin D for their own needs. In these cells, the active form of vitamin D acts as gene expression regulator.[2] The most convincing evidence of the many vitamin D actions came from reports that correlate vitamin D deficiency with higher risk of death - from any cause - through unknown mechanism.[5]

The study of the association of vitamin D status with various diseases requires the measurement of 25$(OH)D_3$ status because it is the most accurate measurement of vitamin D status.[1,3,6] One of the studies showed that the 25$(OH)D_3$ status was inversely related to TNFα level in healthy women so that it explains part of the role of this vitamin in the prevention and treatment of inflammatory diseases.[2]

PHYSIOLOGY OF VITAMIN D

Vitamin D is naturally obtained from two sources: sunlight and dietary consumption.[1,2,7-9] Vitamin D3 (cholecalciferol) is a form of vitamin D that is synthesized in the skin and is also found in the diet. Vitamin D2 (ergocalciferol) that is derived by irradiation of fungi is much less efficient as a precursor of active vitamin D (calcitriol).[7]

Vitamin D has two metabolic pathways: endocrine and autocrine (intracellular) and possibly paracrine (around the cell).[7] This view that has been recently reviewed by Heany is very important because it can expand our understanding about the concept of vitamin D from "bone nutrient that is important only for preventing rickets and osteomalacia" to "an amazing molecule that has a broad effect on various cells and tissues". Furthermore, Heany's differentiation between "short-latency deficiency diseases" such as rickets and "long-latency deficiency diseases" such as cancer can be used as a basis to understand the difference between acute manifestation of severe nutritional deficiency and slow manifestation of chronic subclinical nutritional deficiency.[10]

Vitamin D3 is synthesized in the skin from the precursor (7-dehydrocholesterol) after exposure to sunlight. Dark skin and elderly skin are not that effective in synthesizing vitamin D. Also,

that are known to contain 1-OHase and hence can produce their own calcitriol are cells of the breast, prostate, lung, skin, lymph nodes, colon, pancreas, medulla of the adrenal and brain.[7,13] As there are a lot of cells and tissues being able to metabolize vitamin D, it is not surprising that vitamin D is also involved in the functions of the above cells and we can understand the biological potential of vitamin D in affecting the function and pathophysiology of various metabolic processes and diseases. Calcitriol is known to modulate the transcription of several genes, modulate neurotransmitter/ neurological function as can be seen from the effect of antidepressants[7] and anticonvulsants.[14]

Vitamin D has evidently an immunoregulating property as seen from its ability to reduce inflammation.[6,7] suppress and/ or prevent certain autoimmune diseases, reduce cancer risk, and possibly reduce the severity and frequency of infectious diseases such as acute pneumonia in children.[7] Researchers in Belgium have shown that vitamin D lowers CRP and IL-6 levels in critically ill patients. Another researcher showed that vitamin D deficiency is associated with increased risk of inflammation in otherwise healthy people. Furthermore, increased inflammation will increase the risk of chronic inflammatory conditions such as coronary heart disease and DM.[6]

Generally, vitamins play a role in the immune system either in innate or adaptive immunity. Although some vitamins such as vitamin C and E and some vitamins of the vitamin B complex play a role in the immune system non-specifically (for example, as antioxidant), some other vitamins such as vitamin A and D can affect the immune response in highly specific ways. Vitamin D is obviously different from other vitamins (except for vitamin A) in which its bioactive metabolite has hormone-like properties. The active metabolite of vitamin D – $1,25(OH)_2D_3$ – is synthesized from its precursor by various cells and tissues of the body and stimulate its effect on distant target cells by binding to the nuclear-hormone receptors.[8]

Most autoimmune diseases are found in people who have a genetic predisposition to such disease if exposed to unfavourable conditions such as virus or altered nutritional factors. A classical example is the increase in autoimmune thyroiditis incidence after consumption of iodine supplements in an iodine deficient population. Recently, vitamin D deficiency has been implicated as a trigger factor in autoimmune diseases such type I DM, inflammatory bowel disease (IBD), and MS. Vitamin D modulates the differentiation of T cells towards Th2 phenotype, inhibits the development of Th1 and could result in predisposition to various autoimmune diseases. Epidemiology studies support the association between vitamin D deficiency and the seasonal pattern in the onset of type I DM, IBD, and MS.[15]

Calcitriol may possibly mediate the immune effect by attaching to the nuclear VDR of almost all immune cells and thereafter increase the defensive gene expression.[2] Vitamin D insufficiency may also disturb the development of T cell regulator and increase the risk of autoimmune disease such as MS and type I DM. The evidence of this effect is that the further the region is from the equator, the higher is the prevalence of MS suggesting that the population with lower vitamin D uses of sunscreen inhibit the UV light needed for vitamin D3 synthesis.[9] The synthesized vitamin D3 is then carried by the blood circulation to the liver where vitamin D is converted to $25(OH)D_3$ (calcidiol) by vitamin D-25-hydroxylase enzyme.[7] Next, $25(OH)D_3$ will travel through the blood circulation to enter the kidney and undergo its final transformation to become $1,25(OH)_2D_3$ (calcitriol) by 25-hydroxy vitamin D3-1-alpha-hydroxylase (1-OHase)/(CYP27B[1]). Calcitriol is the active form of vitamin D that increases the absorption of calcium and phosphate in the intestine, induces osteoclast maturation for bone remodelling, promotes calcium deposition in bone and a reduction in parathyroid hormone level (PTH).[7]

Calcitriol is a prohormone. Calcitriol is bound to a cytoplasmic receptor. Then the calcitriol/receptor complex is transported to and into the nucleus of the cell. Next, this hormone complex acts as a transcription factor by binding to the specific control elements of the genes and controlling gene expression. Hence, the amount of calcitriol/receptor complex determines the presence of calcium transporter proteins on the surface of the kidney or intestinal epithelial cells and the amount of calcium loaded into the serum. Because calcitriol is synthesized in the kidney, calcium reuptake by the kidney is directly correlated with calcitriol production. If the level of serum calcium is not adequate, the level of calcium in the kidney cells that synthesize calcitriol will also be lower and this will increase the activity of calcitriol/receptor complex. This must be adequate to produce sufficient calcitriol in the serum to increase the calcium uptake in the intestine. If the calcium level is still not adequate, the parathyroid gland will secrete PTH that stimulates both more calcitriol production and release calcium from the bones. Prolonged calcium release from the bones will result in osteoporosis.[11] In other words, calcitriol regulates the distribution of calcium supplied from the diet, serum, and bones. The level of calcium must remain constant so that the basic cell processes such as signalling and secretion are not disturbed. A decrease in serum calcium level will decrease nerve and muscle functions.[11]

Without vitamin D, only 10 to 15% of dietary calcium and about 60% of phosphorus is absorbed. The interaction of $1,25(OH)_2D_3$ with the vitamin D receptor increases the efficiency of intestinal calcium absorption to 30 to 40% and phosphorus absorption to approximately 80%.[1]

While increased calcium absorption is clearly important from the nutritional aspect, suppression of PTH by vitamin D is also important from the clinical aspect because a relatively low PTH level appear to promote and protect health. A higher PTH level is correlated with increased risk of myocardial infarction, stroke, and hypertension.[7] In line with the above, Fujita proposed "calcium paradox" in which calcium or vitamin D deficiency will result in an increase in PTH level that will increase intracellular calcium so that it will facilitate a cascade of cellular dysfunction that play a role in the development of DM, neurological diseases, malignancy, and degenerative joint diseases.[12]

In the autocrine pathway, $25(OH)D_3$ is taken up by various cells that contain both 1-OHase and nuclear VDR. Therefore, these cells can produce their own calcitriol without being dependent on the hematogenous supply. Cells and tissues

levels has a higher risk of suffering from this disease. Recent studies also showed that higher blood vitamin D levels can reduce the risk of MS.[16]

The discovery of vitamin D receptor in tissues other than in the intestinal and bone tissues - mainly in the brain, breast, prostate, and lymphocyte- and the latest research suggesting that higher level of vitamin D protects a person from diseases such as DM, osteoporosis, osteoarthritis, hypertension, cardiovascular disease, metabolic syndrome, depression, some autoimmune diseases and breast cancer, prostate, and colon enable us today to use vitamin D for a wider range of preventive and curative measures to maintain and improve the health of our patients.[7]

The immune system has evolved to protect us from micro organisms that cause diseases. To do this, the immune system must be able to distinguish between the self tissue and that of non-self. Sometimes the process of distinguishing is disturbed, so that an autoimmune disease occurs in which the immune system attacks the self tissue. In autoimmune diseases, the peripheral T cells attack the target tissue such as the central nervous system (MS), intestine (IBD), joint (arthritis), and pancreas (type I DM). The similarity among these diseases is that the T cells-mainly Th1-control the pathology of disease. The Th1 cell mediated autoimmune disease is characterized by T cells that express TNF-α and IF-γ that are located in the self tissue and induce inflammation in that particular location (intestine, CNS, etc). Generally, if treatment of Th1-mediated autoimmune disease succeeds, it is because of suppression of the number of Th1 cells and/or cytokine (especially TNF-α) produced. In addition, successful treatment of a Th1 driven disease may also be successful in treatment of other Th1 driven autoimmune diseases.[9]

The cause of autoimmune disease is not known. The complex interactions between genes and the environment determine which individual will suffer certain autoimmune disease. Vitamin D may possibly be one of environmental factors that play a role in the development of autoimmune diseases. Autoimmune diseases such as MS and IBD occur because of attacks on the self tissue. Gene analysis of identical twins showed that besides genetic factors, the environment is also an important factor in the occurrence of MS and IBD. The supply of vitamin D from sunlight exposure or diet may play a role in the occurrence of MS and IBD. Convincing data of laboratory animals showed that vitamin D and signalling by VDR determine the results of the experimental MS and IBD. Furthermore, the evidences showed that vitamin D regulates either directly or indirectly the development and function of T cells. Because of the absence of both vitamin D and signal carried by VDR, the autoreactive T cell will develop. With the presence of $1,25(OH)_2D_3$ and functional VDR, the balance of T cell response returns to normal and autoimmunity is avoided.[9]

CLINICAL IMPORTANCE OF VITAMIN D

Although there is no consensus on optimal levels of $25(OH)D_3$ as measured in serum, vitamin D deficiency is defined by most experts as a $25(OH)D_3$ level of less than 20 ng/ml (50 nmol/l). A level of $25(OH)D_3$ of 21 to 29 ng/ml (52 to 72 nmol/l) can be considered to indicate a relative insufficiency of vitamin D, and a level of 30 ng/ml or greater can be considered to indicate sufficient vitamin D.[1] While a universal consensus is lacking, most researchers have agreed that a minimum $25(OH)D_3$ serum level of about 30 ng/ml or more is necessary for favorable calcium absorption and good health.[17] Vitamin D intoxication is observed when serum levels of $25(OH)D_3$ are greater than 150 ng/ml (374 nmol/l).[1]

Risk factors for vitamin D deficiency in otherwise healthy persons include darker-skinned individuals, the obese, the elderly, and those living in northern or southern latitudes greater than 42 degrees. Numerous factors in modern society also may contribute to the problem, including the popularity of non-dairy beverage consumption, diets devoid of the relatively few foods rich in vitamin D, lifestyles of work or leisure spent predominantly indoors, and concerns about sun exposure with the attendant use of lotions that completely block UVB radiation.[17]

The council of vitamin D makes the statement that current research has demonstrated that vitamin D deficiency is a major factor in the pathology of at least 17 types of cancer besides other diseases such as coronary disease, stroke, hypertension, autoimmune disease, DM, depression, chronic pain, osteoarthritis, osteoporosis, muscle weakness, muscle wasting, congenital defect, periodontal disease, etc.[11]

Vasquez et al in their paper stated that although the data is yet to be perfected, administration of vitamin D is seen to give significant benefits in many human diseases such as cardiovascular diseases, hypertension, type II DM, osteoarthritis**,** MS, type I DM prevention, depression, epilepsy, migraine, polycystic ovarian syndrome, musculoskeletal pain, critical illness, autoimmune/ inflammatory condition and cancer prevention/ treatment.[7]

Autoimmune diseases

Living at higher latitudes increases the risk of type 1 DM, MS, and Crohn's disease. Among white men and women, the risk of MS decreased by 41% for every increase of 20 ng/ml in $25(OH)D_3$ above approximately 24 ng/ml (60 nmol/l) (odds ratio, 0.59; 95% CI, 0.36 to 0.97; P = 0.04). Women who ingested more than 400 IU of vitamin D per day had a 42% reduced risk of developing MS. Several studies suggest that vitamin D supplementation in children reduces the risk of type 1 DM. Increasing vitamin D intake during pregnancy reduces the development of islet autoantibodies in offspring.[1]

In another study, vitamin D deficiency increased insulin resistance, decreased insulin production, and was associated with the metabolic syndrome. Another study showed that a combined daily intake of 1200 mg of calcium and 800 IU of vitamin D lowered the risk of type 2 DM by 33% (relative risk, 0.67; 95% CI, 0.49 to 0.90) as compared with a daily intake of less than 600 mg of calcium and less than 400 IU of vitamin D.[1]

Osteoporosis and fracture

Approximately 33% of women 60 to 70 years of age and 66% of those 80 years of age or older have osteoporosis. It is estimated that 47% of women and 22% of men 50 years of age

or older will sustain an osteoporotic fracture in their remaining lifetime. One study reported that among 3270 elderly French women given 1200 mg of calcium and 800 IU of vitamin D3 daily for 3 years, the risk of hip fracture was reduced by 43%, and the risk of nonvertebral fracture by 32%.[18] A 58% reduction in nonvertebral fractures was observed in 389 men and women over the age of 65 years who were receiving 700 IU of vitamin D3 and 500 mg of calcium per day. In studies using doses of 700 to 800 IU of vitamin D3 per day, the relative risk of hip fracture was reduced by 26% (pooled relative risk, 0.74; 95% CI, 0.61 to 0.88), and the relative risk of nonvertebral fracture by 23% (pooled relative risk, 0.77; 95% CI, 0.68 to 0.87) with vitamin D3 as compared with calcium or placebo.[1]

Muscle strength and falls

Vitamin D deficiency causes muscle weakness.[1,2,7,17,19] Skeletal muscles have a VDR and may require vitamin D for maximum function. Performance speed and proximal muscle strength were markedly improved when $25(OH)D_3$ levels increased from 4 to 16 ng/ml (10 to 40 nmol/l) and continued to improve as the levels increased to more than 40 ng/ml (100 nmol/l). A metaanalysis of five randomized clinical trials (with a total of 1237 subjects) revealed that increased vitamin D intake reduced the risk of falls by 22% (pooled corrected odds ratio, 0.78; 95% CI, 0.64 to 0.92) as compared with only calcium or placebo.[1]

Cancer

Brain, prostate, breast, and colon tissues, among others, as well as immune cells have a VDR and respond to $1,25(OH)_2D_3$, the active form of vitamin D. In addition, some of these tissues and cells express the enzyme 25-hydroxyvitamin D-1α-hydroxylase. Directly or indirectly, $1,25(OH)_2D_3$ controls more than 200 genes, including genes responsible for the regulation of cellular proliferation, differentiation, apoptosis, and angiogenesis. It decreases cellular proliferation of both normal cells and cancer cells and induces their terminal differentiation. One practical application is the use of $1,25(OH)_2D_3$ and its active analogues for the treatment of psoriasis. $1,25(OH)_2D_3$ is also a potent immunomodulator[1,6,7].

People living at higher latitudes are at increased risk for Hodgkin's lymphoma as well as colon, pancreatic, prostate, ovarian, breast, and other cancers and are more likely to die from these cancers, as compared with people living at lower latitudes. Both prospective and retrospective epidemiologic studies indicate that levels of $25(OH)D_3$ below 20 ng/ml are associated with a 30 to 50% increased risk of incident colon, prostate, and breast cancer, along with higher mortality from these cancers. An analysis from the Nurses' Health Study cohort (32,826 subjects) showed that the odds ratios for colorectal cancer were inversely associated with median serum levels of $25(OH)D_3$ (the odds ratio at 16.2 ng/ml [40.4 nmol/l] was 1.0, and the odds ratio at 39.9 ng/ml [99.6 nmol/l] was 0.53; $P \leq 0.01$). Serum $1,25(OH)_2D_3$ levels were not associated with colorectal cancer.[1]

Osteoarthritis

Vitamin C and D have been hypothesized to be beneficial for osteoarthritis patients. Patients with hip and knee osteoarthritis show low vitamin D levels.[20] Hypovitaminosis D is already an established risk factor for fracture in OA patients. It has been proven that higher intake of vitamin D is associated with a lower risk of osteoarthritis in elder women (55-69 years old).[21]

Cardiovascular Disease

Living at higher latitudes increases the risk of hypertension and cardiovascular disease. In a study of patients with hypertension who were exposed to ultraviolet B radiation three times a week for 3 months, 25(OH)D levels increased by approximately 180%, and blood pressure became normal (both systolic and diastolic blood pressure reduced by 6 mmHg). Vitamin D deficiency is associated with congestive heart failure and blood levels of inflammatory factors, including C-reactive protein and interleukin-10.[1]

A prospective study involving 3258 individuals found that the low levels of $25(OH)D_3$ and $1,25(OH)_2D_3$ were independently associated with cardiovascular mortality and all-cause mortality. In spite of that, an interventional study with vitamin D is needed to determine whether or not there is a causal association between the two.[5]

Schizophrenia, depression, and cognitive performance

Vitamin D deficiency has been linked to an increased incidence of schizophrenia and depression. Maintaining vitamin D sufficiency in utero and during early life, to satisfy the VDR transcriptional activity in the brain, may be important for brain development as well as for maintenance of mental function later in life.[1] Cross-sectional studies in older adults show vitamin D deficiency is associated with low mood and worsened cognitive performance, as well as greater severity of dementia.[2]

VITAMIN D AND INFLAMMATION

As reported above, the classical function of vitamin D is to regulate the homeostasis of calcium and thereby the formation and absorption of bones.[9] The discovery of VDR in the peripheral blood mononuclear cell has raised the interest in the study of vitamin D as an immune system regulator.[22,23] This vitamin D receptor is expressed in the peripheral blood monocytes, macrophages, dendritic cells, leukocytes, and activated $CD4^+$ and $CD8^+$ T cells so that vitamin D deficiency can have a very broad effect on the immune response.[15] A further study did show that the active form of vitamin D evidently affected the immune response.[9,24]

This immunomodulation activity occurs through nuclear VDR that is expressed in the APC and the activated T cell. This regulation is mediated through interference with nuclear transcription factors such as NF-AT and NF-κB or through direct interaction with vitamin D responsive elements in the promoter regions of cytokine genes. The dendritic cells are the main target of $1,25(OH)_2D_3$ immunomodulator activity that can be seen from the inhibition in the differentiation and maturation of dendritic cells leading to down regulated expression of MHC-II, costimulatory molecules and IL-12. Moreover, $1,25(OH)_2D_3$ increases IL-10 production and promotes apoptosis of dendritic cells. Together, these effects

of $1,25(OH)_2D_3$ inhibit DC-dependent T cell activation. Immunomodulation by $1,25(OH)_2D_3$ and its analog in vivo have been demonstrated in various models of autoimmune disease and transplantations. In addition, the combination of analog and other immunosuppressants results in synergism in models of autoimmune and transplantation. The availability of $1,25(OH)_2D_3$ analog with immunomodulator activity in non-hypercalcemic dose makes it possible to take advantage of this immunomodulator effect in a clinical setting of treatment of autoimmune diseases and prevention of allograft rejection.[24] $1,25(OH)_2D_3$ that mediates its action through vitamin D receptor has been reported to inhibit the Th1 helper cells proliferation and cytokine secretion such as IL-2 and gamma interferon (IF-γ). Vitamin D enhances IL-4 response because of its stimulatory effect on Th2 cells.[15]

The antiinflamatory properties of vitamin D has been proven in laboratory animals.[17] Recent clinical studies showed that vitamin D supplement modulates or lowers proinflammatory cytokines (for example: CRP, IL-6, IL-12, and TNF-α) while increasing antiinflammatory cytokines (for example, IL-10). Furthermore, researchers suggest that vitamin D can be used as an adjuvant therapy in moderate painful chronic inflammatory autoimmune conditions caused by excessive cytokine activity such as IBD and Crohn's disease. As a result, vitamin D might reduce musculoskeletal pain caused by or associated with the inflammatory process, but this needs further study.[17] Another researcher showed that vitamin D can reduce the susceptibility to gingival inflammation through its anti-inflammatory effect.[25]

Obesity becomes a problem because of the property of vitamin D that dissolves in fat. Vitamin D is transported to the fat cell the way it is transported to the liver. Therefore, there is a balance between vitamin D stored in the fat droplet in the fat cell and vitamin D stored in the liver. Unfortunately the capacity of the fat cell is quite larger than that in the liver. Hence, large amounts of vitamin D are needed to saturate the fat storage in the obese person although there is always vitamin D deficiency in each meal. This is one of the reasons why most degenerative and autoimmune diseases increase in prevalence in obese people.[11] Sun et al found that calcium diet can decrease inflammatory stress or oxidative stress associated with obesity in mice. They also showed that calcitriol regulates local inflammation by modulating the interaction between adipocytes and macrophages as well as regulating the inflammatory cytokine production in each type of cell through the calcium-dependent and mitochondrial uncoupling dependent mechanisms.[26]

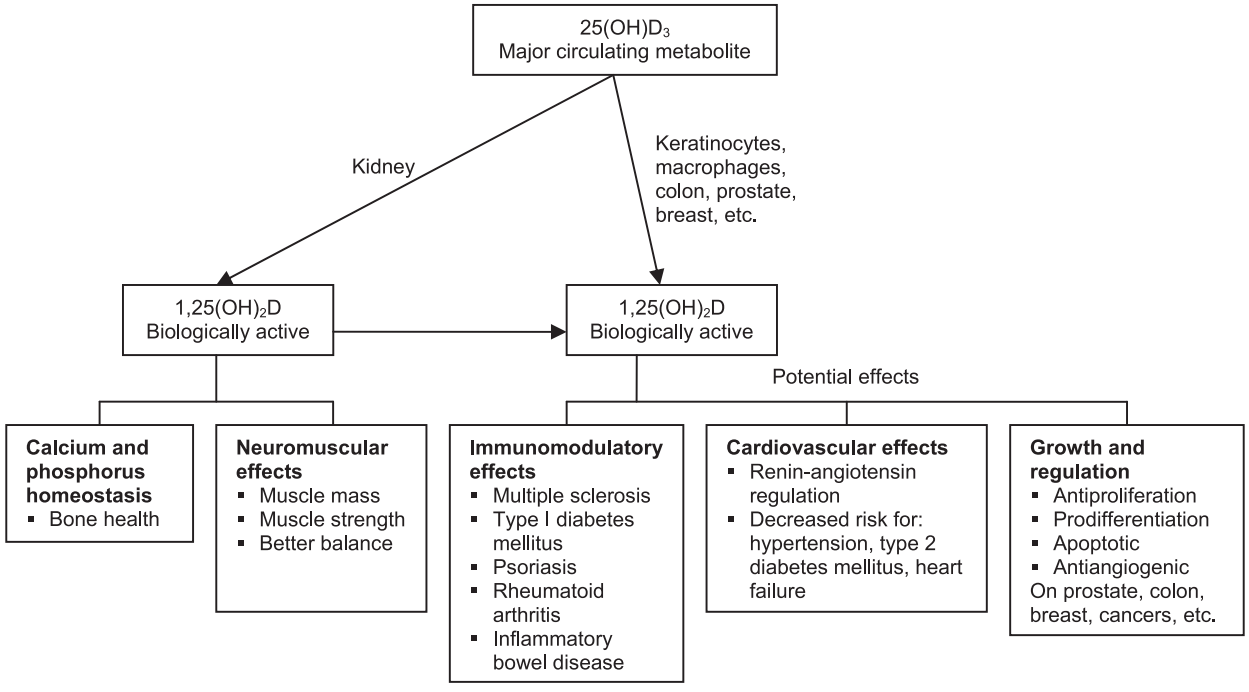

Figure 1 Potential effects of vitamin D (adapted from Rothenberg R, 2008)[27]

VITAMIN D THERAPY

It is clear that before starting vitamin D therapy we have to make sure that there is vitamin D deficiency (this term is preferred to hypovitaminosis D). Researchers have stressed that the "gold standard" for a presumptive diagnosis of inadequate vitamin D is a review of patient history, lifestyle, and dietary habits that might pose risks for deficiency, along with the recognition of signs/symptoms that could indicate defects in bone metabolism.[28] This clinical examination would occur prior to laboratory assessments of serum $25(OH)D_3$ or measurements of other biochemical markers.[17]

Clinical suspicion based upon history and an awareness of risk factors should remain the gold standard for requesting serum vitamin D measurements. Inadequate sunlight exposure (through veiling and poor outdoor exposure) and poor dietary intake are highly prevalent features of vitamin D deficiency in severely affected patients. Routine measurements of calcium, phosphate, and alkaline phosphatase are not reliable predictors of vitamin D deficiency, even when vitamin D insufficiency has been sufficient to produce a PTH response.[28] Diagnosis can also be suspected based on symptoms and signs of rickets, osteomalacia, or neonatal tetany and characteristic bone changes seen on X-ray.[29] The diagnosis is then verified by measuring the $25(OH)D_3$ status because it is the most accurate measurement of vitamin D status.[1,3,6]

Adequate sunlight exposure remains the simplest effective way to maintain levels of vitamin D. Exposure of around 15% of body surface (that is, the hands, face and arms or legs) to around one-third of a minimal erythemal dose of sunlight (the amount that causes faint redness), most days, is recommended for adequate endogenous vitamin D synthesis. Although sun exposure can be used to treat vitamin D deficiency, this has to be balanced against the risk of skin damage.[8-11,19] A 20 minutes of sun exposure can produce 20,000 IU of vitamin D.[11]

The present Recommended Daily Allowance (RDA) for vitamin D intake is insufficient.[6,7,11] The old RDA of 400 units was only put forward to prevent rickets. It was established long before the appreciation of sun exposure and optimized vitamin D levels. The requirements for vitamin D are far closer to 10 times the current RDA, or 4,000 units.[6] However, the optimal daily intake of vitamin D for health is still being debated, and there are differences of opinion based on available evidence. In 1997, the US Institute of Medicine determined that there was insufficient data to specify a RDA. Instead, the organization developed very conservative Adequate Intake (AI) values of 200 IU to 600 IU per day of vitamin D, based on an assumption as people age they would need extra vitamin D supplementation. According to available evidence, at least 1000 IU/day of vitamin D3 is necessary to maintain adequate serum $25(OH)D_3$ levels at or above 30 ng/ml in healthy person.[17]

The most recent 2005 Dietary Guidelines for Americans from the US government and recommendations from researchers at the Harvard School of Public Health conclude that healthy children and adults of any age should consume no less than 1000 IU/day of vitamin D3 to reach and maintain minimum serum $25(OH)D_3$ levels of at least 30 to 32 ng/ml. There are some concerns about this guidance. The US Agency for Healthcare Research and Quality (AHRQ 2007) concluded: "Given the limitations in the measurement of $25(OH)D_3$ concentrations and the lack of standardization and calibration, it is difficult to suggest precise recommendations for adequate intakes, especially since optimal levels of serum $25(OH)D_3$ have not been defined." Many experts stress that 1,000 IU/day of vitamin D may be inadequate for maintaining health.[17]

Vieth and colleagues (2001) had found that 1,000 IU/day of vitamin D3 was ineffective for achieving optimal $25(OH)D_3$ concentrations. Whereas, 4,000 IU/day of D3 in their study assured more adequate levels >30 ng/ml. In 2004 they demonstrated that 4,000 IU of D3 per day was well tolerated during 15 months of therapy. Concentrations of $25(OH)D_3$ were increased to more optimal levels and parathyroid hormone was reduced, while calcium levels remained normal.[17] Vitamin D supplementation with doses of 4,000 IU/day for adults is clinically safe and physiologically reasonable since such doses are consistent with physiologic requirements. The physiologic requirement for vitamin D in adults may be as high as 5,000 IU/day, which is less than half of the >10,000 IU that can be produced endogenously with full-body sun exposure.[30] Higher doses up to 10,000 IU/day appear safe and produce blood levels of vitamin D that are common in sun-exposed equatorial populations. Periodic assessment of serum $25(OH)D_3$ and serum calcium will help to ensure that vitamin D levels are sufficient and safe for health maintenance and disease prevention. Until proven otherwise, the balance of the research clearly indicates that oral supplementation in the range of 1,000 IU/day for infants, 2,000 IU/day for children, and 4,000 IU/day for adults is safe and reasonable to meet physiologic requirements, to promote optimal health, and to reduce the risk of several serious diseases. Safety and effectiveness of supplementation are assured by periodic monitoring of serum $25(OH)D_3$ and serum calcium.[7]

Oral cholecalciferol may be the most appropriate agent to treat vitamin D deficiency. To be most effective, vitamin D supplements should be administered with adequate amounts of calcium supplements because of a likely combined deficiency. Calcitriol is not considered ideal for treating patients with simple vitamin D deficiency, in part because of the potential risk of hypercalcaemia. A larger dose is probably required for cancer prevention, aiming to maintain levels of serum $25(OH)D_3$ above 75 nmol/l. In patients with a mild to moderate vitamin D deficiency, supplementation with 3,000 to 5,000 IU (75 to 125 μg) per day oral cholecalciferol is recommended (three to five capsules of oral cholecalciferol 1,000 IU per day). At least six weeks of therapy is required to achieve levels of serum $25(OH)D_3$ above 75 nmol/l. In patients with a moderate to severe vitamin D deficiency, higher dosages of vitamin D supplementation (above 5,000 IU per day) are usually required. Higher oral dose formulations (10,000 to 25,000 IU capsules) can be used and are available through local compounding chemists. Cholecalciferol can be administered by intramuscular injection to facilitate compliance in elderly patients.[19] Vitamin D intoxication is extremely rare but can be caused by inadvertent or intentional ingestion of excessively high doses. Doses of more than 50,000 IU per day raise levels of $25(OH)D_3$ to more than 150 ng/ml (374 nmol/l) and are associated with hypercalcemia and hyperphosphatemia.[31]

CONCLUSION

With the discovery of vitamin D receptor in various cells and tissues of the body, we can conclude that vitamin D plays a role in the function of those cells. Therefore, besides the traditional function of its effect on calcium metabolism and muscle function, vitamin D also has other functions that have been demonstrated in many studies. One of the non traditional functions is the role as immunomodulator through the regulation of gene expression that in turn determines its role in the inflammatory process. Adequate sun exposure remains the simplest effective way to maintain levels of vitamin D.

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