Current Perspective on Vitamin D Deficiency: A Mini Review

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Abstract

Vitamin D deficiency is a very common global problem today. Children, pregnant mothers, young adults and the elderly, all are at risk. This is an unexpected revelation since it is presumed that people in countries with abundant sunshine would have adequate levels of the vitamin. Various socio-cultural practices are responsible for this scenario. The decrease in vitamin D levels could be due to diet, lifestyle or disease. This mini review brings out the causes of vitamin D deficiency, regional and global scenario of the problem, as well as physiological and clinical conditions associated with the variation in the vitamin levels. Various clinical disorders where the deficiency has been documented, and possible mechanism suggested by different authors have been highlighted, with the aim to encourage in-depth reading. An attempt is made to reinforce to every doctor, the importance of vitamin D deficiency and how this awareness may be useful to them to understand various symptoms experienced by patients and to modulate their treatment protocols of various clinical disorders.

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Introduction

Vitamin D has gained recognition, acceptability, and shifted its role from a vitamin to a hormone of varied importance. Although many countries have abundant sunshine, there is still vitamin D deficiency in most parts of the world and in most age groups. This could be due to reduced synthesis, decreased absorption and increased catabolism. This mini review is an attempt to reinforce the importance of vitamin D to every physician, and to make them aware that cases they see every day may be accompanied by a latent or preclinical levels of vitamin D deficiency which, when also treated, can further improve the patient's health.

A Global Problem

The problem is global with reports from Asia, Europe, Latin America, Africa and America.[1] In north and south Europe, values of vitamin D reported were 40-50 nmol/l and 20-30 nmol/l, respectively. The higher values in the northern region irrespective of unfavorable latitude were related to the consumption of fatty fish, cod liver oil and more sun seeking behaviour.[2] In a systemic literature review, it was found that the highest 25-hydroxyvitamin D [25(OH)D] values were observed in North America.[3] Age-related differences were observed in Asia Pacific and Middle East/Africa regions. No sex-related differences were observed. In a historical perspective written by Holick and Chan, the measures taken by different countries and their consequences have been mentioned.[4]

The South-East Asian Scenario

Recent reviews have highlighted that deficiency exists even in South-East Asian countries. Data from China, South Korea and Thailand have been mentioned.[5,6] A reported deficiency of 70-100% in otherwise healthy individuals has been reported in India. The prevalence of deficiency is 86% in less than 3 months old, 61% in 2-60 months age group and 53.35% in postmenopausal women. Deficiency exists in both sexes and in both rural and urban population. Awareness, clothing, vegetarian food preferences, and unaffordable supplements are some causes mentioned in various studies. Twenty to forty five minutes of sun exposure may be required for adequate synthesis of vitamin D and, surprisingly, this also is not obtained in day-to-day activities.[7-11]

Normal Values of Vitamin D, And Its Deficiency

Serum 25(OH)D, available from sunlight and dietary sources with a half-life of 3-4 weeks, being the circulating and storage form, serves as the best available indicator of vitamin D status of the body. Serum levels of 1,25-dihydroxycholecalciferol, the active metabolite of vitamin D, is subject to variations, secondary to changes in parathyroid hormone levels of the body. The US Institute of Medicine defines serum 25(OH)D levels of >50 nmol/l as sufficient, 30-50 nmol/l as inadequate and <30 nmol/l as deficiency.[12] Similarly, WHO refers to

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<50 nmol/l as insufficiency.[13] The Endocrine Society Task Force defines vitamin D deficiency as a serum 25(OH)D concentration below 20 ng/ml (<50 nmol/l) and an optimum level being 30-50 ng/ml for maximum effects of vitamin D on calcium, bone and muscle metabolism.[14] Deficiency may be classified according to the levels of 25(OH)D (in ng/ml) as severe deficiency <5, deficiency <15, insufficiency 15-20, sufficient 20-100, excess (hypervitaminosis) >100, and intoxication >150.[15] For comparison of values, different units are mentioned, but 1 nmol/l is equivalent to 0.4 ng/ml.

Requirement and Sources of Vitamin D

The adequate intake, or estimated average requirement, of infants, 1-18 years old, pregnant and lactating women is 400 IU/d. A daily supplementation of 400 IU under situation of minimal exposure to sunshine is recommended by the Indian Council of Medical Research. The upper limit is 1,000 IU/d for 0-6 months old, 1,500 for 6-12 months old, 2,500 for 1-3 years old, 3,000 for 4-8 years old, 4,000 for 9 years old and above, pregnant and lactating mothers. A US study suggests recommended daily allowance for women and children as 600 IU/d.[16-19] The two forms of vitamin D may have different sources: ergocalciferol (vitamin D_2) is formed in plants and yeast; cholecalciferol (vitamin D_3), is synthesized in skin and obtained from animal dietary sources. Sunlight, diet, supplements, and prescription drugs are the major sources when there is a state of deficiency. The various sources of vitamin D are listed in Table 1. It is recommended that vitamin D should be obtained from a healthy diet and not unprotected exposure to UV radiations.[20-22]

Metabolism of Vitamin D

The precursor of vitamin D_3 (7-dehydrocholesterol) is found in the epidermis. Ultraviolet ray exposure (280-320 nm) converts it to a previtamin. Its cis form then converts to vitamin D_3 (cholecalciferol) by a thermal non-enzymatic process. In the bloodstream its half-life is 36-78 h. It is then taken up by adipocytes in subcutaneous and omental fats. When vitamin D_3 and D_2 are acted upon by an enzyme 25-hydroxylase of the cytochrome P450 enzyme system, it gets converted to 25(OH)D or calcidiol, whose half-life is 21-30 days. This is further converted into 1,25-dihydroxy vitamin D [$1,25(OH)_2D$] by 1α-hydroxylase in the proximal convoluted tubule of kidney. This enzyme is also present in extra renal sites like prostate, breast, colon, keratinocytes, and monocytes. Locally produced $1,25(OH)_2D$ is under autonomous endocrine control. $1,25(OH)_2D$ inversely regulates its own concentration by inducing synthesis of the enzyme, 25-hydroxyvitamin D-24-hydroxylase, and is converted into an inactive water soluble metabolite calcitroic acid. 24-Hydroxylase also acts on 25(OH)D forming inactive $24,25(OH)_2D$.[22-25]

Table1 Sources of vitamin D (natural sources, food and therapeutic drugs)[20-22]

Sunlight	Fish, mackerel, tuna, salmon
UV light	Milk, yogurt, cheese
Artificial lamps	Vitamin D_2 ergocalciferol (capsule)
Human breast milk	Vitamin D_2 ergocalciferol liquid (injection)
Cod liver oil	Vitamin D_3 calcitrol
Egg yolk	Vitamin D_3 calcitrol liquid
Mushroom	Multivitamin
Cereal	Vitamin D_3 cholecalciferol
Orange juice	

Mechanism of action

A steroid hormone, $1,25(OH)_2D$ links with vitamin D receptor (VDR), binds to a retinoic acid X receptor, and forms a heterodimer. This binds to promoter regions of target genes and modifies transcription. VDR also interacts with other transcription factors like co-activator proteins, transcription integrators like calcium-binding proteins, and transcriptional apparatus like steroid receptor activator complex (SRC). Vitamin D regulates some 200-2000 genes involved in many processes, like cell proliferation, differentiation, and apoptosis; synthesis of bactericidal proteins; immunomodulation; and angiogenesis. Its levels are influenced by parathyroid hormone (PTH) activity. This raises the calcium levels in the body by increasing its absorption from intestine, resorption from the bone and decreased excretion from the kidneys.[26,27]

Physiological Factors Affecting Vitamin D Levels

Sunlight, lipids, enzymes and various host factors contribute to a normal level of vitamin D. An exposure to sun rays to bare face, arms, and legs, for about 45 minutes daily, is adequate for normal synthesis of vitamin D.[11] Some factors which cause its deficiency are endemic to regions and populations; others arise from rapidly changing lifestyles, industrialization and urbanization. Table 2 gives a list of such factors. These are responsible for deficiency and must be kept in mind while calculating therapeutic dose and duration of therapy.[2,4,11,19,20,22,24,28-36]

Clinical Disorders Associated With Vitamin D Deficiency

Suddenly, increased awareness and research make us feel there is a vitamin D deficiency epidemic. However most cases of vitamin D deficiency are asymptomatic and remain undetected until deficiency becomes severe and prolonged. Classically, vitamin D deficiency presents as metabolic bone disease, as rickets in children and as osteomalacia in adults, with or without accompanying hypocalcemia and tetany. Bones become demineralized and softened, epiphyses of long bones become enlarged, and there is growth

Table 2 Physiological variations in vitamin D levels and proposed mechanisms

Factors	Vit. D levels	Mechanisms
Genetics, migrants from Asia, Africa compared to non-Hispanic white[2,28]	variable	Genetic traits; vitamin D receptor genotypes; cultural behavior
Athletes[31]	variable	Insufficient UV ray exposure, indoor sports, early morning or late evening training, sunscreen use
Old age[4,30]	↓	Decreased dehydrocholesterol concentration
Ozone[22]	↓	Blocks sunlight
Pollutants[22]	↓	Absorb, scatter, or reflect rays
Latitude below 35^{O} N [2]	↑	More sunlight
Clothes (wool, silk, nylon, polyester); sunscreen; cultural beliefs, keeping skin covered[22]	↓	Block sunlight
Indoor staying, crowded areas, elderly, disability, hospitalized[2]	↓	Less exposure to sunlight
Melanin[22]	↓	Block sunlight
Adiposity, obesity[34]	↓	Concentration of vitamin in large amount of adipose tissue
Scar/burn[35]	↓	Blocks sunlight
Dietary practices, boiling, calcium deficient, rich in phytate, lactose intolerance[11]	↓	Less availability
Pregnant mothers[19,29]	↓	More requirement
Postmenopausal symptoms, vaginal atrophy, urinary incontinence, cardiovascular[36]	↓	Urothelium, smooth muscle of detrusor has vitamin D receptor. Other associated problems
Breast fed infants[33]	↓	Indoors, availability and metabolism
Poor sleep quality[32]	↓	Time spent indoors, less physical activity
Drugs: phenobarbitone, phenytoin, carbamezapine, rifampicin, isoniazid, antiretroviral, glucocorticoids[20,33]	↓	More catabolism

retardation, bone discomfort and muscle aches, lower back pain, leg deformities and stress fractures. Older women may have proximal muscle weakness, frequent falls, and heaviness in legs, chronic musculoskeletal pain and fatigue.[1,3,4,37-40] The role of vitamin D in several nonosseous diseases is being documented as shown in Table 3.[22,35,41-72] However we should be cautious while associating each disease with vitamin D deficiency, because in some conditions like schizophrenia its importance is doubtful.[73]

Treatment of Vitamin D Deficiency

Exposure to sunlight and artificial UVB radiation

Controlled, sensible exposure of skin to sunlight /UVB, arms and legs alone to sunlight, for 5-30 minutes between 10 am and 3 pm, two to three times per week, synthesizes enough vitamin D in skin to prevent its deficiency. Although skin pigmentation does not affect the amount of sunlight reaching, but the duration of exposure required may vary, being more in dark skinned individuals. The concerns with UVB exposure, both, natural and artificial, are those of sunburn, skin aging, melanoma and non-melanoma skin cancers.

Vitamin D supplementation

Both vitamin D_3 (cholecalciferol) and vitamin D_2, (ergocalciferol) are available as prescription drugs and as oral dietary supplements. Doses for treatment are 2000 IU/d or 50,000 IU once a week for 6 weeks (infant to 18 years of age), and for adults, 6000 IU/d or 50,000 IU/once a week for 8 weeks. Maintenance dose of 400 IU/d is given to infants, 600 IU/d for 1-18 years old and 1500-2000 IU/d for adults. Similarly a higher dose of vitamin D is needed in older, obese patients with mild to moderate hepatic failure and intestinal fat malabsorption syndrome. The dose response curve shows that a supply from 20 µg (800 IU/d) to 500 µg (20,000 IU/d) will maintain serum levels of 25(OH)D within a range of 75-220 nmol/l by homeostatic control mechanisms.[74,75]

Calcium supplementation

In children, especially on stoss therapy with vitamin D, calcium supplementation 30-75 mg/kg/d in three divided doses for 1-2 weeks as a preparation of either citrate, carbonate, gluconate, or lactate may be needed until parathyroid and vitamin D levels normalize.[33] This aids remineralization, and prevents hypocalcemia and hungry bone syndrome. Thereafter, the dose may be reduced.

Monitoring

It is recommended that after one month of initiating therapy, serum calcium, phosphorous, and alkaline phosphate levels are measured. After 3 months, these along with serum magnesium, vitamin D and PTH levels may be estimated. Repeated investigations should be done if there is no clinical improvement or if otherwise required. Calcium and phosphorous levels are the earliest to normalize, within 6-10 days. Serum vitamin D and PTH levels take 1-2 months,

Table 3 Proposed mechanism linking insufficient vitamin D levels to clinical conditions

Disease/Disorder	Mechanism of vitamin D abnormality or improvement with therapy
Rickets, osteoporosis, fractures, fall in elderly, joint/back pains[41,42]	Alterations in bone metabolism and calcium levels
Rheumatoid arthritis[43]	TNF-α activity not suppressed; increased IL-6, IL-10, CRP and inflammatory markers
Decreased testosterone, estrogen, FSH, LH levels[44,45]	Influencing testosterone-to-estrogen conversion by aromatase
GI diseases: celiac, Crohn, pancreatitis, cystic fibrosis, liver failure, gastric bypass	Decreasing absorption of oral intake
Inflammatory bowel disease[22]	Preventing suppression of Th-1 cell response in inflammation
Kidney disease[22]	Phosphate retention and loss of function inhibit 25(OH)D-1α hydroxylase.
Hypertension, stroke, atherosclerosis[46,47]	Vitamin D treatment decreases renin and arterial stiffness, improves vascular dysfunction, reduces oxidative stress. Higher incidence of cardiovascular events and mortality
Diabetes, hyperlipidemia, metabolic syndrome[48]	With therapy, insulin resistance decreases and insulin sensitivity increases. Statin therapy associated with lower vitamin D levels
Preeclampsia, impaired glucose intolerance[49]	Increasing chances of cesarean section; deficit in bone mineral accrual in children up to 9 years; low birth weight of offspring
Infertility[50]	Treatment improves cell survival and sperm motility, PCOS, IVF outcome by steroid genesis of sex hormones, placental development and tolerance
Congenital rickets, neonatal hypocalcemic seizure, low birth weight, tooth decay, fractures, childhood immune disorders[35, 51]	Maternal 25(OH)D and vitamin D-binding protein might regulate expression of placental amino acid transporter.
Autism[52]	Decreased tryptophan hydroxylase (TPH)1; increased TPH2 (brain); decreased serotonin
Influenza, asthma, bronchiolitis[53]	Seasonal deficiency; vitamin D treatment enhances innate immune response
Tuberculosis[54,55]	Vitamin D upregulates antimicrobial peptides, cathelicidin.
HIV[56,57]	Vitamin D supplementation reduces HIV transmission and comorbidity.
Depression[58,59], dementia[60], Alzheimer[61], Parkinsonism[62]	Vitamin D therapy improves symptoms.
Multiple sclerosis[63]	Severity of disease decreases with vitamin D therapy.
Lupus erythematosus[64]	Reducing memory B cells and effector T cells; increasing regulatory T cell
Psoriasis, atopic dermatitis, vitiligo, icthyosis, skin cancer[65,66]	Modulating markers of epidermal proliferation; suppressing inflammatory response; enhancing antimicrobial activity; promoting integrity of permeability barrier
Malignancies: epithelial, breast, prostate, non-small cell, colonic, pancreatic, ovarian, non-Hodgkin lymphoma[67-70]	Increasing calcium which protects integrity of intercellular junction; decreasing angiogenesis; producing cathelicidin; reducing proliferation Apoptosis Cancer cells enhance 25(OH)D-1-hydroxylase expression, affecting 1,25$(OH)_2$D levels.
Susceptibility to severe infection and mortality of critically ill[71]	Treatment decreases mortality.
Hyperparathyroidism[72]	Increasing catabolism of 25(OH)D

and serum alkaline phosphatase levels correct in about 3-6 months. Radiological improvement can be appreciated within 4 weeks.[33]

Contraindications to vitamin D therapy

Hypervitaminosis, hypersensitivity and toxicity are absolute contraindications and they must be clearly understood. The liver is able to hydroxylate vitamin D but chronic liver disease and nephrotic syndrome may decrease vitamin D-binding protein. Vitamin D hypersensitivity syndromes occur when extra renal production of 1,25$(OH)_2$D causes hypercalcemia. This may be seen in some granulomatous diseases like tuberculosis and sarcoidosis, and some cancers e.g. non-Hodgkin's lymphoma and oat cell carcinoma of the lungs. In skin conditions like porphyrias, albinism, xeroderma pigmentosum, skin cancers like melanoma, when there is intake of photosensitizing drugs like tetracycline, phenothiazines, sulfonamides, or psoralens, UV vitamin D therapy is avoided. Hypercalcemia, hypercalciuria, nephrocalcinosis are results of overdosage. Various symptoms associated with toxicity have to be treated.[22,26,76]

Future Scope and A Word of Caution

Research has progressed to the extent that it has been reported that newborns have lower cord vitamin D levels if their mother had a low vitamin D level. Roles in placental tolerance, development, fetal imprinting, fetal programming and epigenetic modification are being talked about.[1] Awareness, screening of at risk individuals, diagnosis, treatment and food fortification is required today.[77] Over-enthusiastic, uncontrolled treatment, overdose, and commercialization of knowledge without proper understanding are to be avoided. Nevertheless increased identification of vitamin D deficiency in the sunny countries of the world is a cause of concern and has to be addressed.[78,79]

Conclusion

A Pandora box of information has opened, showing us the status of vitamin D, its role in the manifestation of diseases and therapy. All practicing doctors must use this information, read more, and aim to eradicate this deficiency and prevent it from becoming a pan epidemic of modern society.

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Conflict of Interest

None.

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