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***Review Article***

# Vitamin D Deficiency in Sun Drenched India – Can D-lightful Sunlight Be a Respite? – Sunlight D lemma

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Vitamin D is one of the oldest hormones; 500 million-years old phytoplankton species in Sargasso Sea were found to contain large amount of ergosterol (vitamin $D_2$ precursor). Ergosterol is transferred along the food chain into the sea food, where it is stored and concentrated. Vitamin D was essential for calcium and bone homeostasis to cope with higher gravity in terrestrial animals.

In humans Vitamin D is synthesized on exposure to mid-day sunlight (UV-B rays 290-315 nm). The widespread vitamin D deficiency [25(OH)D< 20 ng/ml] in India appear to be due to changes in lifestyle–sun shy attitude, dress code and, lack of dietary calcium. Experimental studies from India have shown that, Indians can synthesise enough vitamin D on exposure to sunlight.

Vitamin D orchestrates the "Ca-vitamin D-Parathyroid hormone endocrine axis. Calcitriol, the active form of vitamin D follows either of the two-pathways. Genomic responses–takes anything from few hours to days to become fully manifest (*osseous benefits*); Chemical messengers that transmits signals and rapid responses (RR) which vary from few seconds to an hour (*non-osseous benefits* e.g., insulin secretion, intestinal calcium absorption). Association with vitamin D deficiency has been reported in hypertension, diabetes, psoriasis, Chron's disease, multiple sclerosis, prostatic and colonic cancer.

For osseous benefits the vitamin D levels should be above >20ng/ml, while for non-osseous benefit requires 25(OH)D levels >30 ng/ml. Adequate dietary calcium intake of 1gm/day has to be ensured.

**Keywords: Calcium; Parathyroid Hormone; Sunlight; Ergosterol**

## Introduction

Billions of years ago, life started in the primordial oceans. The primitive unicellular organism derived its calcium from the sea water. The calcium concentration of sea water is 10mM and extra cellular fluids (of fresh water fish and tetrapodes) is 2.5mM **(**Hernigou *et al*., 2018; Bouillon and Suda, 2014). Vitamin D found in plankton is a major part of food chain of many fish (0.08-0.27%). This high nutritional supply is the reason for high vitamin D content of fish liver – cod and deep-water fish. High vitamin D content was necessary for efficient protection of life in early marine organisms against the DNA damage induced by UVB (Bouillon and Suda, 2014). Multicellularity and terrestrial life necessitated a rigid skeleton for survival of life in the land. Two systems developed during the course of evolution – the neurological system [wired communications – by nerves (precision grip and, orientation to time and space is the highest sign of evolution)] and the Endocrine system[wireless communications – by hormones (endocrinology is the science which deals about the language of communication between the cells – the language is hormones)]. While becoming terrestrial, tetrapodes and amphibians had to cope with six-fold higher gravity compared to marine animals, and they required a solid bone structure to support

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muscles and body mobility. This required a highly efficient system for intestinal calcium absorption from a calcium poor milieu. Vitamin D and parathyroid hormone (PTH) maintain the serum calcium (extra cellular calcium) in a narrow normal range, which is essential for nerve, muscle (including cardiac muscle) and blood coagulation which is more essential for survival than bone homeostasis.

Vitamin D is synthesized by the body and functions as a hormone. It has a pivotal role in calcium homeostasis and bone mineral metabolism. Its role in endocrine system in now recognized. Vitamin D sub serves a wide range of fundamental biological functions, in inhibition of cell growth, in cell differentiation and immune modulation (Holick, 2000;Deluca and Cantorna, 2001).

**Synthesis of Vitamin D**

UVB photons (wavelengths 290-315 nm) from sunlight enter the exposed epidermis of skin and cause photochemical transformation of *pro* vitamin-$D_3$ (7-DHC-7-dehydrocholesterol in lipid bilayer) to *pre*vitamin $D_3$. *cis, cis* (CZC) and *cis, trans* (CZT) are the two conformeric forms. The CZC is thermodynamically less stable form than CZT (Chen 1998). The only form of Previtamin-$D_3$ that can convert to vitamin $D_3$ is the CZC conformer. The vitamin $D_3$ that is formed is sterically altered and ejected from plasma membrane into extracellular space. At body temperature, it takes 12 hours for this reaction to be complete (~99% conversion). On excessive exposure to sunlight this photolabile *pre*vitamin-$D_3$ is converted to lumisterol and tachysterol (biologically inert products) (Chen 1998). Liver converts Cholecalciferol into 25 $(OH)D_3$ (calcidiol). 25$(OH)D_3$ (calcidiol) is a prehormone. It is made directly from cholecalciferol and has steroid like properties. Kidneys and other tissues synthesize Calcitriol [1,25$(OH)_2D_3$]. The most potent steroid hormone derived from cholecalciferol is Calcitriol [1,25$(OH)_2D_3$] (Fig. 1) (Harinarayan 2014). Vitamin $D_2$ (ergocalciferol) is derived from plant sources. Vitamin $D_3$ (Cholecalciferol) is the naturally occurring form of vitamin D. It is synthesized in substantial quantities in skin when exposed to sunlight. When serum calcium levels fall below the normal range, PTH is secreted which helps in bone resorption to normalise the serum calcium (secondary hyperparathyroidism-SHPT). PTH converts 25(OH) $D_3$ to 1,25 $(OH)_2D_3$ and helps in calcium absorption from gut. PTH also conserves calcium form the kidneys, thus maintaining the serum calcium level in normal range. Vitamin D acts through genomes (genomic actions) and chemical messengers (Rapid responses-RR) (Fig. 1).

**Factors affecting Vitamin D Synthesis**

Latitude, rotation of earth about the sun (season) and its own axis (day and night) – time of day, the solar zenith angle (SZA) affect the ability of skin to synthesize-$D_3$. Solar radiation is attenuated by atmospheric pollution. Factors limiting production of previtamin-$D_3$ by the skin are dress code, skin pigmentation, and application of sun protection factor (SPF). A SPF of 15 and above reduces more than 95% of UVB penetration into epidermis and limits the production of previtamin-$D_3$ by the skin. With age, the ability of the skin's capacity to produce vitamin $D_3$is reduced. In winter, sun angle becomes more oblique (SZA increases). Hence more UVB photons are absorbed by the stratospheric zone and few UVB photons penetrate to earth's surface. Hence cutaneous production of previtamin-$D_3$is reduced. The amount of UVB radiation reaching earth's surface is a function of the following SZA (time of day), season of the year, amount of cloud, ozone, and aerosols, Latitude and altitude, skin colour, also influence the cutaneous production of vitamin $D_3$ (Chen1998). Amongst them the most important are SZA, UV index and geographical location and, minimal erythemal dose (MED) and skin type. "Solar zenith angle*"* is the angular distance between an object directly overhead and an object in the sky (sun) (Fig. 2A). Skin type of human races are categorized based on skin pigmentation (skin colour), reaction to sun whether it freckles, burns, peels, blisters or tans, eye and hair colour,. There are six skin types. Indians come under the skin type V category. The amount of vitamin D synthesized by the skin of an individual is determined by the quantum of UV-B rays (290 to 310nm). For latitudes above and below 35°N and 35°S during the winter months, the cutaneous production of previtamin $D_3$ is little (Chen 2007; Webb *et al*., 1988). In winter months for latitude above 51° (north and south of equator) the UV index is less than 0.5. During these periods, there may not be any appreciable vitamin $D_3$ synthesis from casual exposure to sunlight and is called "vitamin D winter" (Webb *et al*., 1988).

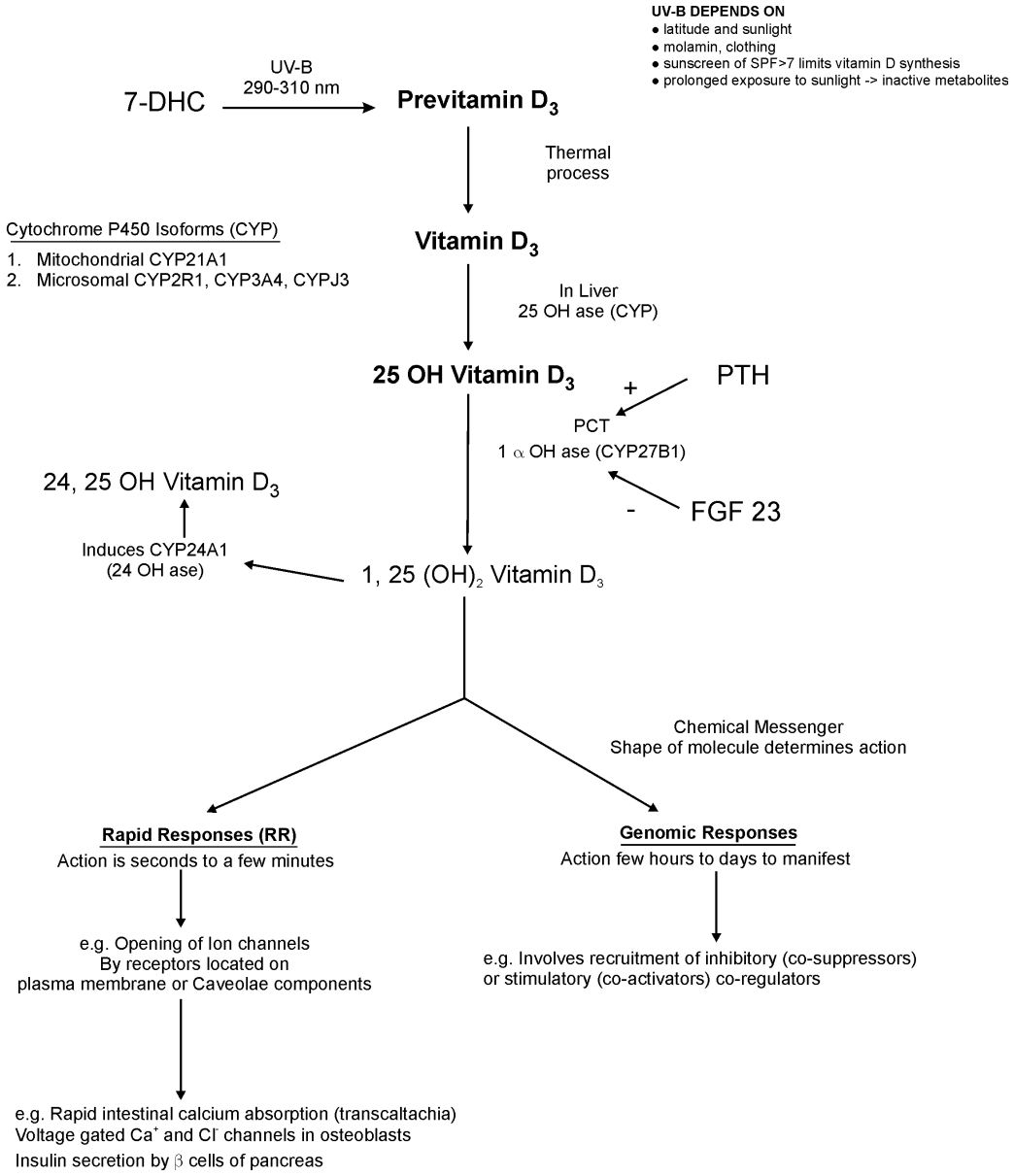



**Fig. 1: Vitamin D synthesis and target actions**

## Experimental Model of Vitamin D Synthesis

The influence of season and time of the day on synthesis of previtamin-$D_3$ was evaluated in an experimental model (ampoule model) at Tirupati (latitude 13.40°N and longitude 77.2°E) south India (from May 2007 to August 2008) (Harinarayan *et al*., 2013). The study was conducted beginning from 8 a.m. until 4 p.m. on a cloudless day on an open terrace of the hospital when possible with no interference from vegetation or buildings. About 50 μg of 7-DHC (in 1 ml of methanol) in sealed borosilicate glass ampoules were exposed to sunlight hourly. The hourly solar zenith angle was obtained from the website *http//solardat.uoregon.edu/SolarPositionCalculator.html* for the study period. Satellite picture of the country showing clouds on the day of study at 1130 a.m. was obtained from the website *www.hinduonnet.com* (Fig. 3). The study was repeated around the same day every month, for a period of fifteen months in the same location. From the ampoules 7-DHC, previtamin-$D_3$ and photoproducts (lumisterol and tachysterol) were analysed. For the whole duration of the study, there was a strong negative correlation between percent conversion of 7-DHC to previtamin-$D_3$, vitamin $D_3$, and zenith angle. With decreasing zenith angle, the

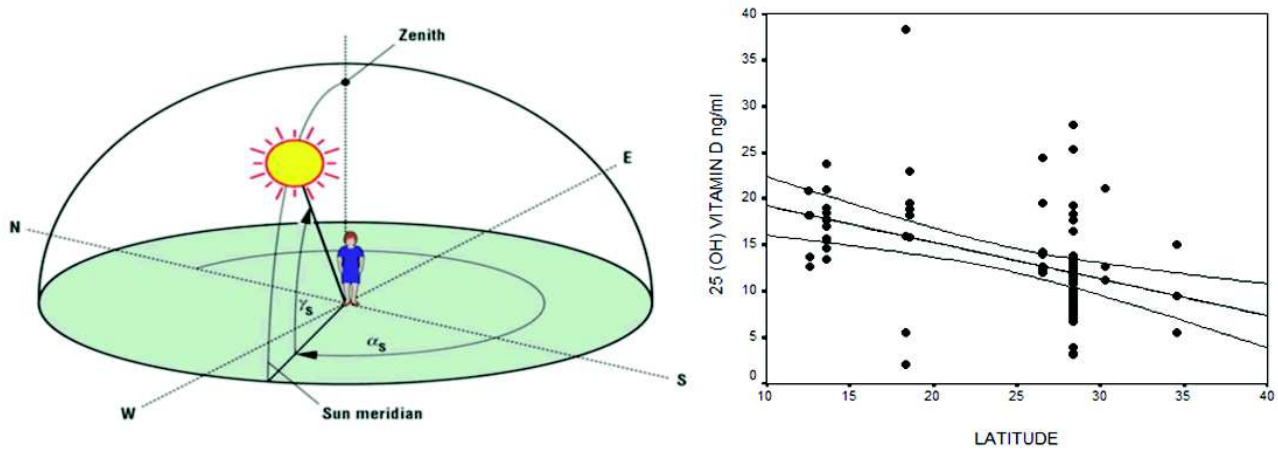



**Fig. 2: A - Zenith angle; B - Graph showing the inverse correlation between the 25 (OH ) D levels and latitude (r = -0.48; p < 0.0001) from various studies conducted in the country – *Adapted fromDermato Endocrinology – copyright permission*. http://dx.doi.org/10.4161/derm.23873**

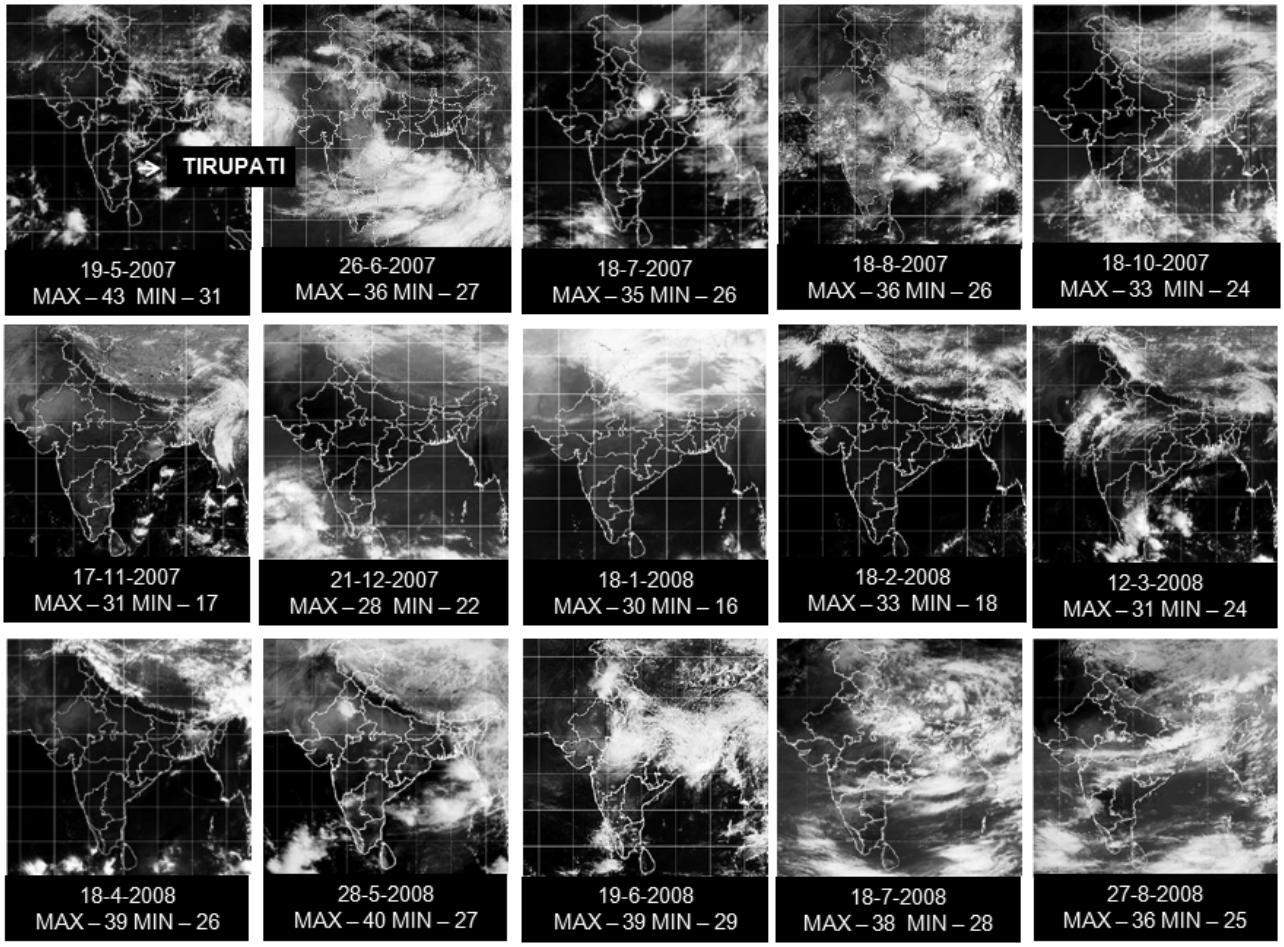
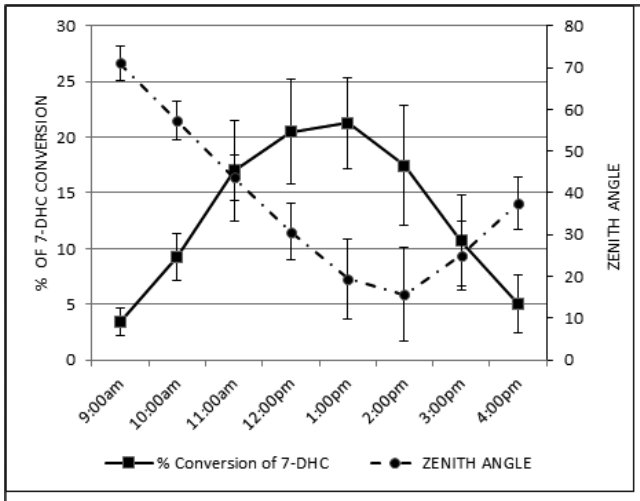
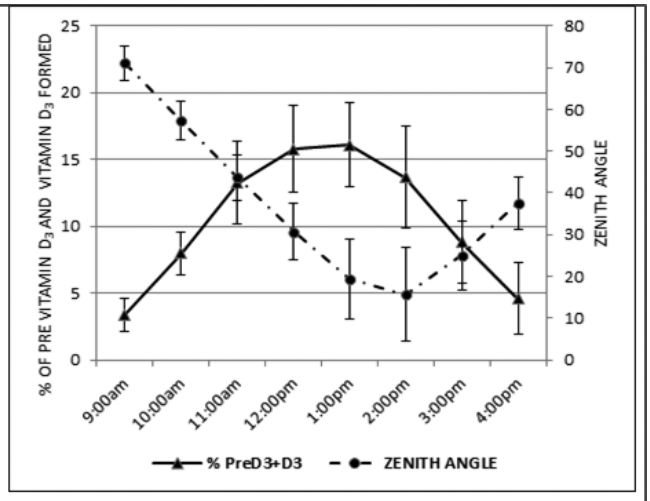



**Fig. 3: Satellite picture of the country on the day of study at 11.30 hours. First picture on the left upper panel (row -1) Shows the location of study site (TIRUPATI - latitude 13.40 $^0$ N and longitude 77.2 $^0$ E). The date and maximum and minimum temperature on the day of study is shown in each picture. The satellite picture is downloaded from www.hinduonnnet.com under section miscellaneous - whether chart.– *Adapted fromDermato Endocrinology – copyright permission*. http://dx.doi.org/10.4161/derm.23873**




| | ZENITH ANGLE ° | | | | % CONVERSION OF 7-DHC | | | | % PREVITAMIN $D_3$ AND VITAMIN $D_3$ FORMED | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| TIME | Mean | SD | Min | Max | Mean | SD | Min | Max | Mean | SD | Min | Max |
| 9:00am | 57 | 5 | 53 | 67 | 3.40 | 1.25 | 1.27 | 5.68 | 3.40 | 1.25 | 1.27 | 5.68 |
| 10:00am | 44 | 5 | 39 | 55 | 9.25 | 2.13 | 4.57 | 11.44 | 7.97 | 1.61 | 4.57 | 10.80 |
| 11:00am | 31 | 7 | 25 | 44 | 16.98 | 4.50 | 7.69 | 22.91 | 13.24 | 3.08 | 7.69 | 17.59 |
| 12:00pm | 20 | 10 | 11 | 38 | 20.50 | 4.70 | 10.30 | 26.97 | 15.78 | 3.21 | 9.68 | 20.50 |
| 1:00pm | 17 | 11 | 5 | 37 | 21.26 | 4.11 | 14.96 | 28.22 | 16.08 | 3.16 | 11.86 | 21.40 |
| 2:00pm | 26 | 8 | 18 | 42 | 17.46 | 5.37 | 6.82 | 25.62 | 13.65 | 3.83 | 5.97 | 19.71 |
| 3:00pm | 38 | 6 | 32 | 50 | 10.71 | 4.06 | 2.76 | 18.34 | 8.83 | 3.08 | 2.76 | 14.29 |
| 4:00pm | 51 | 5 | 46 | 61 | 5.02 | 2.65 | 2.02 | 10.44 | 4.91 | 2.47 | 2.02 | 9.86 |

**Fig. 4: Figure showing the mean±SD of the zenith angles, percent conversion of 7-Dehydrocholesterol (7-DHC) to previtamin $D_3$ and photoproducts, and the percentage of previtamin $D_3$ and vitamin $D_3$ against time (for the study duration). The table below gives the individual values, minimum and maximum of the variables.There was negative correlation between the zenith angle and percent conversion of 7-DHC to previtamin D3 and its photoproducts (r = -0.84; p < 0.0001) and zenith angle and percent of previtamin D3 and vitamin D3 formed (r = -0.83; p < 0.0001).– *Adapted fromDermato Endocrinology – copyright permission*. http://dx.doi.org/10.4161/derm.23873.**

percent conversion of 7-DHC to previtamin-$D_3$ and vitamin $D_3$ was higher. At noon and 1 p.m., there was 7-fold higher previtamin-$D_3$ was formed from conversion of 7-DHC and its photoproducts, lumisterol and tachysterol. There was five times more previtamin-$D_3$ and vitamin $D_3$ formed compared 9 a.m. to 10 a.m. (Fig. 4). It has been assumed that enough vitamin $D_3$ is produce in the skin in those residing in tropics throughout the year (Harinarayan, Joshi 2009). Recent studies have shown high prevalence of vitamin D deficiency both in rural and urban India (north and south India) populations (Harinarayan *et al*., 2008) It has been shown in population surveys from Tirupati (south India -rural) (latitude 13.40°N and longitude 77.2°E) there is high prevalence of vitamin D deficiency. Agricultural labourers with at least 35% of their body surface area, exposed to sunlight for more than 4 h have vitamin D deficiency. From the various studies published in literature it has been shown that the 25(OH)D levels in South Indian subjects are relatively higher compared with the subjects from North India. 25(OH)D levels inversely correlate with latitude (r = –0.48; P< 0.0001) from various studies conducted in the country (Fig. 2B; Tables 1-4).

## Prevalence of Vitamin D Deficiency in India

The 25(OH)D levels along with latitude and location are shown in Table 1 to 4 for children under five, school age children, pregnant women and adults from various studies in India. There is varying degree of vitamin D deficiency across all the age groups in the population as a whole.

## Factors Responsible for High Prevalence of Vitamin D Deficiency in India

The contributing factors for low vitamin D status in the Indian population are

**Table 1: Vitamin D status of subjects under 5 year age from India along with latitude and location from various studies conducted in the country. All values are Mean ± SD unless specified**

| Location | n | AGE (Yrs) | 25 OH D | UNIT |
|---|---|---|---|---|
| Delhi (31) | 29 | new born | 16.72±4.99 | nmol/l |
| Delhi (20) | 26 (5) | 16+4 mo | 12.4±07 | ng/ml |
| | 1 | 16+4 mo | 28 ±07 | ng/ml |
| Delhi Slums (32) | 47 | 9-30 mo | 96±25.7 | nmol/l |
| | 49 | 9-30 mo | 23.8±27 | nmol/l |
| | 48 | 9-30 mo | 17.8±22.4 | nmol/l |
| | 52 | 9-30 mo | 19±20 | nmol/l |
| Delhi (37, 34) | | 14 weeks | 10.1 | ng/ml |
| | | 6 weeks | 22.3±10.5 | nmol/l |
| Lucknow (40) | 29 | Cord Blood | 12±8 | ng/ml |
| | 178 | | 14.3±9.5 | ng/ml |
| Mumbai (44) | 42 | | 19.5±9.6 | ng/ml |
| | 35 | 3 months | 18.2±9.8 | ng/ml |
| Pune (46) | 25 | 2.26±0.8 | 95.86 (91.6)** | nmol/l |
| | 25 | 2.53±0.8 | 130.2 (67.7)** | nmol/l |
| | 31 | 2.94±0.6 | 14.0 (32.0)** | nmol/l |
| | 29 | 2.70±0.6 | 5.2 (21.1)** | nmol/l |

Delhi Latitude 28.35°N Longitude 77.12°E; Lucknow Latitude 26.55°N; Longitude 80.95°E; Mumbai Latitude 18.56°N Longitude 72.54°E; Pune Latitude 18.31°N Longitude 73.55°E. All values are Mean ± SD unless specified.
To convert ng/ml to nmol/L multiply by 2.5.
**Values are median and inter-quartile range; LONG-Longitude. Mo–Months. Reference number in above table, corresponds to table a*dapted fromDermato Endocrinology – copyright permission.*http://dx.doi.org/10.4161/derm.23873

- The summers are very hot and arid and many people stay indoors.
- Throughout the year, the photo conversion of 7-DHC to previtamin-$D_3$ and its photoproducts is maximal between 11 a.m. to 2 p.m. (Harinarayan *et al*., 2013).
- Based on the experimental and observational data,it is possible that Indians can synthesize enough vitamin D from sunlight.
- Exposure of 18% body surface-exposure of face and forearm without sunscreen to sunlight between 11 a.m. and 2 p.m. for an amount of time to cause a MED would be equivalent to ingesting about 3600 IU Vitamin D.
- Vitamin D produced in the skin lasts two times longer in the body. Hence, casual exposure to an amount of sunlight that is equivalent to 0.5 MED of arms and legs, three times a week can provide adequate amount of vitamin D.

Factors that might be responsible for the high prevalence of vitamin D deficiency in Indians are (Harinarayan and Joshi 2009).

- Changing work culture and modernization result in an increase in the number of hours spent indoors, thereby preventing adequate exposure to sunlight, especially in urban Indians.
- Sun-shy nature of Indians
- Traditionally the clothing habits of Indians, is to keep their bodies well covered even when out in the sun.
- Skin with darker pigmentation, requires a longer duration of sun exposure to synthesize an equivalent amount of vitamin D as compared to Caucasian skin.
- High atmospheric pollution as in Delhi, India (28.35°N) (Agarwal *et al*., 2002; Tiwari *et al*., 2004).
- The phosphates and phytates in high-fiber diet can deplete vitamin D stores and increase calcium requirement (Harinarayan *et al*., 2004).
- The dietary calcium intake is far less than the recommended dietary allowances (RDA) which further aggravates the problem (Harinarayan *et al*., 2007; Harinarayan *et al*., 2008; Harinarayan *et al*., 2015).
- It has been shown that increments in serum 25(OH)D in response to treatment depend on the heritability of vitamin D binding protein.
- Vitamin D deficiency in the mother and the fetus can be aggravated when there are repeated, unplanned and unspaced pregnancies in women (who are already deficient in dietary calcium).

It is quite possible that with nutrition education of the population on improving dietary calcium intake, getting adequate exposure there can be a reduction in vitamin D deficiency in sun drenched India. Vitamin D supplementation may also be required in populations

**Table 2: Vitamin D status of school childrenfrom India along with latitude and location from various studies conducted in the country**

| Location | n | sex | AGE (Yrs) | 25 OH D | UNIT |
|---|---|---|---|---|---|
| Delhi (33) | 193 | LSES girls | 12.4±3.2 | 34.6±17.43 | nmol/l |
| | 211 | USES girls | 12.3±3 | 29.4±12.7 | nmol/l |
| Delhi (34) | 42 | LSES Boys | 10-12 | 12.4 ±5.5 | ng/ml |
| | 85 | LSES Boys | 13-15 | 11.3 ±5.8 | ng/ml |
| | 40 | LSES Boys | 16-18 | 11.3±5.3 | ng/ml |
| | 33 | USES Boys | 10-12 | 19.3±8.8 | ng/ml |
| | 70 | USES Boys | 13-15 | 13.1±7 | ng/ml |
| | 55 | USES Boys | 16-18 | 13.5±7 | ng/ml |
| | 78 | LSES Girls | 10-12 | 11±6.5 | ng/ml |
| | 123 | LSES Girls | 13-15 | 10±6.2 | ng/ml |
| | 62 | LSES Girls | 16-18 | 11±5.7 | ng/ml |
| | 47 | USES Girls | 10-12 | 12.5±8.9 | ng/ml |
| | 62 | USES Girls | 13-15 | 10.2±5.7 | ng/ml |
| | 63 | USES Girls | 16-18 | 12.9±10.5 | ng/ml |
| Lucknow (41) | 28 | Girls - winter | AgeAdju | 31.3±1.5 | nmol/l |
| | 34 | Boys - winter | AgeAdju | 67.5±29 | nmol/l |
| Tirupati (8, 48) | 30 | Urban children Male* | 11±1 | 15.57±1.2 | ng/ml |
| | 34 | Rural children Male* | 12±0.7 | 17±1.3 | ng/ml |
| | 39 | Urban children Female* | 13.5±0.6 | 18.5±1.66 | ng/ml |
| | 36 | Rural children Female* | 12.6±0.5 | 19±1.6 | ng/ml |

Location in Table 1 and Tirupati Latitude 13.62ºN Longitude 79.4ºE. All values are Mean ± SD unless specified.*Mean ± SEM;Age Adju, Age Adjusted;for conversion from nmol to ng—multiply by 0.4; LAT- Latitude; LONG-Longitude. Reference number in above table, corresponds to table a*dapted fromDermato Endocrinology – copyright permission.*http://dx.doi.org/10.4161/derm.23873

**Table 3: Vitamin D status of pregnant women from India along with latitude and location from various studies conducted in the country**

| Location | n | Study population | AGE (Yrs) | 25 OH D | Unit |
|---|---|---|---|---|---|
| Delhi (38) | 97 | Mothers 1st Trimester - summer | 24.4±2.67 | 23.4±11.3 | nmol/l |
| | 97 | Mothers 1st Trimester - winter | | 19.6±9.2 | nmol/l |
| | 97 | Mothers 2nd Trimester - summer | 25±2.94 | 25.7±15.1 | nmol/l |
| | 97 | Mothers 2nd Trimester - winter | | 20.2±10.6 | nmol/l |
| | 97 | Mothers 3rd Trimester - summer | 24.26±2.82 | 27.7±9.2 | nmol/l |
| | 97 | Mothers 3rd Trimester - Winter | | 21.1±12.4 | nmol/l |
| | 97 | Mothers 6 wks post-partum | | 19.6±8.3 | nmol/l |
| Lucknow (40) | 140 | Pregnant Women (Urban) | 24±4.1 | 14±9.5 | ng/ml |
| | 67 | Pregnant Women (Rural) | 24.7±5.1 | 14±9 | ng/ml |
| Lucknow (41) | 139 | Pregnant women - summer | Age Adju | 55.5±19.8 | nmol/l |
| | 139 | Pregnant women - winter | Age Adju | 27.3±12.3 | nmol/l |

Location in Table 1. All values are Mean ± SD unless specified.Age Adju, Age Adjusted; for conversion from nmol to ng—multiply by 0.4; LAT- Latitude; LONG-Longitude. Reference number in above table, corresponds to table a*dapted fromDermato Endocrinology – copyright permission.*http://dx.doi.org/10.4161/derm.23873

**Table 4: Vitamin D status of adults from India along with latitude and location from various studies conducted in the country**

| Location | n | Study population | AGE (Yrs) | 25 OH D | Unit |
|---|---|---|---|---|---|
| Kashmir Valley (28) | 64 | Men | 28.8±4.9 | 37.7±0 30 | nmol/l |
| | 28 | Women | 26.8±4.8 | 13.8±0 11 | nmol/l |
| Chandigarh (29) | 329 | Males and Females (Summer) | 19.4±1.48 | 52.9±0 33.7 | nmol/l |
| | 237 | Males and Females (Winter) | 19.4±1.43 | 31.8±0 21.1 | nmol/l |
| Delhi (30) | 12 | Controls (Resident Doctors) | 25-35 | 8.3±2.5 | ìg/ml |
| Delhi (31) | 29 | Pregnant Women in summer | 23±0 3 | 21.9±10.73 | nmol/l |
| | 31 | Soldiers males in winter | 21.2±0 2 | 41.17±11.73 | nmol/l |
| | 19 | Phys. & nurse in summer | 23±0 5 | 7.89±3.49 | nmol/l |
| | 19 | Phys. & nurse in winter | 24±0 4 | 17.97±7.98 | nmol/l |
| | 15 | Depigmented persons in winter | 43±0 16 | 18.2±11.23 | nmol/l |
| Delhi (35) | 40 | Indian Paramiltary forces Men | 20-30 | 18.4 ±5.3 | ng/ml |
| | 50 | Indian Paramiltary forces Women | 20-30 | 25.3±7.4 | ng/ml |
| Delhi (36) | 32 | Rural Males | 42.8±16.6 | 44.2±24.4 | nmol/l |
| | 32 | Rural females | 43.4±12.6 | 26.9±15.9 | nmol/l |
| Delhi (37) | | Mothers | NA | 9.8 | ng/ml |
| Delhi (39) | 703 | Women | 50±9.5 | 9.78±8.3 | nmol/l |
| | 643 | Males | 50±9.5 | 9.81±6.79 | nmol/l |
| Lucknow (43) | 92 | Healthy volunteers | 34.2±6.7 | 12.3±11 | ng/ml |
| Mumbai (44) | 42 | Mothers Suppl Ca 250 - 500 additional | 20 to 35 | 23±11 | ng/ml |
| Mumbai (45) | 558 | Males | 30.11±3.53 | 18.9±8.9 | ng/ml |
| | 579 | Females | 30.52±3.57 | 15.8±9.1 | ng/ml |
| Tirupati (47) | 191 | Tirupati Rural* | 44±1.03 | 21±0.46 | ng/ml |
| Tirupati (8, 48) | 125 | Tirupati Urban* | 45.5±0.95 | 13.52±0.59 | ng/ml |
| | 134 | Urban men* | 47±1.5 | 18.54±0.8 | ng/ml |
| | 109 | Rural Men* | 45±1.4 | 23.7±0.8 | ng/ml |
| | 807 | Urban Women* | 46+0.4 | 15.5±0.3 | ng/ml |
| | 96 | Rural Women* | 41±1.4 | 19±0.9 | ng/ml |
| Tirupati (49) | 164 | Post-menopausal | 54±0 8 | 14.6 ±7 | ng/ml |
| Tirupati (50) | 55 | Women in reproductive age group* | 37.5±0.94 | 15.7 ±1.38 | ng/ml |
| | 55 | Post-menopausal* | 53.3+0.72 | 17.7±0.94 | ng/ml |
| Bengaluru (51) | 150 | Males* | 50 ±1.44 | 12.69±0.55 | ng/ml |
| | 606 | Females* | 51±0.6 | 13.72 ±0.38 | ng/ml |
| Vellore (52) | 150 | Post-menopausal women | 60.1±5 | 20.85 ±8.63 | ng/ml |

Location in Table 1 and Kashmir Valley Latitude 34.6ºN Longitude 74.48ºE; Chandigarh Latitude 30.3ºN Longitude 76.47ºE; Bengaluru Latitude 12.58ºN Longitude 77.38ºE; Vellore Latitude 12.55ºN Longitude 79.08ºE.

All values are Mean ± SD unless specified. *Mean ± SEM;for conversion from nmol to ng—bcmultiply by 0.4; LAT- Latitude; LONG-Longitude. Reference number in above table, corresponds to table a*dapted fromDermato Endocrinology – copyright permission*. http://dx.doi.org/10.4161/derm.23873

where there is limited exposure to sunlight (Srinivasa and Harinarayan, 2015).

**Dietary Calcium Intake**

At the cellular level, vitamin D and Calcium are closely linked in their action. Adequate dietary calcium intake favours bone mineral accrual. There is high prevalence of inadequate dietary calcium intake across rural, urban and metro population compared to the RDA. The average dietary calcium intake in India is 560±310 mg/day in adults and 430±180 mg/day in children (Harinarayan *et al*., 2004; Chittari V Harinarayan *et al*., 2007; Harinarayan *et al*., 2008). The dietary calcium intake of rural, urban and metropolitan city subjects in India is 269±2; 308±2.3; 526±8 mg/day respectively (P<0.001). This is far lower than the Recommended Daily/Dietary Allowance (RDA) norms of Indian Council of Medical Research (ICMR) (ICMR web-site; Harinarayan *et al*., 2015). In India, it is essential that vitamin D supplementation therapy should be accompanied with calcium supplementation.

Phytates retard/prevent the absorption of calcium from gut. The dietary phytate is significantly different in the rural, urban as well as the metropolitan city groups (p<0.0001) (Harinarayan *et al*., 2015). Low calcium intake leads to SHPT. Excess PTH increases conversion of 25(OH)D to 1,25-dihydroxyvitamin D. Also, 1,25-dihydroxyvitamin D induces its own destruction by increasing 24-hydroxylase (Clements *et al*., 1987).

**Normal Range of 25 OH D**

Vitamin D stores of an individual is evaluated by estimating the serum 25-hydroxyvitamin D[25(OH)D](Calcidiol) levels. The production of 25(OH)D is not regulated. The serum concentration of 25(OH)D reflects both cutaneous synthesis and absorption from the diet. The half-life of 25(OH)D is about six weeks. Biochemically, levels <20 ng/ml are defined as 'deficiency' and 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' (Lips, 2001; Heaney *et al*., 2003).

**Vitamin D and Bone Health**

The 25(OH)D status of an individual decides the calcium absorptive performance of the gut **(**Heaney *et al*., 2003). Calcium absorption is optimal at 25(OH)D levels >30 ng/ml. The effective calcium absorption from the gut is reduced when the 25(OH)D levels are low. The PTH levels rise when the 25(OH)D levels are less than 20ng/ml. The resulting SHPT (at 25(OH)D levels <20ng/ml), is a "physiological adaptive phenomenon". Accelerated bone remodelling, bone resorption, and increased risk of fracture results because of SHPT (Lips 2001).

The progression of Vitamin D deficiency is well understood. It begins with hypovitaminosis D and is followed by SHPT. Defective mineralization of bone manifests as osteomalacia in adults and rickets in children**.** The parathyroid response to vitamin D insufficiency further amplifies low dietary calcium intake (Clements *et al*., 1987).

**Vitamin D and Peak Bone Mass**

The adequacy of dietary calcium intake and vitamin D status decides the "peak bone mass" attained at the end of growth period of an individual. An increase in dietary calcium intake, favours, bone mineral accrual during infancy, childhood and adolescence. The 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) compared to Europeans and Americans. For attaining bone development and bone growth potential, sufficient physical activity and adequate nutrition are critical. Increased bone mineral density correlate with vitamin D and calcium status. They have the potential to increase the peak bone mass and effectively prevent osteoporosis at a later age (Slemenda *et al*., 1997; Johnston *et al*., 1992).

**Vitamin D and Muscle Strength**

Muscle strength plays an important role in determining risk for falls. Falls result in fractures and other injuries. Muscle wasting is a multi-factorial process. There are studies to show moderate inverse relationship between muscle strength and vitamin D status of an individual (Mithal *et al*., 2013). In a study conducted from India, 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 (Goswami *et al*., 2012).

**Vitamin D and Osteoporosis**

In a study of post-menopausal women, 85% had either insufficiency or deficiency of 25(OH)D and elevated PTH and serum alkaline phosphatase levels (Harinarayan 2005). Studies from south India in postmenopausal women, showed that vitamin D deficiency co-exists with low bone mineral density (BMD). In treatment of postmenopausal women Calcium and vitamin D supplementation should be an integral part (Harinarayan *et al*., 2011).

**Vitamin D and Diseases**

Obese individuals need 2 to 3 times more vitamin D per day (i.e. 3000 to 6000 IU). Vitamin D supplementation in obese persons, reduce the occurrence of aches and pains, may improve muscle strength, and enable increased physical activity. It may also help in weight reduction and improve insulin metabolism. It is important to remember that drugs like Orlistat used for reducing fat, inhibit not only the absorption of fat but also vitamin D.

In type 2 diabetes mellitus (T2DM), vitamin D may influence both insulin secretion and sensitivity (Harinarayan 2014). In a recent study, our group has shown that optimal treatment with vitamin D as per current Endocrine Society guidelines (Harinarayan *et al*., 2014, 2015) and supplementation with calcium improves pancreatic $\alpha$ cell function in normoglycemic subjects with vitamin D deficiency.

Local application of skin ointment of activated vitamin D(calcitriol) dramatically reduces the symptoms of psoriasis.

Vitamin D may be the coordinator of the cross talk between various subcellular events in bone formation and the immunological system in the gut (Harinarayan 2009). Absorption of fat soluble vitamin D is impaired in individuals with Crohn's disease. The pathophysiology of Crohn's disease have revealed the so-called north–south gradient from recent studies (Peyrin-Biroulet *et al.*, 2009). Sunlight and vitamin D might protect against Crohn's disease by down-regulating the T helper-1(TH1)-driven immune response Harinarayan (1019). Subjects withCrohn's disease should receive vitamin D supplementation to maintain their 25(OH)D levels at >30 ng/ml.

In *cirrhosis* 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.

The risk of developing prostate cancer is inversely related to the level of exposure to sunlight (Luscombe *et al*., 2001). 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

***Cancers of the Digestive Tract*** (colon, rectum, mouth, oesophagus, stomach and pancreas) are associated with low 25(OH)D levels (Freedman *et al*., 2002).

Data from the National Health and Nutrition Examination Survey [NHANES I] (John *et al*., 1999) has shown that with increased exposure to sunlight there was 35 to 75% reduction in the incidence and death rate of breast cancer. It has been reported that postmenopausal women who took 1100 IU/day of vitamin D and 1500 mg/day of calcium for four years had a 60% reduction in the risk of developing all cancers as compared to placebo group.

It has been reported that patients with multiple sclerosis treated with vitamin D in the early stages of the disease had shown slower progression of the disease.

Drugs used in the treatment of epilepsy destroy 25(OH)D, putting these patients at risk for osteomalacia and rickets (Menon *et al*., 2010a; Menon and Harinarayan, 2010b). They require higher doses of supplementation to maintain serum 25(OH)D levels at >30 ng/ml alongwith calcium.

In thyrotoxicosis, acceleration of excess bone remodelling leading to fractures. Treatment with vitamin D leads to reversal of bone loss and reduced fracture rate (Harinarayan 2012; Amreshreddy *et al*., 2012a; Amreshreddy *et al*., 2012b).

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. It was shown that Vitamin D Receptor gene polymorphisms and hypovitaminosis D might predispose to multidrug resistant tuberculosis (MDR-TB). Lower serum 25OHD may increase time to

MDR-TB sputum smear negativity (Rathode *et al*., 2012).

### Prevention and Management of Vitamin D Deficiency

Casual exposure to the mid-day sun for 15 to 30 minutes exposing 12% of body surface area (face and forearms) without sun screen will synthesize enough vitamin D for the day (Webb & Engelsen 2006; Srinivas & Harinarayan, 2015). The synthesis of vitamin D from skin decreases with age. Hence exposure of larger skin surface area and longer duration of exposure is required in the elderly. Vitamin D synthesized in the skin lasts twice as long.

In India, most of the supplementation schedules for correcting vitamin D deficiency use vitamin D plus calcium. It has been shown that normal levels of vitamin D can be achieved a with a dosage of 60,000 IU weekly for 8 weeks along with elemental calcium of 1 gm/day at the end of two months (Goswami *et al*., 2008; Holick *et al*., 2011; Harinarayan *et al*., 2012; Harinarayan *et al*., 2015). Supplementation with vitamin D, if not sustained in the long term, may not yield the desired vitamin D levels and health benefits. The maintenance dose is 60,000 IU vitamin D monthly along with elemental calcium of 1 gm/day.

### Conclusion

A wide spectrum of the action of Vitamin D continues to intrigue the scientific community. 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. 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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