NFI BULLETIN
Bulletin of the Nutrition Foundation of India
Volume 35 Number 3 July 2014

The Multiple Roles Of Vitamin D

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For more than a century, vitamin D deficiency has been of interest to specialists in diverse fields - internists, pediatricians, physicians, radiologists, orthopaediacians, pathologists, endocrinologists, nutritionists, ecologists, environmentalists and geneticists- because of its wide spectrum of clinical, biochemical, and pathological presentations. Vitamin D has been traditionally known as the 'anti-ricketic factor' or 'sunshine vitamin'. It is unique because it is an endogenously synthesized vitamin that also functions as a hormone. Besides its pivotal role in calcium homeostasis and bone mineral metabolism, the vitamin D endocrine system is now recognized to subserve a wide range of fundamental biological functions in cell differentiation, inhibition of cell growth, and immunomodulation[1-5].

Terminology and synthesis

Vitamin D occurs in different forms, namely, cholecalciferol, calcidiol [25(OH)D], and calcitriol [1,25$(OH)_2D_3$]. Vitamin D_2 (ergocalciferol) is derived from plant and vegetable sources. Vitamin D_3 (Cholecalciferol) is the naturally occurring form of vitamin D. It is synthesized in substantial quantities in skin exposed to sunlight, and is transported to the liver where it is metabolized into the prehormone, calcidiol, or 25-hydroxyvitamin D [25(OH)D]. Vitamin D orchestrates the "Calcium (Ca)-vitamin D-parathyroid hormone (PTH) endocrine axis".

Casual exposure to solar radiation of wavelengths 290 – 315 nm results in the cutaneous production of previtamin D_3[6]. During exposure to the sun, the UVB photons (290-315 nm) that enter the epidermis cause a photochemical transformation of 7-dehydrocholesterol (7-DHC) (provitamin D_3) into cholecalciferol (previtamin D_3). The previtamin D_3 thus formed is also photolabile, and therefore excessive sunlight exposure results in its photoisomerization to at least two biologically inert products, lumisterol and tachysterol[7]. In the liver previtamin D_3 is converted into calcidiol [25(OH)D].

Tissue-specific actions

Calcidiol has steroid-like properties. After hepatic conversion of cholecalciferol into calcidiol [25(OH)D], calcitriol[1,25$(OH)_2D_3$] is produced in the kidneys and in other tissues. It is the most potent steroid hormone derived from cholecalciferol (Figure 1). Calcitriol follows either of two pathways (Figure 2).

Genomic responses: These generally take anything from a few hours to days to become fully manifest. The vitamin D receptor (VDR) forms a heterodimer with the retinoid X receptor (RXR) to form a 1,25$(OH)_2D_3$-RXR-VDR complex. This receptor complex interacts with specific DNA sequences and vitamin D-responsive elements (VDRE) located within introns and/or at large distances from the transcription start site[8]. The control of transcription requires additional recruitment of co-regulators that may be either inhibitory (co-suppressors) or stimulatory (co-activators)[8,9]. Certain genes are selective for the co-regulators that combine with VDR and regulate their transcription. These genomic responses can be blocked by inhibitors of transcription and translation[10].

Chemical messenger: 1,25$(OH)_2D_3$ serves as a chemical messenger that transmits signals and rapid responses (RR) (e.g. opening of ion channels). The RR are mediated by a variety of receptors located in proximity to or associated with plasma membrane or its caveolae components[9]. Caveolae are flask-shaped membrane invaginations that are rich in spingolipids and cholesterol commonly found in both caveolae and/or lipid rafts[11]. The time required for RR to manifest vary from just a few seconds (opening of ion channels) to as long as 10-60 minutes (e.g. activation of phosphotidylinsoitol-3'-kinases, endothelial nitric oxide synthatase). Examples of RR include rapid intestinal absorption of calcium (transcaltachia), secretion of insulin by pancreatic β-cells, opening of voltage-gated Ca+ and Cl- channels of osteoblasts, and rapid migration of endothelial cells[8,11]. One isomeric form of 1,25$(OH)_2D_3$ is used for genomic response and a different isomeric form serves as an agonist of rapid response[11]. The ability of individual tissues to produce their own 1,25$(OH)_2D_3$ in a tissue-specific fashion explains how vitamin D regulates many functions in many tissues so selectively (Figure 2).

Factors affecting vitamin D synthesis

The ability of the skin to synthesize previtamin D_3 is affected by latitude, the revolution of the Earth around the sun (season of the year), and the rotation of the Earth on its own axis (day/night). Atmospheric pollution attenuates solar radiation. [Clothes, skin pigmentation, and application of sun protection factor (SPF) of 15 in combination can reduce UVB penetration into epidermis by >95 thereby limiting the production of previtamin D_3 by the skin. With advancing age, the cutaneous 7-DHC levels decline, reducing the skin's capacity to produce vitamin D_3. With the increase in solar

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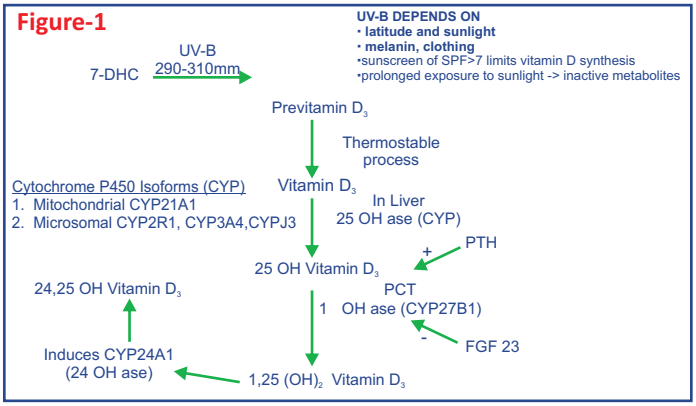

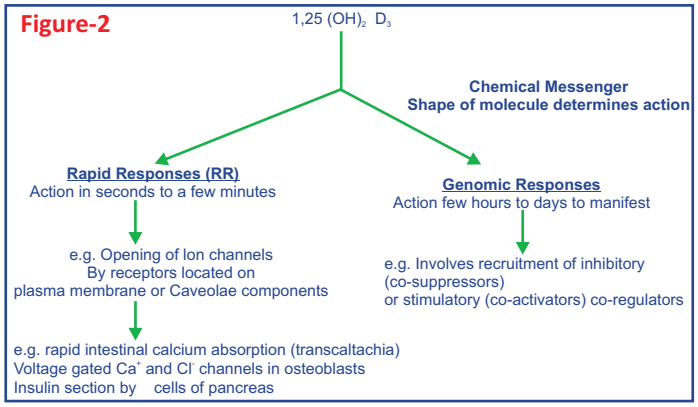

zenith angle in winter (the angle of the sun's rays becomes more oblique), fewer of the UVB photons penetrate the atmosphere to stimulate the production of cutaneous previtamin D_3. In addition, the amount of UVB radiation reaching the earth's surface is a function of the ozone, cloud cover, aerosols in the atmosphere, latitude, and altitude; all these, therefore, influence the cutaneous production of vitamin D_3[12]. Chen et al.[13] reported that little, if any, cutaneous production of previtamin D_3 occurs at latitudes above 35° N and below 35°S during winter months. At latitudes greater than 51° (north and south of the equator) the UV index is less than 0.5 in winter months. Casual exposure to sunlight will not result in any appreciable vitamin D_3 synthesis during these periods, which are therefore called "vitamin D winters"[14]. It has been assumed that those residing in the tropics can produce enough vitamin D_3 in the skin throughout the year[15].

In healthy individuals, therefore, vitamin D levels are influenced by a wide variety of factors. The most important of these are the solar zenith angle (SZA), minimal erythemal dose (MED), skin type, UV index and the geographical location where the study is conducted[16]. Whenever we interpret 25(OH)D levels, it should be done against the background of the factors mentioned above. The UV index is calculated from a combination of latitude, time of year and day, total ozone overhead, elevation above sea level and amount of cloud cover. The UV index for any specific location can be obtained from the following websites [17]:
http://sedac.ciesin.columbia.edu/ozone/rtm/mval.html
http://www .temis.nl/ uvradiation/nrt/uvindex.php

Minimal Erythemal Dose (MED) is the amount of sun exposure which causes barely perceptible skin burn (erythema) appears within 24 hours in previously unexposed skin[18]. Skin type of various races are categorized based on skin color (pigmentation), eye color and hair color, reaction to sun whether it freckles, burns, peels, blisters or tans[14,18-20]. There are six skin types. These six types of skin are based on degree of pigmentation and propensity to burn or tan. The lightest north European skin is classified as type I and African skin as category VI. Indians come under the skin type V category. India is located 8.4° and 37.6° N. The time required to obtain recommended UV dose for adequate vitamin D synthesis is "1 Standard Vitamin D Dose" (SDD)[21,22]. Throughout the year 1 SDD for skin type V (Asians) at 11.5°N is 10-15 minutes, and at 29°N is 10-45 minutes at noon, with longer duration in winter. Clouds, aerosols and thick ozone can reduce vitamin D synthesis and force "Vitamin D winter" even at equator.

Assays for vitamin D
Normal range

Earlier, serum vitamin D estimation was plagued by methodological issues[23-25]. The first ever assay carried out by our group was a titrated assay (^{3}H) for evaluating the vitamin D status in patients with primary hyperparathyroidism and in a control group[26]. With the evolution of ^{125}I radioimmunoassay (RIA) for estimation of serum 25-hydroxyvitamin D [25(OH)D] the methodological differences have vanished, permitting an inter-laboratory comparison of values. The currently available assays have antibodies co-specific to both 25(OH)D_2 and 25(OH)D_3, and hence the terminology 25(OH)D assays are used. Laboratories generally estimate 25(OH)D levels and not 25(OH)D_2 or 25(OH)D_3[27-30]. Presently, ECLISA is replacing the RIA because of its greater simplicity of usage. This assay measures 25OHD and its products. LCMS (Liquid Chromatography Mass tandem Spectrophotometry) is the gold standard method of measuring vitamin D; in this method, 25(OH)D_2 and 25(OH)D_3 are measured separately and added to get the "total 25(OH)D".

In clinical chemistry departments, the normal ranges for most of the analytes measured are derived from the values found in 95 percent of the population. However, such reference data would be unreliable in the case of 25(OH)D[30]. Since vitamin D levels are subject to variations in diet, clothing, latitude and altitude of residence, skin color, climate etc., the normative data vary among laboratories[31-34]. These genuine geographic variations in calcium homeostasis restrict the locally estimated reference range to be used across countries. On the other hand, the use of a locally developed "population based reference value" could result in a person becoming 'vitamin D deficient' enroute from one country to another! A "functional health based reference value" which physiologically defines hypovitaminosis D as the concentration of 25(OH)D at which PTH begins to increase is largely replacing the hitherto used "population based reference value". It is no longer appropriate to analyze serum 25(OH)D levels with respect to ranges supplied by a manufacturer[35-38].

Vitamin D deficiency

Serum 25-hydroxyvitamin D [25(OH)D], Calcidiol, is the storage form of vitamin D, and the most reliable indicator of the vitamin D stores of an individual. It is therefore the one tested for in routine assays to determine deficiency/adequacy of the vitamin[30]. The production of 25(OH)D is not regulated, and therefore the concentration of the compound in serum reflects both cutaneous synthesis and absorption from the diet. The half-life of 25(OH)D is about six weeks. Biochemically, levels of 25(OH)D >30 ng/ml (*to convert ng/ml to nmol/ml multiply by 2.5*) are considered as 'normal'. Levels between 20 and 30 ng/ml are defined as 'insufficiency', and levels <20 ng/ml are defined as 'deficiency'.

Vitamin D levels and bone health

It is well documented that calcium absorptive performance of the gut is a function of the 25(OH)D status of an individual[37-39]. Absorption is optimal at 25(OH)D levels >30 ng/ml, and when the levels are low, the effective calcium absorption from the gut is reduced. The resulting SHPT, a "physiological adaptive phenomenon", leads to accelerated bone remodeling, bone resorption, and increased risk of fracture[40-42].

The progression of Vitamin D deficiency is well understood. It begins with hypovitaminosis D and is followed by SHPT (a prolonged phase

of high bone turnover with possible irreversible bone loss, especially cortical bone), and culminates in defective mineralization of bone manifesting as osteomalacia in adults and rickets in children. [43]. Low dietary calcium intake further amplifies the parathyroid response to vitamin D insufficiency[44].

Vitamin D status in India

Vitamin D deficiency is a new emerging global health threat. This hidden problem, now being unraveled, is a much larger potential health burden than just merely rickets or osteomalacia. It is reaching epidemic proportions in both the developed and the developing countries. The problem has increased to alarming proportions after the new definition of 25(OH)D norms and the consequences for bone health. It has generally been believed that rickets and vitamin D deficiency are uncommon problems in India because of the abundant sunshine[45]. There is now increasing evidence to contest this belief. The first ever observation of vitamin D deficiency in India was from our studies on patients with primary hyperparathyroidism as compared with normal controls[26]. It is now recognized that vitamin D deficiency is a common problem in India. Some of the factors that are thought to be responsible for the high prevalence of vitamin D deficiency in Indians are:

- Modernization[46] and changing work culture result in an increase in the number of hours spent indoors, thereby preventing adequate exposure to sunlight, especially in urban Indians.
- Culturally, Indians avoid the sun for fear of skin darkening (tanning) or just because of the heat. This sun-fleeing behaviour contrasts with the sun-seeking behaviour of western society (Europeans or North Americans).
- Clothing habits – traditionally, Indians, tend to keep their bodies well covered even when out in the sun; the use of "burqa" and "*pardah*" further reduce skin exposure to sunlight in women.
- Skin pigmentation- Melanin in the skin competes with 7-dehydrocholesterol for UVB rays. The greater the amount of melanin in the skin, the lower is the efficiency of vitamin D synthesis. Skin with darker pigmentation, like those of most Indians, requires a longer duration of sun exposure to synthesize an equivalent amount of vitamin D as compared to Caucasian skin. Indians' skin comes under type V category.
- Atmospheric pollution plays a role in reducing the efficiency of vitamin D photosynthesis. Pollution scatters short UVB wavelengths. There is a report of high incidence of vitamin D deficiency rickets in toddlers living in areas of high atmospheric pollution in Delhi, India (28.35° N)[47,48].
- Food fads and changing food habits often contribute to low dietary intake of calcium and Vitamin D. A high-fiber diet containing phosphates and phytates can deplete Vitamin D stores and increase calcium requirement[49].
- Food habits and lack of fortification: Other than fatty fish (widely consumed in Japan) very little vitamin D comes from the diet. Such fish are hardly ever consumed in India. There is negligible vitamin D available from dietary sources in India., Unlike many Western countries where milk, margarine, orange juice and other commonly consumed food items are fortified with vitamin D, India does not have vitamin D fortification of food. Low dietary calcium intake [far less than the recommended dietary allowances (RDA) further aggravates the problem[49-51].
- Repeated, unplanned and unspaced pregnancies in women who are already deficient in dietary calcium can aggravate vitamin D deficiency in the mother and the foetus.
- It has been shown that increments in serum 25(OH)D in response to treatment depend on the heritability of vitamin D-binding protein.

Dietary calcium intake

At the cellular level, Calcium and vitamin D are closely linked in their action. Vitamin D status surveys from rural south India (Tirupati) have demonstrated that Vitamin D levels are higher in agricultural workers who are exposed to long hours of sunlight as part of their work (~24 ng/mL Vs 19 ng/mL) as compared to urban dwellers[49-51]. In spite of the high exposure to sunlight, serum vitamin D levels were significantly lower than expected for the duration of sunlight exposure. Studies on dietary habits of this population[49-51] have demonstrated that these persons habitually consume low-calcium, high-phytate diets . Of the daily diet of 1700 KJ/day approximately in these rural individuals, carbohydrates provided 75% of the total energy intake, proteins 10%, fat 5%, vegetables 5%, and milk and milk products 5%. The carbohydrate sources were cereals [Rice – 60% and Ragi-40%]. Animal sources of protein were consumed approximately once in two weeks only. In the diets of urban individuals, with a total energy intake of 2200 KJ/day approximately, carbohydrates provided 55% of the total energy intake, proteins 10%, fat 10%, vegetables 10%, and milk and milk products 15%. The carbohydrate sources were primarily cereals (rice 50%, wheat 25%, and ragi 25%). Animal sources of protein were consumed only once a week. There was no other source of calcium or any other mineral in either of the groups. Milk in India is not fortified with calcium or vitamin D. The daily dietary calcium intake reported in both rural and urban populations in the Tirupati study were low (mean + SEM: rural 264 ± 1.94; urban 354 ± 5 mg/day) as compared to the Recommended Daily/Dietary Allowance (RDA) for Indians (800mg/day). The consumption of Ragi (rich in phytates) by the rural population retards the absorption of calcium from the gut. Similar calcium-deficient diets have been reported in other Indian studies as well[49-51]. The average dietary calcium intake in India seems to be 430 ± 180 mg/day in children and 560 ± 310 mg/day in adults [49-51]. All studies have uniformly documented low dietary calcium intake as compared to the ICMR's RDA norms.

Low calcium intake increases parathyroid hormone (PTH), which in turn increases conversion of 25(OH)D to 1,25-dihydroxyvitamin D. In addition, 1,25-dihydroxyvitamin D induces its own destruction by increasing 24-hydroxylase[44]. This probably explains the low 25(OH)D concentrations in persons on a high-phytate or a low-calcium diet. It is, therefore, essential that calcium supplementation should be made an integral part of vitamin D supplementation therapy in India.

Vitamin D and peak bone mass

Adequate calcium intake along with vitamin D helps to maintain bone mineral mass attained at the end of the growth period in an individual (peak bone mass). Low 25(OH)D levels in Indians may at least in part be responsible for lower peak bone mass and lower bone mineral density (BMD) as compared to Europeans and Americans. During infancy, childhood and adolescence, an increase in dietary calcium intake favors bone mineral accrual. Adequate nutrition and sufficient physical activity to provide mechanical impetus for bone development are critical in attaining bone growth potential. Vitamin D and calcium status correlate with increased bone mineral density and have the potential to increase the peak bone mass and effectively prevent osteoporosis at a later age[52-54].

Vitamin D status in adults

Recent studies from India have shown high prevalence of vitamin D deficiency in both rural and urban populations of adults, in north as well as south India[55]. However, the only large population survey of vitamin D and dietary calcium is from rural and urban south India[51]. It has been shown in population surveys from south India (Tirupati latitude 13.40^{0}N and longitude 77.2^{0}E) that even rural adult agricultural labourers, despite being exposed to sunlight for more than 4 hours with at least 35% of their body surface area exposed to sunlight, still show vitamin D deficiency[51,52].

Vitamin D status in pregnancy and lactation

Indian studies on vitamin D status in pregnant and lactating women showed a very high prevalence of hypovitaminosis D (84-93%)[56]. Significant changes occur in maternal vitamin D and calcium metabolism during pregnancy to provide calcium for foetal bone

mineral accretion. Approximately 25-30 gms of calcium is transferred to the foetal skeleton during the last trimester of pregnancy. Dietary calcium deficiency is known to predispose to hypovitaminosis D by rapid inactivation of circulating 25(OH)D[44]. The problem of hypovitaminosis D is worsened in pregnant women because of the active transplacental transport of calcium to the foetus. From the point of view of foetal health, foetal vitamin D concentrations are dependent on maternal concentrations, and therefore maternal vitamin D deficiency may lead to an adverse outcome in the offspring. Vitamin D is known to be involved in skeletal homeostasis in utero; infants born to severely vitamin D - deficient mothers may have tetany due to severe hypocalcemia or may manifest craniotabes (thinning of skull).

Vitamin D status in neonates and infants

Low vitamin D levels in mothers results in low vitamin D levels in offspring. Studies from India have shown significant correlations in 25(OH)D levels between mother-infant pairs. Exclusively breast fed infants have low 25(OH)D levels. It is observed that vitamin D supplementation in young children resulted in significant increase in SD scores for weight, length and arm circumference and a decrease in the proportion of children with stunted growth. Children of mothers who had higher dietary intake of calcium rich foods during pregnancy had higher spinal bone mineral content (BMC)[57]. Intrauterine exposure of foetus to low vitamin D concentrations is associated with less muscle mass and insulin resistance[58]. Foetal vitamin D deficiency is also likely to adversely affect childhood bone development and innate immune function. Studies have shown that vitamin D supplementation during pregnancy is safe and improves the vitamin D status of the offspring[59].

Vitamin D status in Children

Studies show that 60-80% of the variability in bone mass is due to genetic factors, with the rest being attributable to nutrition, lifestyle, physical activity and hormonal factors. Approximately 40-50% of total skeletal mass is accumulated during childhood and adolescence. It is during this period that calcium and vitamin D nutrition and non pharmacologic strategies should be adopted to have the maximum impact on peak bone mass.

The mean serum concentrations of 25(OH)D reported in children and adolescents from urban northern India were 11.8 ± 7.2 ng/ml and 13.84 ± 6.97 ng/ml, respectively[60]. These were lower than those reported in children from southern India[51]. The mean 25(OH)D concentrations in adolescents in urban and rural Andhra Pradesh were 17 ng/ml and 18 ng/ml, respectively[51]. An objective evaluation of the association between nutrition and life style clearly revealed a significant correlation between serum 25(OH)D and estimated sun exposure ($r=0.185$, $p<0.001$) and percentage body surface area exposed ($r=0.146$, $p<0.004$) but not socio-economic status, suggesting that life-style related factors contribute significantly to the low vitamin D status of apparently healthy school girls. The functional significance of low serum 25(OH)D in Indian children is reflected in their serum PTH values[49-51].

Vitamin D status in the reproductive age group

Available data from population surveys indicate that the Vitamin D status of women in reproductive age groups is uniformly low in both north and south India[49-51,61-63]. Low vitamin D status and low dietary calcium in reproductive-age women, coupled with unplanned and unspaced pregnancies, lead to decrease in bone mineral density and consequent low peak bone mass, rendering these women vulnerable to postmenopausal osteoporotic fractures later in life.

Vitamin D status in post menopausal women

Evaluation of daily dietary calcium intake, phytate-to-calcium ratio, and bone mineral parameters in south Indian, postmenopausal women (n=164) showed that their dietary intake of calcium was low compared with the RDA for Indians. Around 85% had either insufficiency or deficiency of 25(OH)D. PTH and serum alkaline phosphatase levels were significantly higher in patients with 25(OH)D deficiency ($p<0.05$) as compared to those with normal 25(OH)D levels. There was a negative correlation between 25(OH)D and PTH ($r= 0.2$; $p<0.007$) and SAP ($r=0.2$; $p<0.001$). The study concluded that the quality of the diet has to be improved, with enrichment/ supplementation of calcium and vitamin D in order to suppress secondary hyperparathyroidism-induced bone loss and risk of fractures in post-menopausal women[17,31]. In a study of vitamin D status in postmenopausal women from south India, it was found that vitamin D deficiency coexists with low bone mineral density (BMD). This points to the need to document serum 25(OH)D levels in women with low BMD. Calcium and vitamin D supplementation should form part of therapy in postmenopausal women[17,31]. Similar findings were reported from studies carried out in north India.

Vitamin D requirements and supplementation

The FAO/WHO Expert Consultation states that the most physiologically relevant and efficient way of acquiring vitamin D, in most locations in the world around the equator (between latitudes 42°N and 42°S) is to synthesize it endogenously from skin from 7-dehydrocholesterol present in the subcutaneous fat through a minimum of 30 minutes of skin exposure (without sunscreen) of the arms and face to the mid-day sun[65].

Vitamin D synthesized in the skin lasts two times longer in the body as compared to supplemental/ ingested doses. It has been concluded from the experimental data that exposure of the body in a bathing suit (almost 100% of body surface area) to sunlight that causes slight pinkness of the skin (1 MED -minimal erythemal dose) is equivalent to ingesting approximately 20,000 IU of vitamin D orally. Therefore, exposure of 6% of the body to 1 MED is equivalent to taking about 600 and 1,000 IU of vitamin D[66]. Applying the rule of nines Burns chart, exposure of both forearms and the face is equivalent to exposing 12% of body surface area. For Caucasian skin (type 2 or 3), exposing the face, arms and legs for a period equal to 25% of the time that it would take to cause 1 MED, two to three times a week can meet the body's vitamin D requirement while minimizing sun damage (" Holick's rule")[67]. Asians have darker skin (type V) and therefore, with the same amount of MED, they would require a longer duration of sun exposure than their light-skinned counterparts to synthesis comparable amounts of vitamin D_3[66].

The time required to obtain the recommended UV dose for adequate vitamin D synthesis is "1 Standard Vitamin D Dose" (SDD). Throughout the year 1 SDD for skin type V (Asians) at 11.5°N is 10 – 15 minutes, and at 29°N is 10-45 minutes at solar noon, with longer durations in winter. SDD for skin types is collected on MED. Clouds, aerosols and dense ozone can reduce vitamin D synthesis and force "Vitamin D winter" even at the equator. India is located at between 8.4 and 37.6°N. In a study from south India (Tirupati latitude 13.4°N and longitude 77.2°E) using 'in vitro' ampoule model with precursors of Vitamin D (7 Dehydrocholesterol), when exposed to sunlight, converted to active vitamin D best between 11 a.m. to 2 p.m (mid-day sun)[67]. The median percentage conversion of 7-DHC to previtamin D_3 and its photoproducts and percentage of previtamin D_3 and vitamin D_3 formed were 11.5% and 10.2%, respectively at a solar zenith angle of 36.8° at 12:30 p.m. From the various studies in the literature, it would appear that the 25 (OH)D levels in South Indian subjects are relatively higher than in subjects in North India. There is a strong inverse correlation between the 25 (OH)D levels and latitude ($r = -0.48$; $p < 0.0001$), clearly establishing the relationship between closeness to the equator (smaller zenith angle) and natural Vitamin D synthesis[67]. Studies from Pune (latitude 18.31°N and longitude 73.55°E) have shown that toddlers exposed to sunlight (playing outside) for more than 30 min a day, exposing more than 40% of their body surface area, had a normal vitamin D status (M: 36.6 ng/ml and F: 27.1 ng/ml), three times more than the toddlers who were indoors for most part of the day (M: 12.8 ng/ml and F: 8.4 ng/ml)[68]. A study in toddlers in Delhi slums (latitude 28.35°N and longitude 71.12° E) demonstrated that those who were exposed to sunlight had better vitamin D levels (~ 25 ng/ml) as

compared to those who were not (~ 8ng/ml). Interestingly, authors of this study also identified (albeit retrospectively) that families whose toddlers were exposed to sunlight had been given educational material by the local healthcare workers explaining the benefits of exposure to sunlight[68].

Muscle strength and Vitamin D

Muscle strength plays an important role in determining risk for falls, which result in fractures and other injuries. Muscle wasting is a multifactorial process involving intrinsic and extrinsic alterations. There are studies to show moderate inverse relationship between vitamin D status and muscle strength[69]. Randomized controlled trials (RCTs) of the effect of vitamin D/calcium supplementation on skeletal muscle strength have not shown positive effects in the elderly. Oral cholecalciferol/calcium supplementation in the dose/schedule that is generally used for increasing and maintaining serum 25(OH)D did not lead to improved skeletal muscle strength in young women[70].

Recommended dietary allowances of calcium and vitamin D for Indians

According to the revised norms for Indians (ICMR 2010), the RDA of calcium (mg/day) for children 1-9 years of age is 600; for children (both genders) 10 – 18 years age is 800; for adults (both men and women) is 600; and for pregnant and lactating women, 1200.

The committee was of the view that the recommendations by international agencies regarding vitamin D fortification and supplementation pertain to populations in developed countries where exposure to sunlight is limited. The committee felt that outdoor physical activity is a means of not only achieving adequate synthesis of vitamin D but also of controlling overweight and obesity in the Indian population. The committee retained the earlier recommendation of 400 IU (10 µg) per day for adults. This is far less than the corresponding norm in the USA and Canada. From a systematic review of available evidence from published data it was calculated that 1 mcg of vitamin D (40 IU) will increase serum 25 (OH)D levels by 0.79 ng/mL (1.95 nmol/L), which means 360 IU of vitamin D are required to rise serum vitamin D levels to more than 10 ng/ml (25 nmol/L)[71].

Human beings can get vitamin D from abundant sunshine, by exposing 18% of body surface area to mid day sun for 30-45 minutes (without sunscreen). Pragmatically, in geographical areas and in seasons with abundant sunshine, school teachers could be educated as part of their curriculum training to encourage students to expose themselves to sunlight as much as possible during the lunch recess, by naming it “sunshine hour”. Toddlers, children, and the elderly should be encouraged to sit/play outdoors in the midday sunlight for about 30 minutes. Such an approach, with equal emphasis on knowledge empowerment (regarding the importance of sunlight exposure) may go a long way towards improving the vitamin D status of the Indian population. In populations where there is limited exposure to sunlight, it may be necessary to promote the avoidance of sunscreen lotions with SPF >8 and the wearing of clothes that allow some skin exposure to sunshine, besides providing vitamin D supplementation as may be required.

Loading dose/therapeutic dose and continued vigilance

In India, most of the supplementation schedules for correcting vitamin D deficiency using either vitamin D alone[72] or vitamin D plus calcium[73,74] have shown that normal levels can be achieved at the end of two months at a dosage of 60,000 IU weekly for 8 weeks along with elemental calcium of 1 gm/day[73]. One Indian study has emphasized the need for maintenance therapy after achieving normal vitamin D levels[74]. These data clearly raise two important concerns. First, at the population scale, at least in the short term, simple supplemental doses without adequate loading doses may not be sufficient to achieve therapeutic levels, particularly in those who would benefit from immediate increase in vitamin D levels (e.g. the elderly at risk of osteoporotic fractures); second, fortification/supplementation with vitamin D, if not sustained in the long term, may not yield the desired vitamin D levels and health benefits. These data suggest that even when food stuffs are fortified with vitamin D the ‘at risk’ groups would require therapeutic doses of vitamin D in a supervised environment. In order to be successful, any programme of food fortification with vitamin D should be so structured that it is robust and sustainable and has good quality assurance.

Endogenous production and supplementation

Casual exposure to the mid-day sun for 15 to 30 minutes exposing 12% of body surface area without sun screen will synthesize enough vitamin D for the day[68,69]. The synthesis of vitamin D from skin decreases with age and hence exposure of larger skin surface area is required in the elderly[68,69]. Vitamin D synthesis in the skin lasts twice as long in the circulating system as compared to ingested doses of vitamin D. The half-life of ingested 25 (OH)D is six weeks[75].

Oral administration of one mcg of vitamin D (40 IU) will increase serum 25(OH)D levels by 0.79 ng/mL (1.95 nmol/L). About 360 IU of vitamin D will raise serum vitamin D levels to more than 10 ng/ml (25 nmol/L)[71]. Those who have been prescribed vitamin D supplementation for any reason should target to attain a 25(OH)D level of 30 ng/ml, which is optimal for calcium absorption from the gut. Supplementation of vitamin D should maintain 25(OH)D levels in the serum at above 30 ng/ml. A 25(OH)D level greater than 150 ng/ml along with high serum calcium is toxic[76]. For cholecalciferol supplementation to be effective, calcium (elemental) intake (dietary/supplementation) should be 1000 mg/day in adults, 1200 mg/day in pregnant and lactating women and 600 to 800 mg/day in children and adolescents.

Routine estimation of serum 25(OH)D is not recommended except in ‘at-risk’ patients[76]. Repeated estimation of 25(OH)D levels in persons receiving vitamin D supplementation is not advised for reasons of affordability to the patient. Serum calcium levels of 10.5 to 11 mg/dl or above point to vitamin D toxicity. The baseline serum calcium level is a good guide for comparison at follow-up. Fasting urine calcium-to-creatinine ratio of 0.02 or higher is also an indirect indicator of vitamin D excess for those on vitamin D supplementation therapy.

Populations at risk require loading doses of vitamin D. This can be given as cholecalciferol 60,000 IU/week/ eight weeks followed by cholecalciferol 60,000 IU/ once a month[76]. A parenteral dose of cholecalciferol 600,000 IU/deep IM stat can be given as a loading dose BUT SHOULD NOT be repeated until the 8th week; after 8 weeks , oral cholecalciferol 60,000 IU/ once a month can be given [77]. Loading doses of vitamin D, either oral or parental, are NOT RECOMMENDED in pregnant women unless the patient shows symptoms of vitamin D deficiency (tetany or symptomatic hypocalcemia). Cholecalciferol can be supplemented as 2000 IU/ daily. In lactating women, the daily requirement of cholecalciferol is 4000 IU/day[76].The upper tolerable limit of cholecalciferol supplementtion is 10,000 IU/day[76].

Non-calcemic benefits of Vitamin D

Obesity and Vitamin D

Obese individuals need 2 to 3 times more vitamin D per day (that is, 3000 to 6000 IU) to compensate for the impairment in ability to maintain 25 (OH)D levels in the blood. With deficiency of dietary calcium, there is an up to five-fold increase in fatty acid synthetase, an enzyme that converts calories into fat. The presence of sufficiently high levels of calcium and adequate vitamin D inhibits the enzyme. In obese persons, vitamin D supplementation may improve muscle strength, reduce the occurrence of aches and pains, and enable increased physical activity. It may also help in weight reduction and improve insulin metabolism. It is important to remember that drugs used for reducing fat, such as orlistat inhibit not only the absorption of fat but also that of vitamin D.

Diabetes and Vitamin D

The vitamin D endocrine system is now recognized as subserving a wide range of fundamental biological functions in cell differentiation, inhibition of cell growth, and immunomodulation. Both forms of immunity, namely, adaptive and innate, are regulated by $1,25(OH)_2D_3$. The immune-modulatory properties of vitamin D suggest that it could potentially play a therapeutic role in the prevention of type 1 diabetes mellitus (T1DM). It is postulated that large doses of vitamin D supplementation may influence the pattern of immune regulation and subsequent progression to T1DM in a genetically susceptible individual. More studies are required to assess the relationship between T1DM and vitamin D/vitamin D analogues in such individuals. In type 2 diabetes mellitus (T2DM), vitamin D may influence both insulin secretion and sensitivity. An inverse relationship between T2DM and vitamin D has been postulated from cross-sectional and prospective studies, but conclusive proof is as yet lacking. The published studies differ in design and in the RDA norms regarding the use of vitamin D in non-skeletal diseases and for improvement of β-cell function[78].

In a recent study, our group has shown that optimal treatment with vitamin D as per current Endocrine Society guidelines[76] and supplementation with calcium[79] improves pancreatic β cell function in normoglycaemic subjects with vitamin D deficiency. Large, well designed, controlled, randomized interventional studies on the potential roles of vitamin D and calcium in prevention and management of T2DM should be carried out in order to document the relationship between vitamin D and glucose homeostasis in T2DM[78].

Skin Diseases and Vitamin D

Psoriasis is a semi-autoimmune disease which affects approximately 50 million people worldwide. It affects mostly adults and is characterized by raised patches of thick, red skin covered with silvery scales. These patches are sometimes called plaques, which generally itch and may burn. Under normal circumstances, skin cells grow, divide and replace themselves in an orderly fashion. But in psoriasis, cells start reproducing in an uncontrolled manner. Psoriatic skin may "turn over" (be replaced) in as little as four days as compared to normal skin which turns over in twenty-one days. Local application of skin ointment of activated vitamin D (calcitriol) dramatically reduces the symptoms of psoriasis.

The role of Vitamin D in other diseases

Crohn's disease affects the proximal small intestine and hampers 25 (OH)D absorption. Recent advances in understanding the pathophysiology of Crohn's disease have revealed the so-called north– south gradient of Crohn's disease[80]. In a genetically predisposed individual, Crohn's disease occurs because of the dysregulated response of the mucosal immune system to intraluminal antigens of bacterial origin. A normally functioning mucosal immune system inhibits immune response to luminal antigens and suppresses gut inflammation (immune tolerance). The mechanism whereby exposure to sunlight is thought to exert a beneficial effect on intestinal inflammation may involve vitamin D. Sunlight and vitamin D might protect against Crohn's disease by down-regulating the T helper-1 (TH1)-driven immune response3. The mechanism through which heliotherapy (UV-B rays) induces immune suppression may include the induction of various TH 2 cytokines such as IL-4 and IL-1012. Vitamin D may be the coordinator of the cross talk between the immunological system in the gut and various subcellular events in bone formation[81].

Approximately 10% of the population has silent Coeliac disease. These individuals have difficulty in absorbing fat-soluble vitamin D. Unless they have enough UV-B to maintain healthy vitamin D levels, they should receive vitamin D supplementation to maintain their 25(OH)D levels at >30 ng/ml. Cystic fibrosis leads to malabsorption of vitamin D. Patients with this disease require aggressive supplementation with vitamin D to maintain 25(OH)D levels at > 30 ng/ml.

In cirrhosis of the liver when more than 80% of the liver is destroyed, there is decreased production of 25(OH)D and poor absorption of fat as well as of vitamin D. Mild to moderate malabsorption is a major cause of vitamin D deficiency in these patients. A similar situation prevails in primary biliary cirrhosis. These conditions call for aggressive treatment with vitamin D. Severe kidney disease can interfere with conversion of 25(OH)D to circulating form of $1,25(OH)_2D_3$, especially in stage 4 and 5 renal failure. These patients need therapy with adequate vitamin D and could also benefit from activated vitamin D (Calcitriol) to control the PTH levels.

Prostate cancer is fatal in about 25% of the cases. It has been reported that the risk of developing prostate cancer is inversely related to the level of exposure to sunlight[82]. Men with prostate cancer who received 2000 IU of vitamin D daily were shown to have a 50% reduction in risk as measured in terms of the levels of prostatic specific antigen (PSA), an indicator of cancer activity. Those living at higher altitudes are generally at increased risk of developing cancer. Studies from Creigton University reported that postmenopausal women who took 1500 mg/day of calcium and 1100 IU/day of vitamin D for four years had a 60% reduction in the risk of developing all cancers as compared to placebo group[83]. Epidemiological studies have shown that people who either worked outdoors or lived nearer the equator (in sunny climates) were less likely to develop cancers of colon and breast. Another study showed the beneficial effect of sunlight on both breast cancer and prostate cancer[84]. Cancers of the digestive tract (colon, rectum, mouth, esophagus, stomach and pancreas) are also associated with low 25(OH)D levels[84]. Ethnicity may also have a role to play. Vitamin D deficiency was found to be more prevalent and pronounced in African Americans than in Caucasian Americans . It has been reported that, after adjusting for multiple dietary, lifestyle and medical risk factors, African American men were at 32% greater risk of total cancers and especially cancers of digestive tract than their Caucasian counterparts.

About 75% of women with breast cancer who are vitamin D deficient at diagnosis die from the disease while mortality risk is lower in women with normal vitamin D levels at diagnosis. Data analysis from the National Health and Nutrition Examination Survey [NHANES I] in 1999 demonstrated that increased exposure to sunlight could, by itself, potentially reduce the incidence and death rate of breast cancer in the US by 35 to 75%[83]. Results pooled from the Harvard Nurses Health study and St. Georges Hospital study in London showed that patients with high 25(OH)D levels had the lowest risk of breast cancer[85].

Multiple sclerosis (MS) is a chronic debilitating disease affecting the brain and spinal cord. In MS, immune cells enter the brain and spinal cord, resulting in damage and leading to slowed or blocked muscle co-ordination, weakness, and loss of response to nerve signals. It has been reported that a few patients treated with vitamin D in the early stages of the disease had shown slower progression of the disease.

Patients with chronic granulomatous diseases such as sarcoidosis, and those with tuberculosis or fungal infections are at risk of vitamin D deficiency, because their immune systems are activating the vitamin D. They need to be treated for vitamin D deficiency but should receive much smaller doses of vitamin D than patients who are otherwise normal and are being treated for vitamin D deficiency alone. Otherwise they may develop hypercalcemia and hypercalcuria. The 25(OH)D levels in such patients should be maintained between 20-30 ng/ml.

Drugs that affect vitamin D metabolism

Anti seizure medication

Drugs used in the treatment of epilepsy destroy 25(OH)D, putting these patients at risk for osteomalacia and rickets. They require higher doses of supplementation to maintain serum 25(OH)D levels at >30 ng/ml. Our group conducted a study in 362 patients with epilepsy who were receiving anti-epilepsy drugs. Their mean age was 29±15 years, the mean energy intake was 2,007 + 211 Kcal/day, carbohydrates 335±33 gm/day; protein 31±7 gm/day; fat 18±2 gm/day; calcium 294+40 mg/day; phosphorus 557+102 mg/day; phytates 179±30 mg/day; and phytate/calcium ratio 0.56±0.2. The dietary consumption of calcium in all these patients was far below

the ICMR's RDA norms. Low dietary calcium could have a confounding effect on patients with epilepsy in all age groups who are receiving anti-epilepsy drugs[86].

In another longitudinal study we sought to assess the effect of anti-epilepsy drugs on serum 25(OH)D levels and bone mineral metabolism markers. Patients with a history of seizures were characterized and included in the study prospectively. The base line bone mineral parameters – serum calcium, phosphorus, alkaline phosphatase (SAP), tartrate resistant acid phosphatase (TRACP), 25(OH)D levels, parathyroid hormone (PTH), urinary calcium creatinine ratio (Ca.Cr), urinary calcium/kg/bodyweight (BW) and phosphate excretion index (PEI) were determined. Patients with normal 25(OH)D levels who had been put on anti-epilepsy drug treatment were followed up and re-evaluated at the end of 6 months. Approximately two-thirds of the subjects recruited were vitamin D-deficient. Subjects with normal 25(OH)D levels at baseline showed a significant fall in 25(OH)D levels, urinary calcium, urinary calcium/kg/BW and TRACP levels at the end of 6 months, irrespective of the drug(s) used and the plasma concentration of the drug(s). The study concluded that hypovitaminosis D is common in our population. Subjects with normal 25(OH)D levels, irrespective of the type of anti-epilepsy medications even at sub-therapeutic serum levels of the drug, went into 25(OH)D deficiency and insufficiency states. Theoretically, it may be worthwhile to supplement calcium and vitamin D for such patients even before initiation of anti-epilepsy therapy[87].

Other drugs which may affect Vitamin D metabolism

Prednisolone, a steroid used in treating a variety of disease conditions, promotes destruction of 25(OH)D and reduces calcium absorption from the gut. These patients therefore require increased intake of both vitamin D and calcium. Cholesytramine resin (Questran) a drug used to lower cholesterol, interferes with vitamin D absorption. People on this drug should take vitamin D supplementation up to 4 hours after taking the drug. Vitamin D deficiency does not cause thyroid disease. But patients with hyperthyroidism experience increased destruction of 25(OH)D and are therefore at higher risk of vitamin D deficiency[88-90]. VDR gene polymorphisms and hypo-vitaminosis D may predispose to multidrug-resistant tuberculosis (MDR-TB). Lower serum 25(OH)D may increase time to MDR-TB sputum smear negativity[91].

Conclusion

The wide spectrum of action of Vitamin D continues to intrigue the scientific community. The calcemic beneficial effects of vitamin D have been fully established through outcome studies, and the guidelines for treatment of vitamin D deficiency for calcemic benefit are established. The non-calcemic beneficial effects are gradually becoming better understood. While we await guidelines for vitamin D supplementation for non-calcemic benefits, it may be prudent to maintain the serum 25(OH)D levels at 30 ng/ml, and also ensure a diet-cum-supplement calcium intake of 1 gm per day.

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FOUNDATION NEWS

Annual Foundation Day and C. Ramachandran Memorial Lecture: The Annual Foundation Day of NFI will be celebrated on 27th November 2014. On this occasion, Dr. V.M. Katoch, Secretary, Department of Health Research and Director General ICMR will deliver the C Ramachandran Memorial Lecture.

NUTRITION NEWS

The 46th Annual Conference of the Nutrition Society of India will be held at Dayanand Medical College and Hospital and Punjab Agricultural University, Ludhiana (Punjab) on 7th-8th November, 2014. There will be a pre-conference workshop on 6th November 2014.

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