Vitamin D
- a nutrient that functions like a hormone

Dr. Prakash SS, MD, DNB, Assistant Professor,
Dr. Anand R, MD, DNB, Assistant Professor, Department of Biochemistry, CMC Vellore

INTRODUCTION

Vitamin D is an essential nutrient required for various physiological processes in our body. It is traditionally known as the vitamin whose deficiency causes rickets and osteomalacia in children and adults respectively. Vitamin D can be obtained from dietary sources such as fish, cheese, butter or fortified foodstuffs. It can also be synthesized by our body. Whether obtained from diet or synthesized, vitamin D has to be converted to its active form, 1,25–dihydroxyvitamin D, in order to exert its action. Just like any other hormone, it is synthesized in a particular organ (kidney) from its precursor (vitamin D), has a specific receptor (present in nucleus), has distinct target organs (bone, intestine and kidney) and is subject to regulation. In this sense, vitamin D may be considered as a pro-hormone and 1,25–dihydroxyvitamin D, a hormone (1-4). It is important to recognize the difference between vitamin D as a nutrient and its active form 1,25-dihydroxyvitamin D although the terms are often used interchangeably (5). The primary role for vitamin D is in calcium and phosphate metabolism and healthy skeletal development (6). In recent years, many additional functions and clinical correlations have been attributed to this vitamin thereby expanding its physiological role beyond bone and calcium metabolism (7). The purpose of this write-up is to give the readers an overview of the metabolism, biological functions and the role of vitamin D in health and disease.

SYNTHESIS, ACTIVATION AND REGULATION OF VITAMIN D

Vitamin D can be synthesized in our body from 7-dehydrocholesterol (an intermediate in the metabolism of cholesterol) in the skin, with the help of ultraviolet rays from sunlight. Vitamin D activation happens in two sequential steps (Figure 1). First, vitamin D is acted upon in the liver by an enzyme called 25α-hydroxylase which converts it to 25-hydroxycholecalciferol. It is then carried in circulation, bound to vitamin D binding protein, and is the major circulating form of vitamin D. It is then converted into 1,25-dihydroxycholecalciferol (also called 1,25-dihydroxyvitamin D or calcitriol) in the kidney by the enzyme 1α-hydroxylase. 1,25-dihydroxycholecalciferol is the biologically active form of vitamin D, responsible for its physiological functions (1-3). 1α-hydroxylase is also expressed in other cells and tissues such as macrophages, bone, placenta etc. (8). In these tissues, the active form of vitamin D can be formed which then has its effects on various tissues in autocrine or paracrine manner (much like a hormone). Synthesis of calcitriol is regulated by a negative feedback loop and serum levels of calcium and phosphorous via parathormone (PTH). Low calcium level stimulates the release of PTH from parathyroid glands. PTH can stimulate the expression of 1α-hydroxylase enzyme in kidneys and thus enhances the synthesis of calcitriol (4).

VITAMIN D RECEPTOR

Calcitriol exerts its actions by binding to its specific receptor present in the nucleus of the target organs. Due to its lipid soluble nature, it is capable of diffusing through the cellular and nuclear membranes and interacts with its receptor. Then, the calcitriol-receptor-complex, binds to specific regions of DNA to enhance the expression of several genes. The proteins that are synthesized in response to calcitriol differ, depending on the cell type and physiological status (1,2). Given that vitamin D receptor is expressed by most of the cells of the body, it is not surprising that the effects produced are quite diverse (3,4,9). It also underscores the fact that polymorphisms in vitamin D receptor is known to be associated with many disease states (9).
The salient functions of vitamin D are summarized in Table 1.

**Classical actions of vitamin D**
Calcitriol is essential for the regulation of calcium and phosphate homeostasis through its action on intestine, kidney and bone. It enhances calcium and phosphate absorption from the intestine by increasing the expression of genes (such as calbindin) involved in the transport of calcium and phosphate. It also promotes reabsorption of calcium and phosphate in the renal tubules and reduces their excretion. Its action on bone helps in bone remodelling (1-3). The overall effect of vitamin D therefore, is to increase serum calcium and phosphate levels.

**Non-classical actions of vitamin D**
Contrary to the classical functions, the non-classical actions of calcitriol are diverse, heterogeneous and complex. Since its receptor is expressed in many tissues and 1α-hydroxylase enzyme also present in these tissues, the circulating 25-hydroxyvitamin D can be taken into these tissues and converted into its active form. The effects are mediated by autocrine/paracrine actions (7,10,11). Some of these actions which are well studied are briefly discussed below.

**As an immunomodulator**
Vitamin D has significant functions in the differentiation and function of immune cells. For example, it increases the synthesis of cytokines such as TNFα, promotes synthesis of antimicrobial peptides, induces differentiation of macrophages and promotes the functions of T cells. Vitamin D thus modulates the immune system. It is also responsible for maintaining immune tolerance (12).

Historically, the role of Vitamin D in promoting immune function has been known for centuries. Cod liver oil which is a rich source of vitamin D has been used to prevent illnesses since the 19th century and TB sanatoria were built in such a way that the patients received ample sunlight.

**As a cell differentiation agent**
Vitamin D is important as an inducer of cell differentiation in various tissues. It is important for normal development of bones, immune cells and organs such as breast, ovary etc (10,11).

**As an antiproliferative agent**
Interestingly, vitamin D has also been shown to be involved with apoptosis and acts as an antiproliferative agent in various tumour cell lines especially that of breast, prostate, ovary etc. When administered along with other antineoplastic agents,
Vitamin D has shown synergistic effects in reducing the tumour burden (10,11).

In kidneys, heart, bones
Vitamin D is essential for the differentiation of bones. In kidneys, they help regulate the renin-angiotensin-aldosterone system. In cardiovascular system, they play an important role in maintaining blood pressure (13).

Table 2: List of common diseases associated with vitamin D deficiency (the list is not exhaustive)

- Rickets in children
- Osteomalacia in adults
- Bone and muscle weakness
- Autoimmune diseases (SLE, rheumatoid arthritis, multiple sclerosis etc.)
- Diabetes mellitus (type 1 and type 2)
- Cancer (especially of breast, colon, ovary, prostate)
- Infections (eg. Tuberculosis)

VITAMIN D DEFICIENCY AND ASSOCIATED DISEASES

The best available indicator of vitamin D deficiency is measurement of 25-hydroxyvitamin D levels in the serum. Some variations exist in the cut-off levels for diagnosing vitamin D deficiency but in general serum 25-hydroxyvitamin D levels less than 20 ng/ml is considered as severe vitamin D deficiency (14-16). The incidence of vitamin D deficiency is common (17). Compared to healthy individuals, vitamin D levels are found to be lower in many disease conditions ranging from diabetes, autoimmune diseases, cancer etc (Table 2) (18-19). Low vitamin D levels have been known to be associated with hypertension, obesity, diabetes mellitus and high triglyceride levels (20). Individuals with 25(OH)D levels < 20 ng/mL have a 30%–50% increased risk of developing cancers of the prostate, breast, pancreas, colon, rectum and esophagus (21,22).

VITAMIN D SUPPLEMENTATION TRIALS

Because of the association of low vitamin D levels in disease states and its pleiotropic effects, many supplementation trials have been carried out. However, randomized control trials and meta-
analyses show conflicting results with some studies showing improvement while others demonstrating null benefit or even harmful. A summary of Cochrane systematic reviews in this regard is shown in Table 3.

**CONCLUDING REMARKS**

Vitamin D has pleiotropic effects and functions in various tissues besides its role in maintaining calcium and phosphate homeostasis. The fact that vitamin D deficiency is associated with many disease states underlies the significance of vitamin D in various physiological processes. In those cases where vitamin D deficiency is documented, it would be worthwhile to consider supplementing vitamin D to patients. At the same time, risk of hypercalcemia due to chronic administration of vitamin D should also be kept in mind. Lastly, precise understanding of the effects of vitamin D in disease conditions might help to make logical decisions on vitamin D supplementation in future.

**References:**

1. Norman AW. From vitamin D to hormone D: fundamentals of the vitamin D endocrine system essential for good health. Am J Clin Nutr 2008;88:491S-499S
3. Lips P. Vitamin D physiology. Prog Biophys Mol Biol 2006;92:4-8
5. Vieth R. Why “vitamin D” is not a hormone, and not a synonym for 1,25-dihydroxy-vitamin D, its analogues or deltaneo. J Steroid Biochem Mol Biol 2004;89-90:571-3
7. Lai YH and Fang TC. The pleiotropic effect of vitamin d. ISRN Nephrol 2013;2013:898125
Table 3: Evidence on vitamin D supplementation trials from Cochrane Systematic Reviews

<table>
<thead>
<tr>
<th>Review title and information</th>
<th>Author’s main conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vitamin D and related vitamin D compounds for preventing fractures resulting from osteoporosis in older people.</strong></td>
<td>Vitamin D alone is unlikely to prevent fractures in the doses and formulations tested so far in older people. Supplements of vitamin D and calcium may prevent hip or any type of fracture.</td>
</tr>
<tr>
<td><strong>Vitamin D supplementation for women during pregnancy.</strong></td>
<td>Vitamin D supplementation in a single or continued dose during pregnancy increases serum vitamin D concentrations as measured by 25-hydroxyvitamin D at term. The clinical significance of this finding and the potential use of this intervention as a part of routine antenatal care are yet to be determined.</td>
</tr>
<tr>
<td><strong>Vitamin D supplementation for prevention of mortality in adults.</strong></td>
<td>Vitamin D₃ seemed to decrease mortality in elderly people living independently or in institutional care. Vitamin D₃ combined with calcium increased nephrolithiasis.</td>
</tr>
<tr>
<td><strong>Vitamin D for the treatment of chronic painful conditions in adults.</strong></td>
<td>A large beneficial effect of vitamin D across different chronic painful conditions is unlikely.</td>
</tr>
<tr>
<td><strong>Vitamin D supplementation for improving bone mineral density in children.</strong></td>
<td>These results do not support vitamin D supplementation to improve bone density in healthy children with normal vitamin D levels, but suggest that supplementation of deficient children may be clinically useful.</td>
</tr>
</tbody>
</table>