Vitamin D Biochemistry and Clinical Co-relation: A Review

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Abstract

There has been tremendous increase in interest in vitamin D in both health and disease in the last two decades. The chief reason for this is the discovery of vitamin D receptor (VDR) in virtually every tissue and thousands of VDR binding sites throughout the genetic machinery controlling multiple genes. This increased interest has been reflected in the request for estimation of serum level and prescription of supplements. In this changing scenario, nurses should be aware of both the basic science and clinical correlation of vitamin D. This article is a summary of the basic science with practical clinical applications relevant for nurses.

Keywords: *Vitamin D, deficiency, health, disease.*

Introduction

Vitamin D is a fat-soluble vitamin also classified a steroid hormone due to similarity in chemical structure and mechanism of action. It is also called a prehormone or prohormone as it is required to be activated to the metabolically functional product[1].

Materials and Method

A literature search was carried out with the key word 'vitamin D deficiency', 'vitamin D and disease', 'vitamin D and health', 'vitamin D and cardiovascular disease', 'vitamin D and diabetes', 'vitamin D and cancer', 'vitamin D and immunity and 'vitamin D and children's health' in PubMed, Google scholar and Medline. The recent articles (from 2016 onward) and review articles were selected except the basic science and few landmark articles.

Metabolism: Vitamin D is sourced by the human body from diet (saltwater fish like Salmon, cod liver oil and egg-yolk) and synthetized under the sun. Biosynthesis starts with the oxidation of cholesterol to 7-dehydrocholesterol and transported to the stratum basale of skin (D3 or cholecalciferol)[2].

There are two inactive forms of vitamin D, D2 (ergocalciferol) and D3 (cholecalciferol). D3 is synthesized in the skin after exposure to UVB light and it may be obtained from animal sources, while D2 is plant derived or synthetic form and is also added during food fortification[3].

This provitamin D is transported to the liver mainly by vitamin D binding protein and partly by albumin for hydroxylation by the enzyme 25-hydroxylase (CYP2R1) to convert it 25-hydroxycholecalciferol[3]. Liver failure prevents this step and results in severe vitamin D deficiency[2] and mutation in CYP2R1 gene results in rickets[3].

The next hydroxylation occurs in the proximal renal tubule cells in response to Parathyroid hormone (PTH) and fibroblast growth factor 23 by the enzyme 1α hydroxylase (CYP27B1) which converts it to the biologically active $1,25\text{-}(OH)_2$ vitaminD or 1,25-dihydroxycholecalciferol (1,25DCC) or calcitriol[2,4].

Mutation in the CYP27B1 gene results in vitamin D dependent rickets[3]. Patients with advanced renal impairment cannot produce 1,25DCC leading to hyperphosphatemia, hypocalcemia and secondary hyperparathyroidism (renal osteodystrophy)[2].

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Hypocalcemia releases PTH which raises Ca^{+2} by two method:

1. PTH stimulates its receptors in osteocytes and osteoblasts which activate octeoclasts to resorb bone and release Ca^{+2} and increases Ca^{+2} reabsorption in the kidneys but at the expense of phosphate (PO_4^{3-}).
2. PTH induces 1α-hydroxylase activity in the kidney and hence 1,25DCC which increases Ca^{+2} reabsorption in the gut and both Ca^{+2} and PO_4^{3-} reabsorption in the kidney.

In vitamin D deficiency due to liver and kidney failure (lack of hydroxylation), the supplementation must be 1,25DCC as any inactive forms could not be hydroxylated to the active form[2]. Another enzyme in the kidney, 24α-hydroxylase (CYP24A1), hydroxylates both 25(OH)D and 1,25DCC to a water-soluble biliary form, calcitroic acid and 25(OH)D to an inactive product 24,25-$(OH)_2$D to terminate action. Mutations in the CYP24A1 gene have been associated with idiopathic infantile hypercalcemia[3].

Mechanism of action: Being fat soluble it crosses the phospholipid bilayer of the cell membrane and binds to VDR and the complex goes inside the nucleus to binds to the vitamin D response element of DNA and enhances the rate of gene expression and protein synthesis responsible for actions of vitamin D which varies in different tissues. For example, in duodenal epithelial cells, it increases synthesis of calcium-binding proteins to stimulate calciumabsorption[2].

Recent advances in therapeutics: On the basis of multitude of actions indifferent tissues, pharmacologic agents(vitamin D analogues) have been developed that have separate effects other than on Ca^{+2} and PO_4^{-3} metabolism. For example, calcipotriol and 22-oxa calcitriol (OCT) are approved for the treatment of psoriasis; paricalcitol, doxercalciferol, and falecalcitriol are approved for secondary hyperparathyroidism etc[3].

There are some non-genomic functions by the activation of signalling molecules, like phospholipase C and phospholipase A2, phosphatidylinositol-3 kinase and p21ras leading to second messengerpathway culminating in the activation of protein kinases. The non-genomic actions also include the opening of Ca^{2+} and Cl^- channels to effect various cellular functions.

Functions:

1. Increase intestinal absorption of Ca^{+2} and PO_4^{-3}.
2. Increase bone mineralization at low levels.
3. Increase bone resorption at higher levels[5].
4. Promotes cellular differentiation and anti proliferative actions in bone marrow (osteoclast precursor and lymphocytes), the immune system, skin, breast and prostate epithelial cells, muscle and intestine[3].

Prevalence of vitamin D deficiency in India: 25(OH)D is the major form found in the blood and due to long half-life and higher concentration, itis commonly measured to assess and monitor vitamin D status. The US endocrine Society defines vitamin D deficiency as a serum level of <20ng/ml with consequent and consistent elevation of PTH and a decrease inintestinal calcium absorption[4]. In a review on vitamin D deficiency in India Aparna et al found that it ranged from 40% to 99%, with most of the studies reporting a prevalence of 80%-90%[5].

Table 1: Vitamin D status[4]

	Serum level in ng/ml
Deficiency	<20
Insufficiency	21-29
Sufficiency	>30
Toxicity	>150

Deficiency: Normally seen in exclusively breast feed infants as it is a poor source even if the mother receives vitamin D and babies need supplementation. Otherwise it is caused by malabsorption with steatorrhea (e.g. cystic fibrosis and celiac disease), decreased sun exposure, poor diet, advanced kidney and liver disease and exacerbated by pigmented skin and premature birth[2,4].

Clinical conditions of deficiency:

1. Rickets in children (characterized by deformity such as bowlegs or genu varum), osteomalacia (bone pain andmuscle weakness) in adult.
2. Hypocalcemic tetany (Chvostek sign and Trousseau sign)[4]

The US Endocrinology Society suggests that obese children and adults on anticonvulsant medications, glucocorticoids, antifungals such as ketoconazole, and medications for acquired immune deficiency syndrome

(AIDS) should be given at least two to three times more for their age group to optimize their level[6].

Obese people have lower vitamin D and it was found that obesity and its genes are responsible for deficiency. Obesity causes wider volumetric distribution but does not necessarily have the adverse skeletal effects. They have lower bone turn-over and higher bone density than people with normal BMI. The cause of bone loss and vitamin D deficiency after Bariatric surgeryis iatrogenic malabsorption. Obese people should be prescribed higher loading doses of vitamin Dto achieve a similar raise in serum vitamin D[7].

Robien, while reviewing the drug interactions mentions that evidence regarding lipase inhibitors, antimicrobial agents, antiepileptic drugs, highly active antiretroviral agents or H2 receptor antagonists to cause change in the serum 25(OH)D concentrations is inadequate. But thiazide diuretics with concomitant calcium and vitamin D supplements may cause hypercalcemia in the elderly, or those with compromised renal function or hyperparathyroidism. The overall effect of anticonvulsants is significant in people with insufficient sources of vitamin D (diet, supplements or UV exposure). Similarly, studies suggest insignificant effect of glucocorticoids on the concentration of vitamin D[8].

Table 2: Recommended intake for persons with risk of deficiency[6]

Age (years)	Minimum daily intake (IU/day)	Daily intake for blood level of >30 ng/ml
0-1	400	1000
1-18	600	1000
19-50	600	1500-2000
50-70	600	1500-2000
>70	800	1500-2000
Pregnancy	600	1500-2000
Lactation	600	1500-2000

Table 3: Recommended therapeutic regimen of D2 or D3 in diagnosed deficiency[6]:

Age (years)	Treatment dose (IU)	Maintenance dose
0-1	2000 IU/day or 50,000 IU weekly for 6 weeks	400-1000 IU/day
1-18	2000 IU/day or 50,000 IU weekly for 6 weeks	600-1000 IU/day
Adults	6000 IU/day or 50,000 IU weekly for 8 weeks	1500-2000 IU/day

The guidelines also mention patients with malabsorption syndromes, on certain medications (as stated above)should be provided at least 6000–10,000 IU/day to treat vitamin D deficiency followed by maintenance therapy of 3000–6000 IU/day[6].

Toxicity of vitamin D[9]: The widespread use of vitamin D has resulted in substantial incidence of toxicity causing hypercalcemia and ranges from thirst and polyuria to seizure, comma and death.

Commoncauses of vitamin D toxicity are:

1. Formulation or fortification errors
2. Inappropriate prescribing or dispensing
3. Inappropriate administration of vitamin D or lifestyle related (e.g. tanning bed)

Well established relations of vitamin D:

As anti-neoplastic: The anti-neoplastic role of vitamin D is by regulating cell proliferation, differentiation and angiogenesis[10]. VDR is expressed in cancer cells and vitamin D have effect on pro differentiating, antiproliferative, antimetastatic activities and controls the cell cycle[11] Sunlight has protective effect on breast, prostate, colon, rectal and ovarian cancer[12] and serum level of 50ng/ml is 50% protective against breast cancer[13].

Effect on infertility: Vitamin D has effects on female reproduction, including IVF outcome, Polycystic Ovarian Syndrome, endometriosis and steroidogenesis and might be related to spermatogenesis, semen quality and testiculopathies as well as male hypogonadism[14]. Excess vitamin D may play a detrimental role in fertility[15].

Vitamin D and Diabetes: There is evidence that vitamin D deficiency is associated with type 1 diabetes following high prevalence in these children[16]. The immune modulatory functionis suggested to be responsible for prevention of immune destruction of beta cells[17]. Although there was some initial evidence that optimizing vitamin D status might prevent type II DM, studies do not support that in subjects of normal glucose tolerance and it remains to be evaluated in high risk population[18].

Vitamin D and Asthma and infection and tumour: Liu et al. documented that vitamin D levels might be corelated to the lung function in Asthma[19]. Pfefferand Hawrylowiczhave raised the inconsistent positive relation of vitamin D interventions in asthma in various randomised controlled trials and attributed this to the design flaws in those studies and found it beneficial after systematic review and opined for supplementation in Asthma care[20].

Vitamin D and neurological disease[21]: Vitamin D has a crucial role in proliferation, differentiation, neurotrophism, neuroprotection, neurotransmission, and neuroplasticity. While the strength of evidence varies for Schizophrenia, Autism, Parkinson's disease, Amyotrophic Lateral Sclerosis, Alzheimer's disease; it is especially strong for Multiple Sclerosis.

Vitamin D and cardiovascular health[22]: Current consensus is that excess of vitamin D over and above that is necessary for maintenance of skeletal health cannot prevent cardiovascular disease and very high dose might precipitate calcification in blood vessels leading to adverse cardiovascular effects.

Vitamin D and immunity: In 2011, Martineau et al. concluded that supplementation of vitamin D did not show significant improvement in clinical outcomes in tuberculosis[23]. Another review article on vitamin D as an adjunctive treatment to standard drugs in pulmonary tuberculosis did not find any clinical benefit[24]. VDR is a critical transcription factor regulating genes involved in inflammation and anti-bacterial defence. During haematopoiesis VDR plays a key regulator in myeloid differentiation towards cells of innate immunity like monocytes and macrophages. Vitamin D can inhibit maturation and differentiation of dendritic cells and reduces autoimmunity (multiple sclerosis and inflammatory bowel disease)[25].

Vitamin D and health of children: Martineau et al., showed that vitamin D supplementation improves severity and duration of acute respiratory tract infections in children[26] while others have found evidence deficiency to be related to higher level of sepsis (64%) and mortality[27,28]. Vitamin D is of benefit to the paediatric Chron's patients[29] and causes dental caries if deficiency occurs during pregnancy and infancy[30]. It also contributes to paediatric multiple sclerosis and its relapse[31,32]. The protective role in asthma is significant only when adequate vitamin D is present in the early pregnancy[33]. Children with higher level of vitamin D at birth are more protected against asthma between 3-9 years of age[34]. Hattangdi-Haridassummarised that supplementation of vitamin D in mild to moderate cases of a topic dermatitis leads to better clinical out-come[35].

Vitamin D with sleep and pain[36]: Sleep deprivation / disorders have been related to hyperalgesia and vitamin D deficiency which is also found to be related to fibromyalgia and rheumatic diseases. Vitamin D possibly has regulatory role in sleep and pain and supplementation helps in good sleep hygiene and prevention of chronic pain conditions.

Conflict of Interest: There is no conflict of interest.

Source of Founding: None

Ethical Clearance: Narrative literature review, ethical clearance is not needed.

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