Review Article Vitamin D Deficiency, Role in Chronic Diseases

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Abstract— Vitamin D is a sunshine vitamin and is key player in Bone diseases (like Osteoporosis, Osteoarthritis, Rheumatoid Arthritis), Autoimmune diseases, Chronic diseases like Diabetes Mellitus, Hypertension, Cardiovascular Diseases, Metabolic Syndromes and Cystic fibrosis. Calcium, Magnesium and Phosphorus are the key ions whose interplay is closely linked to each other in positive bone metabolism and Vitamin D is the regulator of this process. Northern Hemisphere due to its geographic location and westernized lifestyle has a high prevalence of Vitamin D population, which has further been linked to growing numbers of cancers and autoimmune diseases in this region.

This Review article throws light on Vitamin D and its role in chronic diseases. Based on the aspects discussed in this review the article recommends "PCP's should not overlook the levels of this vital vitamin. In all chronic disease sufferers and old age people, Vitamin D levels should be ascertained and Vitamin D supplementation should be a part of treatment regimen. Vitamin D is a preventive Vitamin in itself".

Index Terms— Vitamin D, Chronic Diseases, T2DM, CF, HTN, RA, Autoimmune disease, Rheumatoid Arthritis, Osteoporosis, Osteoarthritis, Bone disease, Metabolic Syndrome, Cystic fibrosis, Calcium

1. INTRODUCTION

Vitamin D deficiency is common in Northern hemisphere due to latitude exposure of sun is limited and more of indoor lifestyles. Vitamin D is a silent disease and linked to T2DM, CF, HTN, RA and a risk factor for Autoimmune diseases and CVD outcomes. Also Symptoms crop up when the levels lower down significantly. Limited evidences exist on specific guidelines of treatment.

Targeting Vitamin D deficient population and treating them with regular vitamin D status assessment will help in designing treatment strategy for such model population. Vitamin D in its active form, vitamin D3 is the most superior treatment modality in such population.

Vitamin D3 to be superior at raising 25-hydroxy vitamin D (25(OH)D), the best marker for vitamin D status. Calcitriol therapy significantly corrects the levels. Vitamin D deficiency is common and can be corrected with adequate vitamin D supplementation. Correct form and dose of vitamin D to and the mechanism for vitamin D's is the main arena of exploration in diseases where Vitamin D levels are the key player in pathogenesis of the disease. Vitamin D deficiency (defined as 25(OH)D < 20 ng/mL) is of epidemiological importance in United States.

Vitamin D deficiency has found its role as a risk factor in a host of conditions osteoporosis and rheumatoid arthritis, immune function, and autoimmune diseases and cancer. In fact, resolution of deficiency may provide inexpensive prophylaxis in many conditions. However, treatment of vitamin D deficiency is largely overlooked in clinical practice. Lack of awareness amongst PCP’s is at the root of the problem (1). In part, this is because vitamin D requirements may vary by disease and even by person which complicates the development of a treatment protocol. Factors that could judge Vitamin D requirement are still to be explored to get the General recommendation of treatment.

Root causes of vitamin D deficiency attributed to factors like malaabsorption and decreased sun exposure related to decreased outdoor activity (2, 3). In RA, vitamin D deficiency is associated with low bone density, and immune function (4). Therefore, the RA Foundation has recommended actively treating vitamin D deficiency.

Conversely RA is a common chronic condition affecting nearly one-third of the US population (5). The cause of...
Vitamin D deficiency is largely unknown but may be due to decreased dietary intake, decreased sun exposure, and excessive excretion of the vitamin D carrier protein, vitamin D binding protein (DBP). Currently, there is no consensus medical opinion regarding treatment of vitamin-D deficiency in RA even though low vitamin D levels are associated with increased blood pressure, diabetes, and cardiovascular disease (7-10).

Vitamin D: History, Structure, and Function

Vitamin D became a nutrient of note when, at the turn of the twentieth century, Sir Edward Mellanby established that cod liver oil had anti-rachitic activity (11). However, it was McCollum who later determined that a nutrient present in cod liver oil was responsible for its anti-rachitic activity and named this nutrient vitamin D (12). Mellanby originally suggested vitamin A in cod liver oil prevented rickets; however, McCollum concluded this was not the case. He destroyed the vitamin A in cod liver oil by heating it and the oil still had anti-rachitic activity. Thus, he declared the new substance remaining in cod liver oil to be vitamin D (13). However, even before the discovery that cod liver oil could cure rickets, Trousseau of France and Palm of Great Britain noted that sunlight could be used to cure rickets, though it was not known that sunlight was through the vitamin D endocrine system (14). It is now known that vitamin D is present in limited foods such as cod liver oil and produced endogenously in the skin.

2. Vitamin D Structure & Function

Figure 1.

Metabolic pathways by which vitamin D exerts its many effects in the body. (A) The prevailing scheme before recognition of the role of peripheral 1-α-hydroxylation. In this scheme, essentially all conversion of 25-hydroxyvitamin D [25(OH)D] to calcitriol occurs in the kidney, and the synthesized calcitriol appears in the serum, where it can be measured. Calcium-binding protein (CaBP) is a stand-in for the complex calcium absorptive apparatus induced in the enterocyte by calcitriol. (B) The current scheme, explicitly incorporating extrarenal 1-α-hydroxylation, with the resulting calcitriol appearing mainly intracellularly, where it is clinically unmeasured. (Copyright Robert P. Heaney, 2008. Used with permission.)

3. Vitamin D

Vitamin D is a group of fat-soluble secosteroids, the two major physiologically relevant forms of which are vitamin D$_2$ (ergocalciferol) and vitamin D$_3$ (cholecalciferol). Vitamin D without a subscript refers to either D$_2$ or D$_3$ or both. Vitamin D$_3$ is produced in the skin of vertebrates after exposure to ultraviolet B light from the sun or artificial sources, and occurs naturally in a small range of foods. In some countries, staple foods such as milk, flour, and margarine are artificially fortified with vitamin D, and it is also available as a supplement in pill form (15). Food sources such as fatty fish, mushrooms, eggs, and meat are rich in vitamin D and are often recommended for consumption to those suffering vitamin D deficiency (16). Vitamin D is produced in the skin of vertebrates after exposure to ultraviolet B light from the sun or artificial sources, and occurs naturally in a small range of foods. In some countries, staple foods such as milk, flour, and margarine are artificially fortified with vitamin D, and it is also available as a supplement in pill form (15). Food sources such as fatty fish, mushrooms, eggs, and meat are rich in vitamin D and are often recommended for consumption to those suffering vitamin D deficiency (16). Vitamin D is carried in the bloodstream to the liver, where it is converted into the prohormone calcidiol. Circulating calcidiol may then be converted into calcitriol, the biologically active form of vitamin D, either in the kidneys or by monocyte-macrophages in the immune system. When synthesized by monocyte-macrophages, calcitriol acts locally as a cytokine, defending the body against microbial invaders (17).
When synthesized in the kidneys, calcitriol circulates as a hormone, regulating, among other things, the concentration of calcium and phosphate in the bloodstream, promoting the healthy mineralization, growth and remodeling of bone, and the prevention of hypocalcemic tetany. Vitamin D insufficiency can result in thin, brittle, or misshapen bones, while sufficiency prevents rickets in children and osteomalacia in adults, and together with calcium, helps to protect older adults from osteoporosis. Vitamin D also modulates neuromuscular function, reduces inflammation, and influences the action of many genes that regulate the proliferation, differentiation and apoptosis of cells [18].

### Forms

Several forms (vitamers) of vitamin D have been discovered. The two major forms are vitamin D₂ or ergocalciferol & vitamin D₃ or cholecalciferol; those are known collectively as calciferol [19]. Vitamin D₂ was chemically characterized in 1932. In 1936 the chemical structure of vitamin D₃ was established and resulted from the ultraviolet irradiation of 7-dehydrocholesterol [20].

<table>
<thead>
<tr>
<th>Name</th>
<th>Chemical Composition</th>
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<tbody>
<tr>
<td>Vitamin D₁</td>
<td>Molecular compound of ergocalciferol with lumisterol, 1:1</td>
</tr>
<tr>
<td>Vitamin D₂</td>
<td>Ergocalciferol (made from ergosterol)</td>
</tr>
<tr>
<td>Vitamin D₃</td>
<td>Cholecalciferol (made from 7-dehydrocholesterol in the skin)</td>
</tr>
<tr>
<td>Vitamin D₄</td>
<td>22-dihydroergocalciferol</td>
</tr>
<tr>
<td>Vitamin D₅</td>
<td>Sitocalciferol (made from 7-dehydroisotociferol)</td>
</tr>
</tbody>
</table>

Chemically, the various forms of vitamin D are secosteroids; i.e., steroids in which one of the bonds in the steroid rings is broken [21]. The structural difference between vitamin D₂ and vitamin D₃ is in their side chains. The side chain of D₂ contains a double bond between carbons 22 and 23, and a methyl group on carbon 24.

Vitamin D₂ (made from ergosterol) is produced by invertebrates, fungus and plants in response to UV irradiation; it is not produced by vertebrates [22]. Little is known about the biologic function of vitamin D₂ in non vertebrate species. Because ergosterol can more efficiently absorb the ultraviolet radiation that can damage DNA, RNA and protein, it has been suggested that ergosterol serves as a sun screening system that protects organisms from damaging high energy ultraviolet radiation [23].

In 1923, it was established that when 7-dehydrocholesterol is irradiated with light, a
form of a fat-soluble vitamin is produced. Alfred Fabian Hess showed that “light equals vitamin D” [24]. Adolf Windaus, at the University of Gottingen in Germany, received the Nobel Prize in Chemistry in 1928, for his work on the constitution of sterols and their connection with vitamins [25]. In the 1930s he clarified further the chemical structure of vitamin D.

In 1923, Harry Steenbock at the University of Wisconsin demonstrated that irradiation by ultraviolet light increased the vitamin D content of foods and other organic materials [26]. After irradiating rodent food, Steenbock discovered that the rodents were cured of rickets. It is now known that vitamin D deficiency is a cause of rickets. Using $300 of his own money, Steenbock patented his invention. Steenbock’s irradiation technique was used for foodstuffs, most memorably for milk. By the expiration of his patent in 1945, rickets had all but been eliminated in the US [27].

The vitamin D receptor belongs to the nuclear receptor superfamily of steroid/thyroid hormone receptors, and VDRs are expressed by cells in most organs, including the brain, heart, skin, gonads, prostate, and breast. VDR activation in the intestine, bone, kidney, and parathyroid gland cells leads to the maintenance of calcium and phosphorus levels in the blood (with the assistance of parathyroid hormone and calcitonin) and to the maintenance of bone content [28].

Vitamin D increases expression of the tyrosine hydroxylase gene in adrenal medullary cells. Vitamin D is involved in the biosynthesis of neurotrophic factors, synthesis of nitric oxide synthase, and increased glutathione levels [29]. The VDR is known to be involved in cell proliferation and differentiation. Vitamin D also affects the immune system, and VDRs are expressed in several white blood cells, including monocytes and activated T and B cells [30]. Apart from VDR activation, various alternative mechanisms of action are known. An important one of these is its role as a natural inhibitor of signal transduction by hedgehog (a hormone involved in morphogenesis) [31-32].

The active form of vitamin D, 1α,25(OH)2D, has many functions including signal transduction and gene transcription. 1α,25(OH)2D binds to its receptor, the vitamin D receptor (VDR), and enters the nucleus where it interacts with vitamin D response elements (VDRE). The VDR has a high affinity for 1α,25(OH)2D as opposed to other forms of vitamin D. It has been estimated that the VDR regulates the expression of 2.5% of the genes in the human genome. The genes range in function from bone metabolism, to cell differentiation and proliferation, to additional cellular regulation at the nuclear transcription level, 1α,25(OH)2D also has rapid actions.

Huttakangas et al. have shown that the VDR present on cell membranes is associated with caveolae involved in signal transduction. Activation of the VDR on the cell membrane results in a variety of signal transduction responses including second messenger systems such as protein kinase-C and phosphateidylinositol-3-kinase (PI3K). Any number of cellular functions could be regulated in this way. The fact that 1α,25(OH)2D could have both rapid and genomic responses explains some of the differences between the acute response to 1α,25(OH)2D and long-term responses outlined later in the chapter.

4. DEFICIENCY

Low blood calcidiol (25-hydroxy-vitamin D) can result from avoiding the sun [33]. Deficiency results in impaired bone mineralization, and leads to bone softening diseases [34] including:

- Rickets, a childhood disease characterized by impeded growth, and deformity, of the long bones which can be caused by calcium or phosphorus deficiency as well as a lack of vitamin D; today it is largely found in low income countries in Africa, Asia or the Middle East [35] and in those with genetic disorders such as pseudovitamin D deficiency rickets [36]. Rickets was first described in 1650 by Francis Glisson who said it had first appeared about 30 years previously in the countries of Dorset and Somerset [37]. In 1857 John Snow suggested the rickets then widespread in Britain was being caused by the adulteration of bakers bread with alum [38]. The role of diet in the
development of rickets [39-40]. Was determined by Edward Mellanby between 1918-1920[41]. Nutritional rickets exists in countries with intense year round sunlight such as Nigeria and can occur without vitamin D deficiency [42-43]. Although rickets and osteomalacia are now rare in Britain there have been outbreaks in some immigrant communities in which osteomalacia sufferers included women with seemingly adequate daylight outdoor exposure wearing Western clothing [44]. Having darker skin and reduced exposure to sunshine did not produce rickets unless the diet deviated from a Western omnivore pattern characterized by high intakes of meat, fish and eggs, and low intakes of high extraction cereals [45-47]. The dietary risk factors for rickets include Abstaining from animal foods [48-49]. Vitamin D deficiency remains the main cause of rickets among young infants in most countries, because breast milk is low in vitamin D and social customs and climatic conditions can prevent adequate UVD exposure. In sunny countries such as Nigeria, South Africa, and Bangladesh where the disease occurs among older toddlers and children it has been attributed to low dietary calcium intakes, which are characteristic of cereal-based diets with limited access to dairy products[47]. Rickets was formerly a major public health problem among the US population; in Denver, where ultraviolet rays are approximately 20% stronger than at sea level on the same latitude[50] almost two thirds of 500 children had mild rickets in the late 1920s[51]. An increase in the proportion of animal protein[50] in the 20th century American diet coupled with increased consumption of milk[53-54] fortified with relatively small quantities of vitamin D coincided with a dramatic decline in the number of rickets cases.

- Osteomalacia, a bone-thinning disorder that occurs exclusively in adults and is characterized by proximal muscle weakness and bone fragility. The effects of osteomalacia are thought to contribute to chronic musculoskeletal pain [55-56] there is no persuasive evidence of lower vitamin D results in chronic pain sufferers [57].

Adequate vitamin D may also be associated with healthy hair follicle growth cycles [58]. There are also associations between low 25 OH vitamin D levels and peripheral vascular disease, certain cancers, multiple sclerosis, rheumatoid arthritis, juvenile diabetes[15 Parkinson’s and Alzheimer’s disease[60]. However these associations were found in observational studies and vitamin D supplements have not been demonstrated to reduce the risks of these diseases[61].

Research shows that dark-skinned people living in temperate climates have lower vitamin D levels[62-63]. It has been suggested that dark-skinned people are less efficient at making vitamin D because melanin in the skin hinders vitamin D synthesis, however a recent study has found novel evidence that low vitamin D levels among Africans may be due to other reasons [44]. Recent evidence implicates parathyroid hormone in adverse cardiovascular outcomes, black women have an increase in serum PTH at a lower 25 OH vitamin D level than white women[63]. A large scale association study of the genetic determinants of vitamin D insufficiency in Caucasians found no links to pigmentation [64-67].

5. MEASURING VITAMIN D STATUS

The serum concentration of 25-hydroxyvitamin D is typically used to determine vitamin D status. It reflects vitamin D produced in the skin as well as that acquired from the diet, and has a fairly long circulating half-life of 15 days. It does not, however, reveal the amount of vitamin D stored in other body tissues. The level of serum 1,25-dihydroxy-vitamin D is not usually used to determine vitamin D status because it has a short half-life of 15 hours and is tightly regulated by parathyroid hormone, calcium, and phosphate, such that it does not decrease significantly until vitamin D deficiency is already well advanced.

There has been variability in results of laboratory analyses of the level of 25-hydroxyvitamin D. Falsely low or high values have been obtained depending on the particular test
or laboratory used. Beginning in July 2009 a
standard reference material became available
which should allow laboratories to
standardize their procedures.

There is some disagreement concerning the
exact levels of 25-hydroxy-vitamin D needed
for good health. A level lower than 10ng/mL
(25nmol/L) is associated with the most severe
deficiency diseases: rickets in infants and
children, and osteomalacia in adults. A
concentration above 15bg.nk (37.5nmol/L) is
generally considered adequate for those in
food health. Levels above 30 ng/ml (750
nmol/L) are proposed by some as desirable for
achieving optimum health, but there is not yet
enough evidence to support this.

Levels of 25-hydroxy-vitamin D that are
consistently above 200 ng/mL (500 nmol/L) are
thought to be potentially toxic, although data
from humans is sparse. In animal studies
levels up to 400 ng/mL (1000 nmol/L) were not
associated with toxicity. Vitamin D toxicity
usually results from taking supplements in
excess. Hypercalcemia is typically the cause
of symptoms, and levels of 25-hydroxy-vitamin
D above 150 ng/mL (375 nmol/L) are usually
found, although in some cases 25-hydroxy-
vitamin D levels may appear to be normal. It
is recommended to periodically measure
serum calcium in individuals receiving large
doses of vitamin D.

In overweight persons increased fat mass is
inversely associated with 25 OH vitamin D
levels [57][58]. This association may confound the
reported relationships between low vitamin D
status and conditions which occur more
commonly in obesity as the circulating 25 OH
vitamin D underestimates their total body
stores.

A study of highly sun exposed (tanned)
healthy young skateboarders and suffers in
Hawaii found levels below the proposed
higher minimum of 30 ng/ml in 51% of the
subjects. The highest 25 OH vitamin D
concentration was around 60 ng/ml
(150nmol/L). A similar (using the same data)
study in Hawaii found a range of (11-71
ng/mL) in a population with prolonged
extensive skin exposure while as part of the
same study Wisconsin breastfeeding mothers
were given supplements.

The range of circulating 25 Oh vitamin D
levels in women in the supplemented group
was from 12-77 ng/mL. It is noteworthy that
the levels in the supplemented population in
Wisconsin were higher than the sun exposed
group in Hawaii (which again included
surfers because it was the same data set).

6. ASSESSING AND TREATING
VITAMIN D DEFICIENCY

The concentration of 25(OH)D is measured in
mg/mL or according to SI units, nmol/L (there are
2.5 nmol/L for each 1 ng/mL). Historically,
a person was considered to be deficient in vitamin
D if 25(OH)D levels were less than 20 ng/mL or 50
nmol/L. These levels were defined based on
circulating 25(OH)D level in the US population that appears
to be adequate in preventing bone disease.

Therefore, most experts believe that vitamin D insufficiency should be defined as serum levels less than 30 ng/mL or 75 nmol/mL.

The US Endocrine Society guideline defines vitamin D deficiency as 25(OH)D less than 20 ng/mL (50nmol/l), vitamin D insufficiency as 25(OH)D between 21 and 29 ng/ml, and the safety margin to minimize the risk of hypercalcemia as 25(OH)D equal to 100 ng/ml (250 nmol/l).
In fact, the primary way to obtain vitamin D is from exposure to sunlight. In particular, older individuals and those with darker skin are at greater risk for deficiency due to decreased production of vitamin D in the skin. The majority of the United States consumption of vitamin D comes from fortified foods (Table 2.2).

### Table 2.2 Amount of Vitamin D in Food

(Adapted from the Office of Dietary Supplements Dietary Fact Sheet)

<table>
<thead>
<tr>
<th>Food</th>
<th>IU per serving^*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cod liver oil, 1 tablespoon</td>
<td>1,360</td>
</tr>
<tr>
<td>Salmon, cooked, 3.5 ounces</td>
<td>360</td>
</tr>
<tr>
<td>Mackerel, cooked, 3.5 ounces</td>
<td>345</td>
</tr>
<tr>
<td>Tuna fish, canned, 3 ounces</td>
<td>200</td>
</tr>
<tr>
<td>Sardines, canned, 1.75 ounces</td>
<td>250</td>
</tr>
<tr>
<td>Milk, vitamin D-fortified, 1 cup</td>
<td>98</td>
</tr>
<tr>
<td>Fortified Cereal</td>
<td>40</td>
</tr>
<tr>
<td>Egg, 1 whole (vitamin D is found in yolk)</td>
<td>20</td>
</tr>
<tr>
<td>Liver, beef, cooked, 3.5 ounces</td>
<td>15</td>
</tr>
</tbody>
</table>

Several treatments exist for restoring vitamin D levels to sufficient status:
- Sun exposure
- Larger quantities of vitamin D
  - a) 100 IU of additional vitamin D each day
  - b) Multivitamins contain between 400 IU of vitamin D
  - c) Another strategy for the individual with vitamin D deficiency is treatment with vitamin D50,000 IU per week for eight weeks
  - d) Correction of vitamin D deficiency depends on the severity of disease and could be achieved by both sunlight and oral therapy

### 7. CO-MORBIDITIES ASSOCIATED WITH VITAMIN D DEFICIENCY

- Hypertension
- Cystic fibrosis (CF)
- Disease of the heart, bones, endocrine, and immune systems
- Osteoporosis-
  - Osteoporosis is a skeletal condition resulting from decreased bone strength and increased risk of fracture
  - Preventing fractures
  - Falls in the elderly
  - From osteoporosis and maintaining muscle health, neurological balance, metabolic bone disease
- Type I and Type II diabetes (hyperglycemia and hypovitaminosis D)
- Risk of complications associated with diabetes such as all-cause mortality, myocardial infarction, and cardiovascular disease
- Vitamin D plays a vital role in reducing inflammation by reducing inflammatory profile of T cells

### Mortality

Using information from the National Health and Nutrition Examination Survey, a large scale study conducted that having low levels of vitamin D (<17.8 ng/ml) was independently associated with an increase in all-cause mortality in the general population. However, it has been pointed out that increased mortality was also found in those with higher concentrations, (above 50 ng/ml). A sophisticated August 2010 study of plasma vitamin D and mortality in older men concluded that both high (>39 ng/ml) and low...
(<18 ng/ml) concentrations of plasma 25(OH)D are associated with elevated risks of overall and cancer mortality compared with intermediate concentrations. These boundaries were less than suggested by the Melamed et al study of National Health and Nutrition Examination Survey data but the immunoassay used by National Health and Nutrition Examination Survey tended to overestimate vitamin D values.

Overall, excess or deficiency in the calcipherol system appear to cause abnormal functioning and premature aging.

Complex regulatory mechanisms control metabolism and recent epidemiological evidence suggests that there is a narrow range of vitamin D blood levels in which metabolic functions are optimized. Levels above or below this natural homeostasis of vitamin D are associated with increased mortality.

8. RECOMMENDATIONS

PCPs should not overlook the levels of this vital vitamin. In all chronic disease sufferers and old age people, Vitamin D levels should be ascertained and Vitamin D supplementation should be a part of treatment regimen. Vitamin D is a preventive Vitamin in itself.

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9. CONCLUSIONS

Vitamin D is more than a vitamin. Pleiotropic substrate for repair and serves multiple gene-regulatory functions in your body.3000 genes are influenced by Vitamin D. Vitamin D receptors are present in every cell of the body. Vitamin D plays a vital role in human health

Optimum Vitamin D levels can fight at least 16 different types of cancer, including pancreatic, lung, ovarian, prostate, and skin cancers, colon cancers. Vitamin D levels play role in prevention and treatment of type 1 and type 2 diabetes, hypertension, glucose intolerance, multiple sclerosis, and other medical conditions.