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REVIEW ARTICLE

Emerging Vistas in Biologic Action and Health Implications of Vitamin D

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Abstract

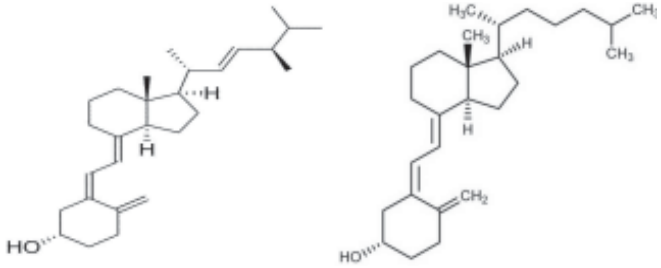
Vitamin D has assumed contemporariness due to the fact that its potential to perform much more than its classical role is gaining recognition. This addition of new facets to the biologic action of vitamin D has immense health implications. However, it is ironical that at the same time, people of all age groups in several countries of the world are stricken with vitamin D deficiency (VDD). With a few food options for vitamin D nutrition, its key source remains the human exposure to sunshine that transforms subcutaneous 7-dehydrocholesterol to vitamin D_3. Despite this natural bounty, a great deal of population suffers from VDD owing to inadequate sun exposure in tropics and scarce availability of sunlight in temperate regions of the globe. A number of reports depict the association of vitamin D deficiency with development of several diseases that include cancer, high blood pressure, multiple sclerosis, inflammatory bowel disease, muscle fatigue and weakness, rheumatoid arthritis, rickets, osteoporosis and diabetes mellitus. Likewise, an equally numerous reports point towards VDD becoming widespread without any let or hindrance, thus ringing an alarm with respect to vitamin D deficiency and disease development. Increasing the public awareness pertaining to VDD and its health repercussions, facilitating VDD diagnosis, making people realize the importance of sun bathing and devising vitamin D intervention strategies that food fortification with vitamin D should become the priority points to combat this problem of immense health consequence.

Keywords

Calcidiol, Calcitriol, Calciotropic, Pleiotropic, Vitamin D deficiency

Introduction

Vitamin D, a group of fat-soluble substances, was identified after the discovery of the anti-rachitic effect of cod liver oil in the early part of the 20th century by McCollum (McCollum *et al,* 1922). The additional vitamin activity detected discovered in cod liver oil was named "D" following earlier discovered vitamins named in alphabetical order as Vitamin A, B and C (Nomenclature policy, 1980). Vitamin D_3 and D_2 are the two major precursors of vitamin D (Holick, 1990; Vieth, 2004). Whereas, vitamin D_3 is synthesized from 7-dehydrocholesterol present in the skin by its exposure to solar ultraviolet B (UVB wavelength range, 290-320 nm), Vitamin D_2, the other plant derived precursor, is produced exogenously by irradiation of ergosterol present in certain leaf and yeast varieties become part of the dietary intake (Wolpowitz and Gilchrest, 2006). Apart from two major forms; ergocalciferol (D_2) and cholecalciferol (D_3) whom we together refer to vitamin D or calciferol, there are three other types namely: Vitamin D_1 – molecular compound of ergocalciferol with lumisterol in 1:1 ratio, vitamin D_4 - dihydroergocalciferol and vitamin D_5 sitocalciferol (made from 7- dehydrositosterol).



Ergocalciferol, D_2 **Cholecalciferol, D_3**

The two major vitamin D forms, D_2 and D_3, derived from diet and exposure to sunshine respectively are converted to 25(OH) D; calcidiol, on being acted upon by the liver microsomal enzyme 25, D hydroxylase (Holick, 2006a). Calcidiol, the most abundant and stable form of vitamin D in the body, is aptly used to assess vitamin D status. For biological activity, an additional hydroxylation (at 1,á position) of calcidiol occurs in the renal mitochondria to form calcitriol (Malone and Kessenich, 2008).

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Apart from exposure to sunlight, humans also get vitamin D through dietary intake. There are only a few foods which contain vitamin D such as fatty fish salmon, mackerel, and sardine, irradiated yeast, leafy vegetables and mushroom varieties. It has been reported that egg yolk also contain vitamin D in highly variable amounts but the sizeable cholesterol content of egg yolk with its adverse health repercussions makes it an impractical source of the vitamin. Other sources include mushrooms, portabella and shitake, raw or exposed to UV B light; Alfalfa (*Medicago sativa* subspecies *sativa)* and lichen (*Cladina arbuscula*). To make up for inadequate dietary supply of vitamin D, some selective foods such as milk and milk products, juices, bread and breakfast cereals are also fortified with vitamin D (Tangpricha *et al,* 2003). However, fortification as an option is not practiced in many developing countries including India. For intervention purposes, the industrial production of cholecalciferol (D_3) is made by irradiating 7-dehydrocholesterol with UV B light followed by purification. The latter is a natural substance in wool grease (lanolin) from sheep or other wool producing animals. Likewise, ergocalciferol (D_2) is produced by using ergosterol from yeast or mushrooms as a precursor for irradiation with UV B light (Holick, 2004).

As vitamin D is scarcely present in the foods consumed by the vast majority of people of the Indian sub-continent they have to look for sunshine option. However, the pigmented dark skin of these people, which otherwise offers protection from deleterious effects of UV rays present in sunlight, goes to adversely affect their dermal efficiency for vitamin D synthesis from 7-dehydrocholesterol present in the layer under the skin. Likewise, low level of 7-dehydrocholesterol in the dermal layer of lean individuals, especially the malnourished children and elderly, is another reason that results in low 7-dehydrocholesterol to D_3 output, despite prolonged sun exposure.

In temperate regions, low intensity of sunlight hampers the skin option for vitamin D synthesis, especially in winter months. Thus climate, latitude and time of the day also dictate the efficiency of this mode of synthesis. Ozone layer, which absorbs UVB radiation above 290nm wave length, is responsible for synthesis of D_3. It is the density of ozone layer that decides the amount of UV B rays that can reach the earth. Thinner the ozone layer more would be the amount of D_3 synthesized due to increased transmission of UVB. Zenith angle, the angle at which sunlight reaches the surface of earth is decided by the thickness of ozone layer. The factors that affect the zenith angle affect no less the synthesis of vitamin D (Webb *et al,* 1988; Lu *et al,* 1992). Enzyme activity depicting synthesis, metabolism and action of the vitamin is charted in Fig. 1.

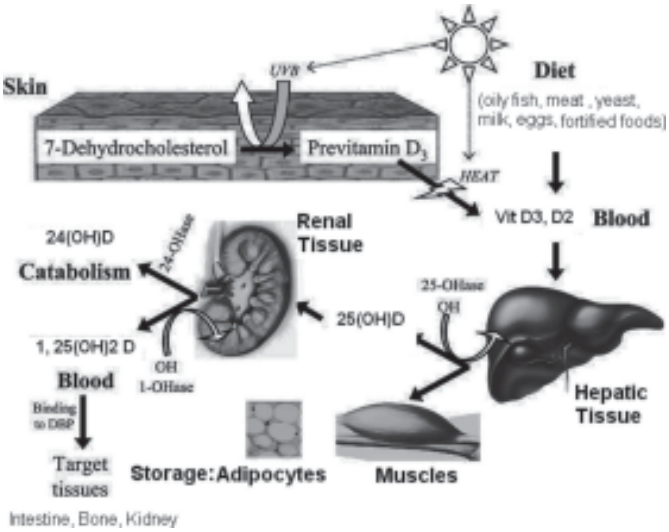
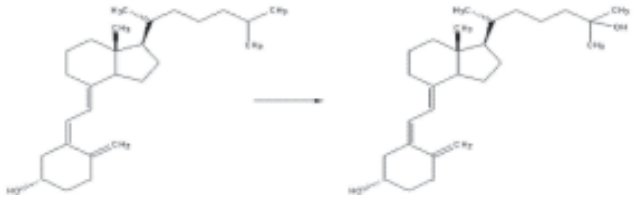


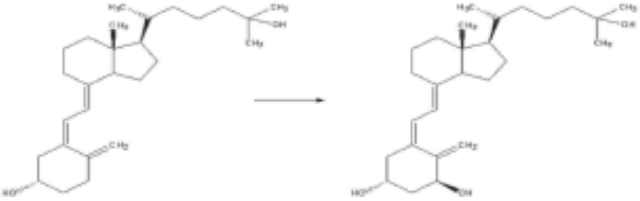
Fig. 1. Synthesis, Metabolism and Action of Vitamin D

1, α hydroxylase is a key factor in calcium homeostasis

Hydroxylations to 25(OH) D in the liver microsomes and subsequently to 1, 25$(OH)_2$ D in the mitochondria of proximal renal tubular cell, lead to the synthesis of functionally active vitamin D metabolites. The fact that Renal 1,α-hydroxylase enzyme activity is strictly regulated in response to low blood calcium level through parathyroid secretion and 1,α-hydroxylase synthesis points towards the important biological role of 1, 25$(OH)_2$ D in the regulation of calcium homeostasis (Bland *et al,* 1998). This is further lent economic edge through quick stimulation of renal 24, D-hydroxylase upon attaining normal serum calcium level to cause formation of inactive metabolite 24,25$(OH)_2$ D in place of the active 1, 25$(OH)_2$ D.



Liver hydroxylation to 25(OH) D; Calcidiol



Renal hydroxylation to 1,25$(OH)_2$ D; Calcitriol

Vitamin D transport

Vitamin D, insoluble in aqueous medium like lipids, is circulated in blood after binding with a carrier protein called vitamin D binding protein (DBP). DBP binds with molecules having vitamin D activity in the following sequence of affinity: 25 (OH) D $\geq$ 24,25$(OH)_2$ D > 1,25$(OH)_2$ D (Tanaka and Deluca, 1973). Blood plasma level of DBP is some 20 fold higher than that of vitamin D metabolites and consequently 99 per cent of the metabolites become protein bound with DBP. Vitamin D metabolites bound with DBP have limited access to vitamin D receptor (VDR) containing target cells and thereby increased half-life in circulation. This offers vitamin D metabolites protection from exposure to cellular metabolic processes. To put it succinctly, DBP protects vitamin D from being transformed by hepatic metabolism and alimentary excretion through biliary channels to maintain its level in the blood. Vitamin D level in blood and availability to the tissues are small. Besides helping in transport, DBP protects the tissues from accumulating toxic levels of vitamin D. In chronic liver diseases, nephrotic syndrome and protein malnutrition, when DBP concentration plummets due to a low protein level in blood plasma, there occurs the situation of susceptibility to vitamin D toxicity. During pregnancy and estrogen therapy, increased DPB concentration adversely affect the amount of vitamin D supplied to tissues (Kochupillai, 2008). 25(OH) D being the circulating metabolite of vitamin D has a concentration 100 to 1000 fold more abundant than that of 1,25$(OH)_2$ D. Likewise, half life of 1,25$(OH)_2$ D is only 4 hours as against 3 to 4 weeks of that 25(OH) D. All these facts point towards serum 25(OH) D level being the best biomarker for diagnosing VDD.

Calciotropic Action of vitamin D

Also known as calcemic or classical action of vitamin D, it has been long known to be less like other vitamins and more akin to steroid hormones making vitamin D acquire the sobriquet *vitamin D endocrine system*. It is serum calcium level getting below normal event that triggers the process of renal 1,α-hydroxylase enzyme mediated conversion of calcidiol (25-hydroxy D) to calcitriol (1,25-dihydroxy D) through the secretion and stimulating action of parathyroid hormone (PTH). The whole action consists of the following steps (DeLuca, 2004);

- PTH secretion in response to low serum Ca^{++} level induces the enzyme 1α-hydroxylase
- 1α-hydroxydase converts 25-hydroxy D into 1,25-dihydroxy D, which acts at the mucosal intestinal cells like a steroid hormone to cause calcium absorption
- Additionally, 1,25-dihydroxy D also acts at kidney and bone to conserve and normalize serum calcium level and bone remodeling
- With serum calcium level gaining normal level, there is resurrection of 24-hydroxylase activity at the expense of 1,α-hydroxylase to arrest the further synthesis and action of 1, 25$(OH)_2$ D

In medical science, vitamin D is very well known for its calciotropic effects on intestine, bone and kidney for a long time by the pioneering work of De Luca and other researchers (DeLuca and Schnoes, 1983). Calcitriol exerts these effects by binding to vitamin D receptors (VDR) a kind of nuclear hormone receptors. In vitamin D sufficient state, the net intestinal calcium absorption is in the range of 30-80%, which goes down to 10-15% in vitamin D insufficient state (Misra *et al*, 2008). As, 1,25$(OH)_2$ D enhances the efficacy of small intestine to absorb calcium and phosphorus with 1,25$(OH)_2$ D and VDR being required for optimal intestinal absorption of calcium. 1,25$(OH)_2$ D induces active calcium uptake by the intestinal mucosal cells and transport mechanisms. It needs epithelial calcium channel TRPV6 majorly and epithelial calcium channel TRPV5 to a small extent in order to transport calcium through the plasma membrane of intestinal mucosal cells. The calcium channels with the support of prealbumin and Na^+, Ca^{++} exchanger, mediate the delivery of calcium to the blood stream (Brown *et al*, 1999).

It is ironical that rickets, a disease of disturbed calcium homeostasis and a scourge from the ninetieth century remains still rampant and all pervasive due to poor sunlight availability in the countries situated towards the poles. A similar situation also develops due to sunlight owing to its intentional or incidental avoidance by poor outdoor activity, heavy clothing coverage and sunscreen application even in the inhabitants residing in the areas around equator that abound in sunlight. Besides, people of the developing countries have little access to vitamin D-fortified foods (Holick, 2006b).

The lactating mothers with insufficient levels of serum 25 (OH)D can, often unknowingly, impart vitamin D deficiency in breastfeeding children and the vicious circle moves on to graduate into intergenerational deficiency cycle of VDD.

A sizeable proportion (approximately 33%) of women in the age group of 60 to 70 and even higher (66%) of those over 80 remain stricken with osteoporosis (Michael, 2007). Osteoporosis has been found to be associated with VDD among elderly people, especially women. VDD causes a marked reduction in intestinal Ca absorption to unfavorably disturb Ca balance, which eventually results in low bone mineral content and density. Low bone mineral density (BMD) increases the risk of fractures,

which significantly increases the risk of morbidity and mortality among old age persons (Mussolino and Gillum, 2008; Suzuki and Yoshida, 2010).

Muscle weakness is still another prominent feature of VDD. People with nonspecific muscle inefficiency, muscle aches and pains have also been found to have insufficient vitamin D levels (Plotnikoff and Quigley, 2003). A normal blood serum 25 (OH)D level improves muscle performance and reduces the incidence of fall. In a randomized controlled trial, elderly people who received 800 IU of vitamin D and calcium daily for 150 days experienced about 70% reduction in the risk of fall as compared with those placed in placebo group (Broe *et al,* 2007).

It is a tribute to the prolific biologic action of vitamin D that $1,25(OH)_2$ D, the active metabolic form of vitamin D (calcitriol), produces its action both at genomic and non genomic levels as summarized below:

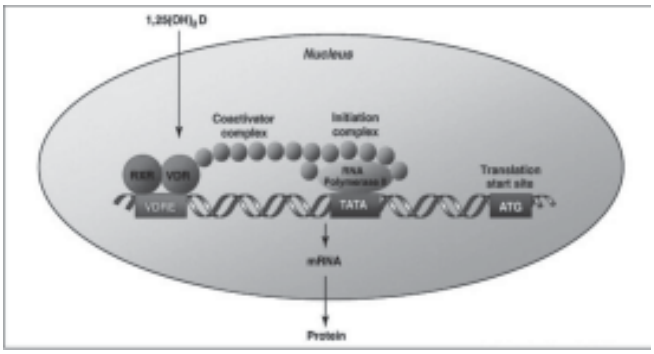


Fig. 2. Action of $1,25(OH)_2$ D (Calcitriol) on Genome

Action of vitamin D at genomic level: VDR, similar in action to the nuclear receptors for steroid hormones, have been categorized as a ligand activated transcription factor (Cooke and Haddad, 1989). The complex inters and intra macromolecular interactions between genomic elements and VDR-vitamin D complex form the basis for initiating transcription and subsequent expression of vitamin D responsive genes. The action of $1,25(OH)_2$ D (Calcitriol) on genome has been depicted schematically in Fig. 2.

Action of vitamin D at Non genomic level: There exist quick fire non-genomic actions of vitamin D, which are mediated through cell surface receptors. Vitamin D induced phosphoinositide metabolism changes the cytosolic calcium, cyclic GMP, mitogen activated protein (MAP) kinase and protein kinase C (PKC) levels along with opening up of chloride channels (Boyan *et al,* 1994), in a process of synergizing cell signals in to a rapid action caused by vitamin D without genomic involvement. In chondrocytes, this non genomic-action of vitamin D causes an increase in membrane-lipid turnover, prostaglandin production and protease activity generation leading to bone matrix modification and calcification (Boyle *et al,* 2003).

Twin evidences for the pleiotropic role of vitamin D

VDRs, first discovered in a number of non-skeletal tissues that include various immune cells and the tissues of heart, intestine, liver, kidneys, lungs, brain, muscle, skin, pancreas. The second, equally enterprising evidence, being the discovery of enzyme CYP27B1 (1,α-hydroxylase responsible for conversion of 25(OH) D into $1,25(OH)_2$D) in various tissues throughout the body (Heaney, 2008; Chesney, 2010), along with its action in an autocrine or paracrine manner (Bartoszewska *et al,* 2010). In a way non skeletal, pleiotropic effects of Vitamin D are mediated through the extra renal synthesis of $1,25(OH)_2$ D catalyzed by the enzyme activity 1, α- hydroxylase (CYP27B1). To emphasize, the nonskeletal autocrine effects of vitamin D are essentially different from it's skeletal effects in that the former operate outside the classical feedback-controlled endocrine loop (independent of regulation by low serum calcium, PTH secretion and subsequent renal 1,α-hydroxylase induction) (Chesney, 2010; Holick, 2007) and are more substrate dependent (Bikle, 2009). This calls for maintaining an adequate blood serum level of 25(OH) D, for regulating it's various non-skeletal functions. In essence, the autocrine pathway of vitamin D has three key features (Heaney, 2008):

(1) The bulk of the daily metabolic utilization of vitamin D is by way of the peripheral autocrine pathway

(2) Autocrine action always culminates in the expression of the 24-hydroxylase leading to the wiping out of locally synthesized calcitriol after it's action is over, so that no locally produced calcitriol enters the circulation

(3) Local concentration of calcitriol required to support various tissue responses remain higher than typical serum concentrations of calcitriol that circulated in blood to perform calciotropic role (Heaney, 2008). The locally synthesized $1,25(OH)_2$D (Calcitriol) becomes bound to VDR and the complex de-represses locked genes of information on DNA to synthesize specific mRNA and make the cells produce proteins through their protein biosynthetic set up for tissue specific responses. As amount of calcitriol produced locally is substrate dependent, optimal serum level of 25(OH) D (calcidiol) is crucial in maintaining ability of the cell to respond to pathological stimuli in a bid to eventually quell it, through autocrine pathway.

Since pleiotropic role of Vitamin D involves numerous bodily processes, it is but natural that VDD increases the

risk of a plethora of diseases ranging from autoimmune, cardiovascular and infectious diseases. An overview of the wide ranging pleiotropic role of vitamin D has been furnished in the text description that follows.

Vitamin D and Immunity

Human immune system is an elaborate network of specialized organs, tissues, cells, and chemical substances devised intricately to protect the host from infectious agents and other noxious injuries. The immune response to invading agents is divided into two interactive components: innate and adaptive immunity. Innate immunity, present at birth, provides first line of defense. It consists of skin, mucus secretions and the acidity of the stomach. Adaptive immunity, acts as the second barrier to invaders and is acquired later in life, such that following an immunization or after an exposure to infection. It retains memory of all the invaders faced by it and uses it to accelerate antibody production when the invasion occurs again. Although defense mechanisms involving innate and adaptive immunity are complex and often intertwined, they can be seen as being organized in three main components: physical barriers (e.g. skin, mucosa and mucus secretions), immune cells and immunoglobulin's or antibodies. Inter-individual variations in many immune functions exist within the normal healthy population and are due to variations of genetics, age, gender and virtues like healthy life style and habitual levels of exercise or of vices like alcohol consumption, lack of exercise, lopsided diets, stages in the female menstrual cycle and stress of one or the other kind (Calder and Kew, 2002). The interactions between nutrition, infection, immunity and health have been studied and conclusion drawn that nutritional status is very crucial in contributing immune competence (Scrimshaw *et al,* 1968; Calder and Jackson, 2000) to the human organism. In the recent decade, substantial research has focused on the role of micronutrients for optimal functioning of the immune system. One of the important micronutrients having a bearing on the immune system is Vitamin D.

As its biologically active metabolite calcitriol ($1,25(OH)_2$ D), vitamin D acts as a powerful immunoregulator (Cantorna *et al,* 2004). The discovery of significant quantities of VDRs in monocytes, macrophages, and thymus tissue suggests special and specific role of vitamin D in the immune system. A large number of cells of the immune system except B cells express VDRs (Veldman *et al,* 2000). It is documented in human epidemiological and animal studies that the occurrences of TH1-mediated autoimmune diseases are influenced by vitamin D status (DeLuca and Cantorna, 2001; Lemire *et al,* 1995). A further confirmation to this effect comes from the fact that supplementation with vitamin D becomes as an independent protective factor controlling the occurrence of T_H1 mediated autoimmunity (Hypponen *et al,* 2001).

All in all, available evidences point towards calcitriol playing the role of a regulator of immune system, preventing excessive expression of inflammatory cytokines and aptly increasing the 'oxidative burst' potential of macrophages. Above all, it seems to stimulate the expression of potent anti-microbial peptide, e.g. cathelicidine or LL-37 that pervades in neutrophils, monocytes and natural killer (NK) cells, as also in epithelial cells lining the respiratory tract where they play the all important role to protect the lung from infection. Human subjects, voluntarily inoculated with the attenuated influenza virus, have been found to develop fever along with serological evidence of immune response much more in the winter, a period of the year characterized by vitamin D insufficiency due to poor sunlight mediated vitamin D formation in skin than that in summer. Likewise, VDD has been seen to make children prone to lower respiratory tract infections. Ultraviolet radiations (either from artificial sources or from sunrays) reduce the incidence of viral respiratory infections, as does cod liver oil (Cannell *et al,* 2006). Incidentally, cod liver oil contains vitamin D in addition to vitamin A, a fact that led to the discovery of vitamin D a century ago by the stalwart of vitamin research McCollum (McCollum *et al,* 1922).

The potent effects of $1,25(OH)_2$ D in preferentially promoting cell-mediated T_H1 immunity have been proposed as one of the key mechanisms by which vitamin D can exert beneficial effects in keeping auto immune diseases under leash (Overbergh *et al,* 2000). The effects also include the generation of IL-10 producing T-regulatory lymphocytes (T_{REG}), also known as T suppressor cells, which promote tolerance to self antigen and thereby play no less role in intimidating auto immune diseases and host graft rejection in organ transplantation (Barrat *et al,* 2002).

A large number of reports point towards the role of vitamin D in the management and prevention of various diseases. Numerous trials have been conducted over the past three decades to probe the effects of vitamin D on disease management throwing lime light on vitamin D as a widely pervasive remedial agent with outcomes briefly recounted below:

Hypertension

Worldwide, hundreds of thousand people are afflicted with hypertension. In recent years, mounting evidence suggests the association of vitamin D with blood pressure.

Animal experiments implicate 1,25-dihydroxyvitamin D (calcitriol) mediated cell signaling (through liganded VDR) as an agent that regulates the expression of renin gene in the renin promoter region by binding to the nuclear CREB transcription factor to interfere with the formation of CRE-CREB-CBP complex and thus to scuttle the initiation of transcription of the rennin gene and cut off its synthesis with consequent deactivation of renin-angiotensin-vasopressin-aldosterone axis. The net effect of this intricate action is a decrease in extracellular fluid volume and lowering of blood pressure (Li *et al,* 2002; Lee *et al,* 2008; Michos and Melamed, 2008). Evidences indicate that VDD might be a determinant in the pathogenesis of cardiovascular diseases (CVD) and congestive heart failure (CHF) due to the possible combination of inhibition of VDR mediated Gla matrix protein expression causing activation of vascular calcification, increase in PTH levels accompanied by myocardial, valvular and vascular calcification as well as activation of pro-inflammatory cytokines and suppression of an anti-inflammatory cytokine IL-10 (Zittermann *et al,* 2005; Doherty *et al,* 2004).

Multiple sclerosis

Multiple sclerosis (MS), an autoimmune disease in which the body's immune system attacks a self antigen myelin, is a key cholesterol containing substance that serves as a nerve insulator to optimize on the transmission of nerve impulse in a steady, systematic manner. It has been long recognized that MS is more common in temperate climates than in the tropics (Martyn, 1991; Gale and Martyn, 1995) and winter season of low sunlight intensities has been found to reciprocally relate with the prevalence of MS (Acheson *et al,* 1960). Studies also documented that individuals with MS are likely to have insufficient serum 25 (OH)D levels (Nieves *et al,* 1994; VanAmerongen *et al,* 2004; Cantorna, 2008; Raghuwanshi *et al,* 2008). Similarly, VDD has been implicated as a triggering factor in inflammatory bowel disease (IBD), another one of auto immune disorders, as epidemiological studies support association between VDD and seasonal pattern in the onset of IBD (Deluca and Cantorna, 2001). Likewise, higher prevalence of IBD has been recorded in the geographical region of North America and Northern Europe with limited sunshine (Loftus, 2004).

Cancer

More than five decades ago, first study indicated that exposure to sun may reduce the risk of cancer (Peller and Stephenson, 1937). Recently, the discovery of increased risks of certain types of cancer in persons with vitamin D deficiency, suggests that VDD may account for high deaths from colon (Garland and Garland, 1980), breast (Garlend *et al,* 1990) ovarian (Lefkowitz and Garland, 1994) and prostate cancer (Schwartz and Hulka, 1990) every year.

Calcitriol or 1,25 $(OH)_2D$ is one of the most potent substances for regulating cell growth. As it has been reported that many cells have VDR which can be activated by complexing 1,25$(OH)_2$ D with then in to induce differentiation into normally functioning cells on one hand and inhibit proliferation, invasiveness, angiogenesis, and a propensity towards metastasis on the other. Further, in tumor model studies such as cancers of the lung (Young *et al,* 1993), colon (Evans *et al,* 2000), kidney (Fujioka *et al,* 1998), breast (Sundaram *et al,* 2003), and prostate (Lokeshwar *et al,* 1999); vitamin D has been observed to play a role in arresting metastasis (Tuohimaa, 2008).

In a study, 41 per cent lower risk of pancreatic cancer found in subjects consuming >600 IU vitamin D in comparison to those consuming a paltry, <150 IU daily and a reciprocal relationship also observed between vitamin D status and colorectal adenomas, endometrial and breast carcinomas (Skinner *et al,* 2006). In a Polyp Prevention Trial, 18 percent lower recurrence of adenomatous polyps among subjects on vitamin D supplementation were documented (Hartman *et al,* 2005). Mechanisms involving anticancer effects of vitamin D include cell differentiation, cell cycle regulation, induction of apoptosis, disruption of growth factor mediated cell survival signals as well as inhibition of angiogenesis and cell adhesion (Schwartz and Skinner, 2007).

Rheumatoid Arthritis (RA)

It is an autoimmune disorder of unknown etiology whereby both genetic and nongenetic factors contribute to disease susceptibility (Symmons, 2002). With the immunomodulatory effect of Vitamin D receiving increasing attention in recent years, the studies explicitly indicate that when confronted by an inappropriate and overly active immune response, vitamin D may act in a paracrine manner to tone down T cell responsiveness through the inhibition of cellular proliferation and reduction in lymphokine production (Leventis and Patel, 2008; Cutolo *et al,* 2007) and accomplish a beneficial, immunosuppressant action providing relief to the patients stricken with rheumatoid arthritis.

Diabetes Mellitus (DM)

A diabetes epidemic has emerged during the 20th century. The prevalence of diabetes for all age groups was estimated to be 2.8% in 2000 and it will increase to 4.4%

by 2030 (Wild *et al,* 2004). It has been reported as early as 1980s that VDD impedes pancreatic secretion and turnover of insulin, resulting in impaired glucose tolerance (Norman *et al,* 1980). An association was found between insufficient serum 25 (OH)D level and high incidence of type 1 diabetes, whereas the incidence rate tended to become low in regions with high UVB irradiance (Mohr *et al,* 2008).

Type 2 diabetes mellitus caused by defects in insulin secretion and insulin action, although its precise aetiopathogenesis is unknown. Environmental factors may have an accelerating or protective effect. Besides, they also act as triggers. Hypovitaminosis D has long been suspected to be a risk factor for glucose intolerance acting as a trigger for the onset of type 2 diabetes mellitus. In fact, prolonged treatment of osteomalacia with vitamin D increases insulin secretion and improves glucose tolerance. It has been shown that in human the risk of type 2 diabetes mellitus may be increased due to insufficient vitamin D levels (Isaia *et al,* 2001). Insufficient vitamin D levels were found in London Bangladeshi population who were at risk for type 2 diabetes compared with those who were not. These patients showed a higher prevalence of type 2 diabetes mellitus than British Caucasian population, suggesting that vitamin D status might contribute to the pathogenesis of the disease. The supplementation of vitamin D for short period increased insulin secretion in Bangladeshi Asian population without altering hyper glycaemia, while longer treatment also improved glucose levels (Boucher *et al,* 1995). The mechanism of action of vitamin D in type 2 diabetes is thought to be mediated not only through regulation of plasma calcium levels, which regulate insulin synthesis and secretion, but also through a direct action on pancreatic α-cell function (Zittermann, 2003).

Likewise, the onset of type 1 diabetes may be reduced by vitamin D supplementation via the potent effect of vitamin D on innate and adaptive immunity (Harris, 2005; Hypponen *et al,* 2001), especially by restoring T_{REG} functions (Gregori *et al,* 2002).

Tuberculosis (TB)

Tuberculosis is a global scourge responsible for 2 million deaths per year. It is estimated that one-third of the global population has latent TB infection (Dye *et al,* 1999), which poses great potential risks of reactivation in the future. In fact, before antibiotics came in to use, high doses of vitamin D were widely used to treat active TB (Martineau *et al,* 2007). Cross-sectional studies found insufficient vitamin D levels in subjects with TB compared to control subjects (Chan *et al,* 1994). The observation pertaining to low serum 25 (OH) D levels due to vegetarian diets has been found to be an independent risk factor for active TB in South Asians (Strachan *et al,* 1995). Similarly, VDD linkage with pneumonia, one of the most acute lower respiratory tract infection, has been the leading cause of death in children worldwide (Rathi and Rathi, 2011).

Thus vitamin D seems to play a role in immunological diseases (type 1 diabetes, asthma, multiple sclerosis, rheumatoid arthritis, inflammatory bowel diseases) through reduced activation of acquired immune system (Litonjua, 2009; Munger *et al,* 2006; Merlino *et al,* 2004; Cantorna *et al,* 2000), in various types of cancers through antiproliferative and prodifferentiating actions (Lappe *et al,* 2007) and in infectious diseases, fetal health, cardiovascular diseases, type II diabetes, and hypertension through enhancement of the innate immune system and production of antimicrobial peptides like cathelicidin or LL-37 (Urashima *et al,* 2010; Karatekin *et al,* 2009; Perez-Lopez, 2007; Mansbach *et al,* 2009). However, prudently planned and exquisitely executed randomized controlled trials need to be undertaken all across the globe to establish unequivocal non skeletal role of vitamin D.

As a matter of fact, the term VDD does not necessarily connote clinically explicit diseases; rather it means an increase in risk for certain diseases. As these diseases are multi-factorial, VDD, rather than being directly causal, acts by hampering the ability of tissues to deal adequately with physiological and pathological stimuli. Though sufficiency in vitamin D status cannot act as a panacea to wipe out these diseases altogether and the same will continue to occur even in the presence of optimum vitamin D levels, their risk will definitely be lowered (27) with favorable health implications for the masses. Fig. 3 gives an overview of the widespread biologic role of vitamin D.

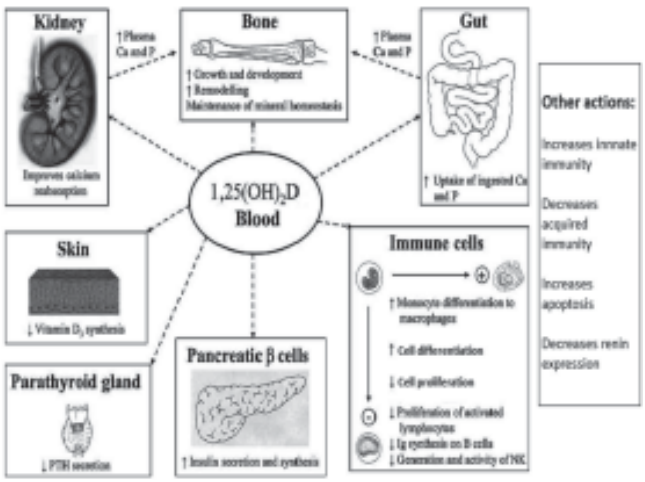


Fig.3. A bird's eye view of the wide spread biologic action of calcitriol

Detection of Vitamin D deficiency

In the face of alarming prevalence of VDD, its status and cut offs have been most appropriately classified on the basis of serum 25(OH) D levels, as depicted in Table 1. It is important to mention here that diagnostic testing for VDD is no easy task as it involves analysis of serum 25(OH) D by radio-immuno assay (RIA) technique which is a technical and costly affair and thus hardly accessible for common masses in developing countries.

Table 1. Cut off values used to detect subclinical VDD (Lips, 2001)

Vitamin D status	Serum 25 (OH) D level (ng/ml)	Serum 25 (OH) D level (nmol/L)
Intoxication	>150	>390
Excess	>100	>260
Sufficiency	20-100	52-260
Normal	?20	?52
Deficiency	< 20	<52
Mild	10-20	26-52
Moderate	5-10	13-26
Severe	<5	<13

• Blood serum equivalence: 20 ng/ml = 52 nmol/L=800IU

Intervention Strategies

WHO expert committee 2004 recommend 200IU/day for adults with good to moderate sun exposure and 400IU/day for those having sparse or no sun exposure. As per FAO/WHO Expert Consultation (FAO/WHO, 2004), in countries falling near the equator (between latitudes 420 N and 420S), the most physiologically relevant and efficient way to acquire vitamin D by an uninterrupted 30 minutes skin exposure of the arms and face (without sunscreen) to sun. A disruption in sun exposure during this period annuls the whole process needing a fresh 30 minutes to start the process from scratch to completion. Since VDD is no less than an epidemic in many developed and developing countries, India being no exception despite sunshine is plentiful (Harinarayan and Joshi, 2009), its alleviation calls for vitamin D supplementation depending upon the severity of inadequacy. One such scheme has been underlined in Table 2.

Table 2. Vitamin D doses based on serum 25(OH) D levels (Holick, 2006b)

Serum 25(OH) D (ng/ml)	Low dose vitamin D therapy (IU/day)	High dose vitamin D therapy (IU)	Total duration of therapy (in months)
<5	8000	50,000/weak (4 weeks) 50,000/fortnight (8 weeks)	3
5-15	4000	50,000/fortnight	3
16-30	2000	50,000/month	3

Vitamin D status

Worldwide Scenario

It is ironical that despite many reports on the association of vitamin D with a number of disease developments, treatment and health maintenance, VDD is becoming widespread in occurrence the world over. It is a significant public health problem in developed as well as developing countries. Worldwide status of vitamin D is as follows:

Asia

Vitamin D status of Indian population is mentioned under Indian scenario. The percentage of 25(OH) D levels <37.5 nmol/L were 38% and 50% in Bangladeshi women from high-income group and low income group, respectively (Islam *et al,* 2002). A mean of 25(OH) D, among healthy females in Sri Lanka, was 35nmol/L and 40.5% of them had serum 25 (OH) D levels less than 25 nmol/L (Rodrigo, 2007). In postmenopausal women, the prevalence of vitamin D deficiency, as serum 25(OH) D levels of less than 75nmol/L, in Thailand, Malaysia, Japan and South Korea the prevalence was 47%, 49%, 90% and 92%, respectively (Lim *et al,* 2008). A mean value of 25(OH) D amongst the women from Indonesia had 48nmol/L (Green *et al,* 2007).

A study in North China (Beijing) recorded 89% of adolescent girls with serum 25(OH) D <50 nmol/L (Foo *et al,* 2005). A dual-centered study from Beijing and Hong Kong documented more than 90% of young women with serum 25(OH) D levels less than 50 nmol/L (Woo *et al,* 2008). In Japan, the mean value of serum 25(OH) D was 30 nmol/L among inactive elderly and 34 nmol/L in women older than 30 years of age (Nakamura *et al,* 2001).

Europe

In Italian postmenopausal women, the mean serum 25 (OH) D was 45 nmol/l and 30% of them had levels lower than 25 nmol/l (Bettica *et al,* 1999; Isaia *et al,* 2003). In another study, the mean value of serum 25(OH) D was found to be 25nmol/l and 30 nmol/l in breastfed children and their mothers (Challa *et al,* 2005).

Africa

In Iran (Moussavi *et al,* 2005) and Saudi Arabia (Siddiqui and Kamfar, 2007), around 70% and 80% adolescent girls had insufficient vitamin D levels. In Saudi Arabia, the first study among adults and elderly revealed that mean 25(OH) D levels were in the range of 10 and 30 nmol/L (Sedrani *et al,* 1983). The mean 25(OH) D level was near 25 nmol/L in Lebanese, Saudi, Emirati and Iranian

women (El-Hajj and Deeb, 1999; Ghannam *et al,* 1999; Saadi *et al,* 2006; Gannage-Yared *et al,* 2000).

North America

In the USA, serum 25(OH) D levels assessed in a representative sample of 20,289 males and females in the national health and nutrition examination survey (NHANES) (Looker *et al,* 2008; Yetley, 2008). In the age categories of 1–5, 20–49, and 70 years and older, the prevalence of 25 (OH) D levels <50 nmol/L among males were found to be 8%, 29%, and 27%, respectively. Among females, serum 25(OH) D levels <50 nmol/L were documented to be 8.5%, 35%, and 34%, respectively in the above mentioned age categories.

Latin America

In Argentina, significant differences in mean values of 25(OH) D among healthy elderly men and women were showed between habitants of northern (52 nmol/L) and southern (36 nmol/L) provinces (Oliveri *et al,* 2004). A study of Mexican postmenopausal women from four different cities, were who were not taking any supplements, screened for osteoporosis, supported a very low level of serum 25(OH) D (Elizondo-Alanís *et al,* 2006).

Indian Scenario

VDD is a significant public health problem in India despite abundant sunshine. It is highly prevalent across all age groups from earlier infancy to elderly. Studies conducted in different regions of India documented high prevalence of VDD. Jain V et al conducted a study amongst 98 children, found 86.5% of children (0-3 months) with serum 25(OH) D <20ng/ml in New Delhi (Jain *et al,* 2011). Marwaha et al found 97.5% and 90.9% of school age children with serum 25(OH) D <20ng/ml from 124 and 166 children in lower and upper socio economic strata in New Delhi (Marwaha *et al,* 2010). Another study carried out in Chandigarh amongst 50 children in the age group of 6-12 years, revealed 32% prevalence of VDD (Borkar *et al,* 2010). In Lucknow, Sahu et al carried out a study amongst 121 children aged 10-20 years found 88.6% of children with serum 25(OH) D <20ng/ml (Sahu *et al,* 2009). In New Delhi, the percentage of children (6-18 years) from lower and upper socio economic strata with serum 25(OH) D <20ng/ml were found to be 89.6% and 91.9% (Puri *et al,* 2008). A recent study from Maharashtra amongst 1137 adults found 62% and 76% of male and female with serum 25(OH) D <20ng/ml (Shivane *et al,* 2011). Goswami et al conducted a study in Uttar Pradesh, documented 68.5% of adults (>18 years) with serum 25(OH) D <20ng/ml (Goswami *et al,* 2008). Marwaha et al conducted a study amongst 1,346 elderly (>50 years), found 91.2% prevalence of VDD (Marwaha *et al,* 2011). One study from 150 elderly in Tamil Nadu, documented 49.5% subjects with serum 25(OH) D <20ng/ml (Paul *et al,* 2008).

Conclusion

VDD prevalence reports from across the continents point towards VDD as a global, untreated, unrecognized pandemic, rampant even in countries with abundant sunshine. Health implications of this vitamin have also assumed importance in the face of research findings that recognize non calcemic or pleiotropic effects of vitamin D as a potentially significant component of the biologic action of vitamin D. Active vitamin D metabolite; $1,25(OH)_2$ D (calcitriol), stimulates innate (microphage) immunity by enhancing bacterial killing on one hand and modulates adaptive (lymphocyte) immunity to minimize inflammation and thereby reduces the occurrence/ management of autoimmune disease on the other. Association of VDD and diseases like cancer, hypertension, multiple sclerosis, inflammatory bowel disease, rheumatoid arthritis, rickets, osteoporosis, muscle weakness and diabetes mellitus has been reported through several studies secularly across the globe. Calcitriol acts on target genomic receptors in several organ systems to control proliferation, differentiation, genetic expression and cell signaling. Diagnosing vitamin D insufficiency, a costly and expert based affair, needs to be made accessible to the masses accompanied by appropriate vitamin D intervention programmes and awareness strategies to raise vitamin D status to sufficient levels.

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