Vitamin D Deficiency: Causes & Treatment

Chapter 1

Causes and Treatment of Vitamin D Deficiency

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Abstract

Vitamin D deficiency is a worldwide public health problem across all age groups including infants, children, adults, and elderly. Very few foods naturally contain or are fortified with vitamin D. The major source of vitamin D is from sunlight exposure. Vitamin D, the sunshine vitamin is synthesized from 7-dehydocholesterol present in the skin of humans by the action of ultraviolet B radiation (290 – 315 nm). The major cause of vitamin D deficiency is lack of adequate sunlight exposure. In utero and during childhood, vitamin D deficiency can cause growth retardation and skeletal deformities and may increase the risk of hip fracture later in life. Vitamin D deficiency in adults can precipitate or exacerbate osteopenia and osteoporosis, cause pain producing osteomalacia and muscle weakness, and increase the risk of fall and fracture. Vitamin D deficiency is associated with increased risk of common cancers, autoimmune diseases, infectious diseases, and cardiovascular mortality. Serum 25-hydroxy vitamin D (25-OHD) is the reliable marker of vitamin D status and a level below 20 ng/ml defines deficiency. However, an optimal level above 30 ng/ml is required to maximize the bone health and non-skeletal benefits of vitamin D. A sensible sun exposure for 5 – 15 min between 1000 and 1500 hours in the spring, summer and autumn and supplementation of atleast 400 IU, 600 IU and 800 IU of vitamin D/day among infants and children, adults and elderly respectively shall guarantee vitamin D sufficiency in at risk population.

1. Sources of Vitamin D

Humans get vitamin D from sunlight exposure, dietary sources and supplements [1]. "Vitamin D" (calciferol) refers to both cholecalciferol (vitamin D_3) and ergocalciferol (vitamin D_2). Cholecalciferol is produced by the action of ultraviolet B light (UVB; wavelength,

290–320 nm) on 7- dehydrocholesterol in the skin of humans, and is the form of vitamin D found in oily fish. Ergocalciferol is formed when ultraviolet (UV) light irradiates the fungal steroid, ergosterol. Few foods naturally contain vitamin D_3 or D_2 [1-3]. Few foods are fortified with Vitamin D. Some of the sources of Vitamin D are given in the **Table 1**.

Table 1: Sources of vitamin D_2 and vitamin D_3

Natural sources	
Cod liver oil	400–1,000 IU/teaspoon vitamin D_3
Salmon, fresh wild caught	600–1,000 IU/3.5 ozvitamin D_3
Salmon, fresh farmed	100–250 IU/3.5 oz vitamin D_3, vitamin D_2
Salmon, canned	300–600 IU/3.5 oz vitamin D_3
Sardines, canned	300 IU/3.5 oz vitamin D_3
Mackerel, canned	250 IU/3.5 oz vitamin D_3
Tuna, canned	236 IU/3.5 oz vitamin D_3
Shiitake mushrooms, fresh	100 IU/3.5 oz vitamin D_2
Shiitake mushrooms, sun-dried	1,600 IU/3.5 oz vitamin D_2
Egg yolk	20 IU/yolk vitamin D_3or D_2
Sunlight/UVB radiation	20,000 IU equivalent to exposure to 1 minimal erythemal dose (MED) in a bathingsuit. Thus, exposure of arms and legs to 0.5 MED is equivalent to ingesting3,000 IU vitamin D_3
Fortified foods	
Fortified milk	100 IU/8 oz, usually vitamin D_3
Fortified orange juice	100 IU/8 oz vitamin D_3
Infant formulas	100 IU/8 oz vitamin D_3
Fortified yogurts	100 IU/8 oz, usually vitamin D_3
Fortified butter	56 IU/3.5 oz, usually vitamin D_3
Fortified margarine	429 IU/3.5 oz, usually vitamin D_3
Fortified cheeses	100 IU/3 oz, usually vitamin D_3
Fortified breakfast cereals	100 IU/serving, usually vitamin D_3
Pharmaceutical sources in the United States	
Vitamin D_2 (ergocalciferol)	50,000 IU/capsule
Drisdol (vitamin D_2) liquid	8,000 IU/cc
Supplemental sources	
Multivitamin	400, 500, 1,000 IU vitamin D_3 or vitamin D_2
Vitamin D_3	400, 800, 1,000, 2,000, 5,000, 10,000, and 50,000 IU

IU=25 ng. [Reproduced from M.F.Holick et al. J Clin Endocrinol Metab, July 2011, 96(7):1911–1930]

2. Photosynthesis of Vitamin D_3

During exposure to sunlight, UVB radiation (290–315 nm) is absorbed by Pro-vitamin D, 7-dehydrocholesterol (relatively rigid 4 – ringed structure) that is present in the lipid bilayer of plasma membranes of both epidermal keratinocytes and dermal fibroblasts [4-6]. The energy is absorbed by the double bonds in the B ring, which results in rearrangement of the double bonds and opening of the B ring to form previtamin D_3. The opening of B ring during the formation of previtamin D_3 by UVB radiation makes it less rigid and increases the membrane permeability to Calcium and various ions. Once formed, previtamin D_3, which is entrapped within the plasma membrane lipid bilayer, rapidly undergoes rearrangement of its double bonds to form the more thermodynamically stable vitamin D_3. During this transformation process, vitamin D_3 is ejected from the plasma membrane into the extracellular space. The vitamin D-binding protein in the dermal capillary bed has an affinity for vitamin D_3 and draws it into the circulation. On excessive exposure to sunlight, previtamin D_3 and vitamin D_3 that has formed and not escaped into the circulation continues to absorb UV radiation and isomerizes into inactive photoproducts, namely tachysterol and lumisterol, thereby preventing Vitamin D intoxication.

3. Metabolism of Vitamin D in The Regulation of Calcium, Phosphorus Homeostasis and Skeletal Metabolism

Vitamin D_2 and vitamin D_3 obtained from dietary and supplementary sources are incorporated into chylomicrons and transported by the lymphatic system into the venous circulation. Vitamin D made in the skin (D_3) or ingested (D_2 or D_3) in the diet can be stored in and then released from fat cells [1,7,8]. Vitamin D (here after "D" represents D_2 or D_3) in the circulation is bound to the vitamin D–binding protein, which transports it to the liver, where vitamin D is converted by vitamin D-25-hydroxylase to 25-hydroxyvitamin D [25-OHD]. Although this is the major circulating form of vitamin D, 25-OHD is biologically inactive and must be converted in the kidneys by 25-hydroxyvitamin D-1α- hydroxylase (1α-OHase) (CYP27B1) to the biologically active form -1,25-dihydroxyvitamin D [1,25 $(OH)_2D$]. Serum phosphorus, calcium, fibroblast growth factor 23 (FGF-23), and other factors can either increase (+) or decrease (–) the renal production of 1,25 $(OH)_2D$. Fibroblast growth factor 23, secreted from the bone, causes the sodium–phosphate cotransporter to be internalized by the cells of the kidney and small intestine and also suppresses 1,25-dihydroxyvitamin D synthesis. 1,25 $(OH)_2D$ decreases its own synthesis through negative feedback and decreases the synthesis and secretion of parathyroid hormone by the parathyroid glands. 1,25 $(OH)_2D$ increases the expression of 25-hydroxyvitamin D-24- hydroxylase (24-OHase) (CYP24) to catabolize 1,25 $(OH)_2D$ to the water-soluble, biologically inactive calcitroic acid, which is excreted in the bile. The free form of 1,25 $(OH)_2D$, a steroid hormone upon entering the target cell interacts with specific nuclear Vitamin D receptor (VDR), which is phosphorylated (Pi). The 1,25 $(OH)_2D$-VDR

complex combines with the retinoic acid X receptor (RXR) to form a heterodimer, which in turn interacts with the vitamin D-responsive element (VDRE), causing enhancement or inhibition of transcription of vitamin D-responsive genes. 1,25 $(OH)_2D$ enhances intestinal calcium absorption in the small intestine by enhancing the expression of the epithelial calcium channel (transient receptor potential cation channel, subfamily V, member 6 [TRPV6]) and calbindin 9K, a calcium-binding protein (CaBP). 1,25 $(OH)_2D$ is recognized by its receptor in osteoblasts, causing an increase in the expression of the receptor activator of nuclear factor-κB ligand (RANKL). RANK, the receptor for RANKL on preosteoclasts, binds RANKL, which induces preosteoclasts to become mature osteoclasts. Mature osteoclasts mobilize calcium and phosphorus from the bone, maintaining calcium and phosphorus levels in the blood. Adequate calcium (Ca^{2+}) phosphorus ($HPO4^{2-}$) product (product of blood concentrations of calcium and phosphorus) is necessary for the mineralization of the skeleton.

4. Non-Calcemic Actions of Vitamin D

The revelation of vitamin D receptor (VDR) and the local production of active form of vitamin D- 1,25 $(OH)_2D$ from the circulating 25-OHD by 1-α hydroxylase activity in almost all the nucleated cells and the tissues of the body has provided insight onto the multitude of biological functions of vitamin D [3,5,6,9]. The VDR is present in the small intestine, colon, osteoblasts, activated T and B lymphocytes, islet cells, parathyroid cells and most organs in the body, including brain, heart, skin, gonads, prostate, breast, and mononuclear cells. It has been reported that the blood concentrations of 25-OHD above 78 nmol/L (30 ng/mL), is necessary for extra renal production of 1,25$(OH)_2D$. 1,25 $(OH)_2D$ is known to control over 200 genes involved in various physiological functions including control of cellular proliferation and differentiation, apoptosis, inhibition of angiogenesis, modulation of immune cells, cathelicidin production against infectious agents, increased insulin production by the pancreas, decreased renin production by the kidneys, increased myocardial contractility, prevention of inflammatory bowel disease, and promotion of thyroid-stimulating hormone secretion [10,11]. The locally produced 1,25 $(OH)_2D$ is converted to inactive calcitroic acid and does not enter circulation. Therefore, it does not influence calcium metabolism. The locally produced 1,25$(OH)_2D$ in parathyroid cells inhibits the expression and synthesis of parathyroid hormone. In addition, skeletal muscle possesses VDR. Performance speed and proximal muscle strength improves markedly when 25-OHD levels increases above 30 ng/ml [8,12].

5. Definition of Vitamin D Deficiency

Serum circulating level of 25- OH vitamin D is the most reliable indicator of Vitamin D status of the body [1,12-18]. 25-OHD is the major circulating form of vitamin D with half-life of about 2 weeks. 25-OHD is measured by various methods such as Radioimmunoassay, High Performance Liquid Chromatography but the gold standard is Liquid Chromatography- Tan-

dem Mass Spectrometry. Adherence of assay methodology to National Institute of Standards and Technology should reduce bias. Although 1,25 $(OH)_2D$ is the active form of vitamin D, it is not used to assess the vitamin D status as it has a short half-life of less than 4 hours in circulation. More importantly, during vitamin D deficiency, there is a compensatory increase in the parathyroid hormone secretion which stimulates the kidney to produce more 1,25 $(OH)_2D$. Therefore, the levels of 1,25 $(OH)_2D$ may be normal or even elevated when the patient is severely vitamin D deficient. However, the measurement of 1,25 $(OH)_2D$ is useful in acquired and inherited disorders in the metabolism of vitamin D and phosphate, including chronic kidney disease, hereditary phosphate-losing disorders, oncogenic osteomalacia, pseudovitamin D-deficiency rickets, vitamin D-resistant rickets, as well as chronic granuloma forming disorders such as sarcoidosis and some lymphomas. 25-OHD is inversely related to parathyroid hormone levels (PTH). The PTH decreases with increase in 25-OHD level and reaches a nadir when 25-OHD levels are between 30 and 40 ng/ml when maximum bone health and non-skeletal benefits are observed. As vitamin D deficiency progresses, parathyroid gland is maximally stimulated leading to secondary hyperparathyroidism. The PTH data with reference to 25-OHD has been used by Institute of Medicine (IOM) and other research committees to define vitamin D deficiency status and inform treatment decisions.

Vitamin D deficiency is defined as serum 25-OHD concentration less than 20 ng/ml. Insufficiency as 25-OHD level between 21 and 29 ng/ml. Vitamin D in toxication occurs when 25-OHD exceeds 150 ng/ml.

Status	Serum 25 OH	Vitamin D Concentration
Severe Deficiency	<10 ng/ml	<25 nmol/liter
Deficiency	<20 ng/ml	<50 nmol/l
Insufficiency	21 – 29 ng/ml	50 – 74 nmol/l
Sufficiency	30 – 100 ng/ml	75 – 250 nmol/l
Optimal	30 – 60 ng/ml	75 – 150 nmol/l
Toxic	>150 ng/ml	>375 nmol/l

6. Assessment of Vitamin D Deficiency

Screening the blood levels of 25-hydroxyvitamin D of the population at risk in reputed laboratory enrolled in Vitamin D External Quality Assessment Scheme (DEQAS) proficiency program is recommended. Screening the general population is not currently recommended [2,14].

7. Causes of Vitamin D Deficiency

The major source of Vitamin D for the human kind is exposure to sunlight. More than 90% of the vitamin D requirement is obtained from casual exposure to sunlight [4-6,19]. The

skin has a large capacity to produce vitamin D. Exposure to 1 Minimal Erythemal Dose (MED) of 54mJ/sq.cm (which imparts light pinkness after exposure) among young adults in bathing suits increases blood concentrations of vitamin D equivalent to that observed with the doses of 10,000 to 20,000 IU of vitamin D. Therefore, 1 MED is equivalent to 10- 50 times the recommended dietary in takes of 400 IU, 600 IU and 800 IU of vitamin D among infants, adults and elderly aged 70 years or above respectively. Lack of adequate exposure to sunlight is the most important cause of vitamin D deficiency.

Any factor that either influences the number of solar UVB photons that penetrate the skin or alters the amount of 7-dehydrocholesterol in the skin influences the cutaneous production of vitamin D_3. The amount of 7-dehydrocholesterol in the epidermis is relatively constant and begins to decline only later in life. Melanin is an effective natural sunscreen and efficiently absorbs UVB photons. Therefore, dark skinned people with increased melanin pigmentation (such as an African American who never burns and always tans with skin type V) requires 5 to 10 times longer exposure to sunlight compared to light skinned individuals (skin type III- always burns, always tans) to produce same amount of vitamin D. Sunscreen absorbs UVB radiation and some UVA (321–400 nm) radiation before it enters the skin. Therefore, a sunscreen with a sun protection factor (SPF) of 8 reduces vitamin D_3 synthesis in the skin by 95% and a SPF of 15 by 98%. Time of day, season, and latitude also dramatically influences vitamin D_3 synthesis by skin. Although the sun is closest to the earth in winter, the sun's rays strikes the earth surface at a more oblique angle (zenith angle). Due to the oblique angle, UVB photons must pass through the ozone for a greater distance and therefore, more UVB photons are efficiently absorbed by the ozone layer. In addition, with the more oblique angle there are fewer photons per unit area striking the earth. Time of day, season, and latitude all influence the zenith angle of the sun [5,6]. Above 37° latitude during the months of November through February, there are marked decreases (80-100%, depending on latitude) in the number of UVB photons reaching the earth's surface. Therefore, very little if any vitamin D_3 is produced in the skin during the winter. However, below 37° latitude and closer to the equator, more vitamin D_3 synthesis occurs in the skin through-out the year. Similarly, in the early morning or late afternoon, the zenith angle is so oblique that very little if any vitamin D_3 is produced in the skin even in the summer.

Thus, sun exposure for 5-15 minutes is safe and sensible between the hours of 1000 and 1500 in the spring, summer, and autumn, because this is the only time when enough

UVB photons reach the earth's surface to produce vitamin D_3 in the skin. This is 25% of what would cause a minimal erythemal response.

Chronic excessive sun exposure is known to cause skin damage, skin wrinkling and skin cancers [20,21]. In New Zealand and Australia, sun exposure causes 99% of non-melanoma

skin cancers such as basal and squamous cell carcinoma and 95% of melanoma [22]. At the same time, a reasonable sun exposure is required to prevent vitamin D deficiency. Therefore, in these region, an application of a sunscreen with a SPF of 15 is recommended after sensible exposure, to prevent the damaging effects of chronic excessive exposure to sunlight. Veiled woman or individuals who remain covered outside for cultural reasons, institutionalized individuals and elderly confined to indoors who have in adequate sun exposure are prone to vitamin D deficiency. The most important determinant of vitamin D deficiency in infants is maternal 25-OHD status. Infants born to veiled, dark skinned mother have vitamin D deficiency. Breast milk is a poor source of vitamin D containing less than 20 IU/liter. Infants who are exclusively breast-fed for prolonged time are prone to vitamin D deficiency.

Malabsorption, celiac disease, cystic fibrosis and Whipple's surgery interferes with the absorption of the vitamin D from dietary sources. Anticonvulsants, glucocorticoids, rifampicin, highly active anti- retroviral therapy and immuno suppressive agents increase the metabolism of 25-OHD. Chronic liver failure and renal failure decrease the synthesis of vitamin D.

Vitamin D is inversely associated with body mass index more than 30 kg/sq.m [12].

Vitamin D is fat soluble and is stored in the body fat. Any excess vitamin D_3 that is produced during exposure to sunlight can be stored in the body fat and used during the winter, when little vitamin D_3 is produced in the skin. However, in obese individuals, vitamin D is sequestered in the abdominal fat and this fat can be an irreversible sink for vitamin D, increasing the risk of vitamin D deficiency [23,24]. Inherited disorders in the metabolism of vitamin D and phosphate also leads to vitamin D deficiency. Polymorphisms in the genes for vitamin D-binding protein, 7- dehydrocholesterol reductase (which affects the amount of substrate 7-dehydrocholesterol in skin) and 25-hydroxylase may contribute to variation in 25-OHD levels. The causes and effect of vitamin D deficiency are summarized in the **table 3**.

CAUSE	EFFECT
Decreased skin synthesis	
Sunscreen use — absorption of UVB radiation by sunscreen	Decreases vitamin D_3 synthesis — SPF 8 by 95%, SPF 15 by 98%
Skin pigment — absorption of UVB radiation by melanin	Decreases vitamin D_3 synthesis by as much as 99%
Aging — reduction of 7-dehydrocholesterol in the skin	Decreases vitamin D_3 synthesis by about 75% in a 70-year-old
Season, latitude, and time of day — number of solar UVB photons reaching the earth depending on zenith angle of the sun (the more oblique the angle, the fewer UVB photons reach the earth)	Above about 35 degrees north latitude (Atlanta), little or no vitamin D_3 can be produced from November to February
Patients with skin grafts for burns — marked reduction of 7-dehydrocholesterolin the skin	Decreases the cutaneous production of vitamin D_3
Decreased bioavailability	

Malabsorption — reduction in fat absorption, resulting from cystic fibrosis, celiac disease, Whipple's disease, Crohn's disease, bypass surgery, medications that reduce cholesterol absorption, and other causes	Impairs the absorption of vitamin D
Obesity — sequestration of vitamin D in body fat	Reduces availability of vitamin D
Increased catabolism	
Anticonvulsants, glucocorticoids, HAART (AIDS treatment), and antirejection medications — binding to the steroid and xenobiotic receptor or the pregnane X receptor	Activates the destruction of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D to inactive calcitroic acid
Breast-feeding	
Human breast milk – Poor source of Vitamin D	Increases infant risk of vitamin D deficiency when exclusively breast-fed
Decreased synthesis of 25-hydroxyvitamin D	
Liver failure	
Mild-to-moderate dysfunction	Causes malabsorption of vitamin D, but production of 25-hydroxyvitaminD is possible
Dysfunction of 90% or more	Results in inability to make sufficient 25-hydroxyvitamin D
Increased urinary loss of 25-hydroxyvitamin D	
Nephrotic syndrome — loss of 25-hydroxyvitamin D bound to vitamin D–binding protein in urine	Results in substantial loss of 25-hydroxyvitamin D to urine
Decreased synthesis of 1,25-dihydroxyvitamin D	
Chronic kidney disease	
Stages 2 and 3 (estimated glomerular filtration rate, 31 to 89 ml/min/1.73 m^2) Hyperphosphatemia increases fibroblast growth factor 23, which decreases 25-hydroxyvitamin D-1α hydroxylase activity	Causes decreased fractional excretion of phosphorus and decreased serum levels of 1,25-dihydroxyvitamin D
Stages 4 and 5 (estimated glomerular filtration rate <30 ml/min/1.73 m^2) In ability to produce adequate amounts of 1,25-dihydroxyvitamin D	Causes hypocalcemia, secondary hyperparathyroidism, and renal bone disease
Heritable disorders — rickets	
Pseudovitamin D deficiency rickets (vitamin D–dependent rickets type 1) — mutation of the renal 25-hydroxyvitamin D-1α-hydroxylase gene (CYP27B1)	Causes reduced or no renal synthesis of 1,25-dihydroxyvitamin D
Vitamin D–resistant rickets (vitamin D–dependent rickets type 2) — mutation of the vitamin D receptor gene	Causes partial or complete resistance to 1,25-dihydroxyvitamin D action, resulting in elevated levels of 1,25-dihydroxyvitamin D
Vitamin D–dependent rickets type 3 — over production of hormone responsive- element binding proteins	Prevents the action of 1,25-dihydroxyvitamin D in transcription, causing target-cell resistance and elevated levels of 1,25-dihydroxyvitamin D
Autosomal dominant hypophosphatemic rickets — mutation of the gene for fibroblast growth factor 23, preventing or reducing its breakdown	Causes phosphaturia, decreased intestinal absorption of phosphorus, hypophosphatemia, and decreased renal 25-hydroxyvitaminD-1α-hydroxylase activity, resulting in low-normal or low levels of 1,25-dihydroxyvitamin D

X-linked hypophosphatemic rickets — mutation of the PHEX gene, leading to elevated levels of fibroblast growth factor 23 and other phosphatonins	Causes phosphaturia, decreased intestinal absorption of phosphorus, hypophosphatemia, and decreased renal 25-hydroxyvitamin D-1α-hydroxylase activity, resulting in low-normal or low levels of 1,25-dihydroxyvitamin D
Acquired disorders	
Tumor-induced osteomalacia — tumor secretion of fibroblast growth factor 23 and possibly other phosphatonins	Causes phosphaturia, decreased intestinal absorption of phosphorus, hypophosphatemia, and decreased renal 25-hydroxyvitamin D-1α-hydroxylase activity, resulting in low-normal or low levels of 1,25-dihydroxyvitamin D
Primary hyperparathyroidism — increase in levels of parathyroid hormone, causing increased metabolism of 25-hydroxyvitamin D to 1,25-hydroxyvitamin D	Decreases 25-hydroxyvitamin D levels and increases 1,25-dihydroxyvitamin D levels that are high-normal or elevated
Granulomatous disorders, sarcoidosis, tuberculosis, and other conditions, including some lymphomas — conversion by macrophages of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D	Decreases 25-hydroxyvitamin D levels and increases 1,25-dihydroxyvitamin D levels
Hyperthyroidism — enhanced metabolism of 25-hydroxyvitamin D	Reduces levels of 25-hydroxyvitamin D

8. Consequences of Vitamin D Deficiency

Signs and symptoms of vitamin D deficiency include hypocalcemic seizures, tetany in infants, rickets in toddlers and children, osteomalacia and osteoporosis in adults. In the presence of $1,25(OH)_2D$, intestinal calcium absorption increases from 10 - 15% to 30% - 40% and phosphorus absorption from 60% to 80%. Vitamin D deficiency causes compensatory increases in parathyroid hormone synthesis and secretion. PTH stimulates 1 alpha-hydroxylase in the kidney and increases the conversion of 25-OHD to $1,25(OH)_2D$, there by enhancing intestinal calcium absorption while worsening vitamin D deficiency. Increased PTH enhances the tubular reabsorption of calcium by the kidney. As the vitamin D deficiency progresses the parathyroid glands are maximally stimulated resulting in secondary hyperparathyroidism. Increased PTH levels enhances phosphaturia resulting in low serum phosphorus or hypophosphatemia. In adequate calcium-phosphorous product causes diminished mineralization of skeleton resulting in classic signs of rickets and osteomalacia. Rickets results from poor osteoid mineralization adjacent to the growth plate and is only seen during growth, with a peak incidence during the periods of rapid growth in early infancy and early puberty [14]. On the other hand, Osteomalacia results from inadequate osteoid mineralization at sites of bone modelling and remodeling and is common to both children and adults. Some of the osseous signs of Vitamin D deficiency are listed in the **Table 4**. PTH also induces transformation of pre-osteoclasts to osteoclasts. Mature osteoclasts dissolve the mineralized collagen matrix in the bone and mobilizes calcium from skeleton causing osteoporosis and increased risk of fracture. Unlike osteoporosis, osteomalacia is associated with bone pain. It is believed that the hydration of the demineralized matrix beneath the periosteum elevates the periosteum and pushes it outwards [1]. The stretching of the periosteum stimulates the sensitive nerve endings to cause pain in osteomalacia.

Table 4. Osseous signs of vitamin D deficiency (common to less common)

• Swelling of wrists and ankles
• Rachitic rosary (enlarged costochondral joints felt lateral to the nipple line)
• Genu varum, genu valgum or windswept deformities of the knee
• Frontal bossing
• Limb pain and fracture
• Craniotabes (softening of skull bones, usually evident on palpation of cranial sutures in the first 3 months)
• Hypocalcemia - seizures, carpopedal spasm
• Myopathy, delayed motor development
• Delayed fontanelle closure
• Delayed tooth eruption
• Enamel hypoplasia
• Raised intracranial pressure
• Brown tumor secondary hyperparathyroidism

Radiological features

• Cupping, splaying and fraying of the metaphysis of the ulna, radius and costochondral junction
• Coarse trabecular pattern of metaphysis
• Osteopenia
• Fractures

Biochemical features of vitamin D deficiency include hypocalcemia, secondary hyperparathyroidism, hypophosphatemia and elevated alkaline phosphatase titers.

9. Non-Skeletal Consequences of Vitamin D Deficiency

Non-osseous features of vitamin D deficiency include cardiomegaly and marrow fibrosis with pancytopenia or microcytic hypochromic anemia. Vitamin D deficiency is associated with increased risk of common cancers in the prostate, colon, breast possibly related to dysregulation in cellular proliferation and differentiation [1,5,11]. Similarly, dysregulation in immune function results in increased risk of autoimmune diseases like multiple sclerosis, type 1 diabetes mellitus and rheumatoid arthritis and many infectious diseases like tuberculosis [23,10,24]. Vitamin D deficiency also causes muscle weakness, gait abnormality and increased risk of fall [11,25].

Table 4: Vitamin D intakes recommended by the IOM and the Endocrine Practice Guidelines Committee

Life stage group	IOM recommendations				Committee recommendations for patients at risk for vitamin D deficiency	
	AI	EAR	RDA	UL	Daily requirement	UL
Infants 0 to 6 months 6 to 12months	400 IU(10 µg) 400 IU (10 µg)			1,000 IU (25 µg) 1,500 IU (38 µg)	400 -1,000 IU 400-1,000 IU	2,000 IU 2,000 IU
Children 1-3 yr 4-8 yr		400 IU(10 µg) 400 IU (10 µg)	600 IU(15 µg) 600 IU(15 µg)	2,500 IU(63 µg) 3,000 IU(75 µg)	600-1,000 IU 600-1,000 IU	4,000 IU 4,000 IU
Males 9-13 yr 14-18yr 19-30yr 31-50yr 51-70yr >70yr		400 IU(10 µg) 400 IU (10 µg) 400 IU(10 µg) 400 IU (10 µg) 400 IU(10 µg) 400 IU (10 µg)	600 IU(15 µg) 600 IU(15 µg) 600 IU(15 µg) 600 IU(15 µg) 600 IU(15 µg) 800 IU(15 µg)	4,000 IU(100 µg) 4,000 IU(100 µg) 4,000 IU(100 µg) 4,000 IU(100 µg) 4,000 IU(100 µg) 4,000 IU(100 µg)	600-1,000 IU 600-1,000 IU 1,500-2,000 IU 1,500-2,000 IU 1,500-2,000 IU 1,500-2,000 IU	4,000 IU 4,000 IU 10,000 IU 10,000 IU 10,000 IU 10,000 IU
Females 9-13 yr 14-18yr 19-30yr 31-50yr 51-70yr >70yr		400 IU(10 µg) 400 IU (10 µg) 400 IU(10 µg) 400 IU (10 µg) 400 IU(10 µg) 400 IU (10 µg)	600 IU(15 µg) 600 IU(15 µg) 600 IU(15 µg) 600 IU(15 µg) 600 IU(15 µg) 800 IU(15 µg)	4,000 IU(100 µg) 4,000 IU(100 µg) 4,000 IU(100 µg) 4,000 IU(100 µg) 4,000 IU(100 µg) 4,000 IU(100 µg)	600-1,000 IU 600-1,000 IU 1,500-2,000 IU 1,500-2,000 IU 1,500-2,000 IU 1,500-2,000 IU	4,000 IU 4,000 IU 10,000 IU 10,000 IU 10,000 IU 10,000 IU
Pregnancy 14-18yr 19-30yr 31-50yr		400 IU(10 µg) 400 IU (10 µg) 400 IU(10 µg)	600 IU(15 µg) 600 IU(15 µg) 600 IU(15 µg)	4,000 IU(100 µg) 4,000 IU(100 µg) 4,000 IU(100 µg)	600-1,000 IU 1,500-2,000 IU 1,500-2,000 IU	4,000 IU 10,000 IU 10,000 IU
Lactation[a] 14-18yr 19-30yr 31-50yr		400 IU(10 µg) 400 IU (10 µg) 400 IU(10 µg	600 IU(15 µg) 600 IU(15 µg) 600 IU(15 µg)	4,000 IU(100 µg) 4,000 IU(100 µg) 4,000 IU(100 µg)	600-1,000 IU 1,500-2,000 IU 1,500-2,000 IU	4,000 IU 10,000 IU 10,000 IU

Abbreviations: AI: adequate intake; EAR: estimated average ewquirement; UL: tolerable upper intake level; [a]mother's requirement, 4,000-6,000 IU/d (mothers's intake for infant's requirement if infant is not receiving 400 IU/d). Reproduced from M. F. Holick et al. J Clin Endocrinol Metab, July 2011, 96(7):1911–1930.

10. Treatment of Vitamin D Deficiency

Cholecalciferol (25-OHD_3) is preferable over ergocalciferol (25-OHD_2) for treatment of vitamin D deficiency [15], although both are efficient. Vitamin D has a high therapeutic index. Vitamin D intoxication manifests only beyond 150 ng/ml (375 nmol/l) of 25-OHD. In general, for every 100 IU of vitamin D taken in, serum 25-OHD concentration increases approximately by 1 ng per milliliter (3 nmol per liter). The treatment and prevention strategies for vitamin D

deficiency across different age groups and specific etiology are summarized in the **Table 5**.

The most serious consequence of Vitamin D deficiency is hypocalcemic seizures and are common in infants less than 6 months of age. Aim of the therapy is to prevent seizures [14]. Intravenous bolus of 10 ml of 10% calcium gluconate over 20 minutes is recommended for seizures. If seizures recur, a repeat bolus or calcium infusion up to 4mmol/kg/day is administered until serum calcium is over 1.8 mmol/L. 1α-hydroxyvitamin D_3 or calcitriol at 60–120 ng/kg/day shall be co-administered with oral calcium until the serum calcium concentration is over 2.1 mmol/L. Australian Pediatrics endocrine group -Consensus statement recommends the following treatment protocol for vitamin D deficiency, depending on the age group. Neonates are given 1000 IU/day for 3 months and a maintenance dose of 400 IU/day. Infants aged 1 to 6 months are given 3000 IU/d for 3 months or 300000 IU over 1- 7 days followed by maintenance dose of 400 IU/day. Children more than 1 year are given 5000 IU for 3 months or 500000 IU over 1- 7 days and a maintenance dose of 600 to 1000 IU/day. High dose Stoss therapy is administration of the total requirement of vitamin D as a single dose either orally or by intramuscular injection. However, a few cases of hypercalcemia and nephrocalcinosis has been reported with such therapy.

Table 5: Treatment and prevention strategies for Vitamin D deficiency

Age/ Cause	Treatment with vitamin D (D_2 or D_3)	End point	Prevention and maintenance dose of vitamin D	Monitoring
0-1 year	2000 IU/d D x 6 weeks Or 50000IU/week x 6 + calcium 50 mg/kg/d x 1-2 week	Repeat if 25-OHD <30 ng/ml	400 – 1000 IU/d	Serum calcium and alkaline phosphatase monthly Serum calcium, magnesium, phosphorus, alkaline phosphatase q 3 months; Wrist X ray- to assess the healing of rickets; 25-OHD annually
1 – 18 years	2000 IU/d x 6 weeks Or 50000IU/week x 6	Repeat if 25-OHD <30 ng/ml	600 – 1000 IU/d	
Adults	6000 IU/d or 50000 IU/week x 8	Repeat if 25-OHD <30 ng/ml	1500 – 2000 IU/d	
Pregnant & Lactating woman	4000 – 6000 IU/d Or 50000 IU/week x 8	Repeat if 25-OHD <30 ng/ml	1500 – 2000 IU/d	
Nephrotic syndrome	50000 IU/week x 8	Repeat if 25-OHD <30 ng/ml	1000 – 2000 IU/d	
Obese	6000 – 10000 IU/d	Repeat if 25-OHD <30 ng/ml	3000 – 6000 IU/d	

Malabsorption	300000 IU per month intramuscularly x 3		300000 or 600000 IU i.m every year	
Extrarenal production of 1,25 $(OH)_2D$; Granulomatous disease or some lymphoma	50000 IU/week x 4	maintain 25-OHD between 20 – 30 ng/ml to prevent hypercalcemia	400 IU/d	Serial 25-OHD and serum Calcium
Primary Hyperparathyroidism and vitamin D deficiency	50000 IU/week x 8	Repeat if 25-OHD <30 ng/ml	800 – 1000 IU/d	Serial level of serum calcium
Chronic kidney disease Stage 2 & 3	50000 IU/week x 8	Repeat if 25-OHD <30 ng/ml	1000 IU/d	Control serum phosphate
Chronic kidney disease Stage 4 & 5	0.25 – 1 mcg/day of 1,25 $(OH)_2$ D Calcitriol or Doxecalciferol 10 -20 mcg PO three times per week		1000 IU/d + calcitriol	

During pregnancy, daily regimen should at least include a prenatal vitamin containing 400 IU vitamin D with a supplement that contains at least 1000 IU vitamin D. Lactating women may need to take a minimum of 1400–1500 IU/d, and to satisfy the requirements of an infant who is exclusively breast fed, the mother requires 4000 to 6000 IU/d to transfer enough vitamin D into her milk.

In adults, Vitamin D deficiency is treated with oral dose of 50,000 IU of D_2 or D_3 weekly once for 8 weeks or until 25-OHD is over 30 ng/ml and maintenance dose of 1500 – 2000 IU/day. Supplementation may be required for long-term in many individuals as the risk factors predisposing to vitamin D deficiency persist life long. In elderly people aged 70 years or more, Level I evidence indicates Calcium supplementation 1000 to 1300 mg/day combined with vitamin D 800- 1000 IU/d reduces the risk of falls and fracture [26,27]. However, long-term calcium therapy is not recommended as it predisposes to hypercalcemia, hypercalciuria, renal stones and non- adherence due to unpalatability.

In the subset of patients with reduced bioavailability of vitamin D (due to malabsorption, post- biliary surgery, Whipple's surgery), a dose of 300000 IU of D_2 or D_3 intramuscular (i.m) route every month for 3 months or until 25-OHD is over 30 ng/ml is recommended. A maintenance dose of 30000 or 60000 IU i.m every year.

In subjects with granulomatous disease or some lymphoma, wherein macrophages or immune cells convert 25-OHD into 1,25-$(OH)_2D$, Vitamin D deficiency is treated judiciously

with 50000 IU every week for 4 weeks maintaining the serum levels of 25-OHD between 20 and 30 ng/ml. A maintenance dose of 400 IU/day is sufficient. These patients should be closely monitored for hypercalcemia and hyperuricemia.

The Endocrine Practice Guidelines Committee suggest that the maintenance tolerable upper limits (UL) of vitamin D, should be 1000 IU/d for infants up to 6 months, 1500 IU/d for infants from 6 months to 1 year, 2500 IU/d for children aged 1–3yr, 3000 IU/d for children aged 4–8yr, and 4000 IU/d for everyone over 8yr and should not exceed the above without medical supervision. However, higher levels of 2000 IU/d for children 0–1 year, 4000 IU/d for children 1–18 yr, and 10,000IU/d for children and adults, 19yr and older may be needed to correct vitamin D deficiency. Treatment and prevention strategies for vitamin D deficiency is summarized in the **Table 3**. Treatment with calcitriol (1,25-$(OH)_2$D) is only indicated for certain cases of hypocalcemia and chronic kidney failure.

11. Conclusion

Vitamin D deficiency is a pandemic. The major cause of vitamin D deficiency is inadequate sun exposure. The serum level of 25-hydroxy vitamin D is the best indicator of vitamin D status. 25-OHD above 20 ng/ml is required to prevent rickets in children and osteomalacia in adults. An optimal range of 25-OHD between 30 and 60 ng/ml not only maximizes bone health but is also necessary for the extra-renal production of 1,25 $(OH)_2$D and are believed to provide preventive as well as therapeutic benefits in a wide variety of common cancers, autoimmune disorders, and infectious diseases. Sun exposure for 5 – 15 min between 1000 and 1500 hours in the spring, summer and autumn is safe and sensible. A minimum of 400 IU, 600 IU and 800 - 1000IU/day from dietary and supplementary sources among infants and children, adults, and elderly respectively, should guarantee vitamin D sufficiency in population at risk.

12. Refernces

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