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Dear Doctor,

Welcome to CME Digest. This fortnightly journal is a new offering from Asian Society of CME, whose vision is to enhance the quality of healthcare service provided through education initiatives. The objective of the journal is to update the knowledge and enhance the skills of physicians in managing both commonly and not so commonly encountered diseases in the clinic. Each issue of the journal would dwell in depth into a disease condition and would be authored by a leading nationally renowned Key Opinion Leader.

The education programme has been designed with well proven learning models that would vastly enhance the learning experience.

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Sincerely

Dr. Sunil Pandey

Director - CME Affairs

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CME DIGEST

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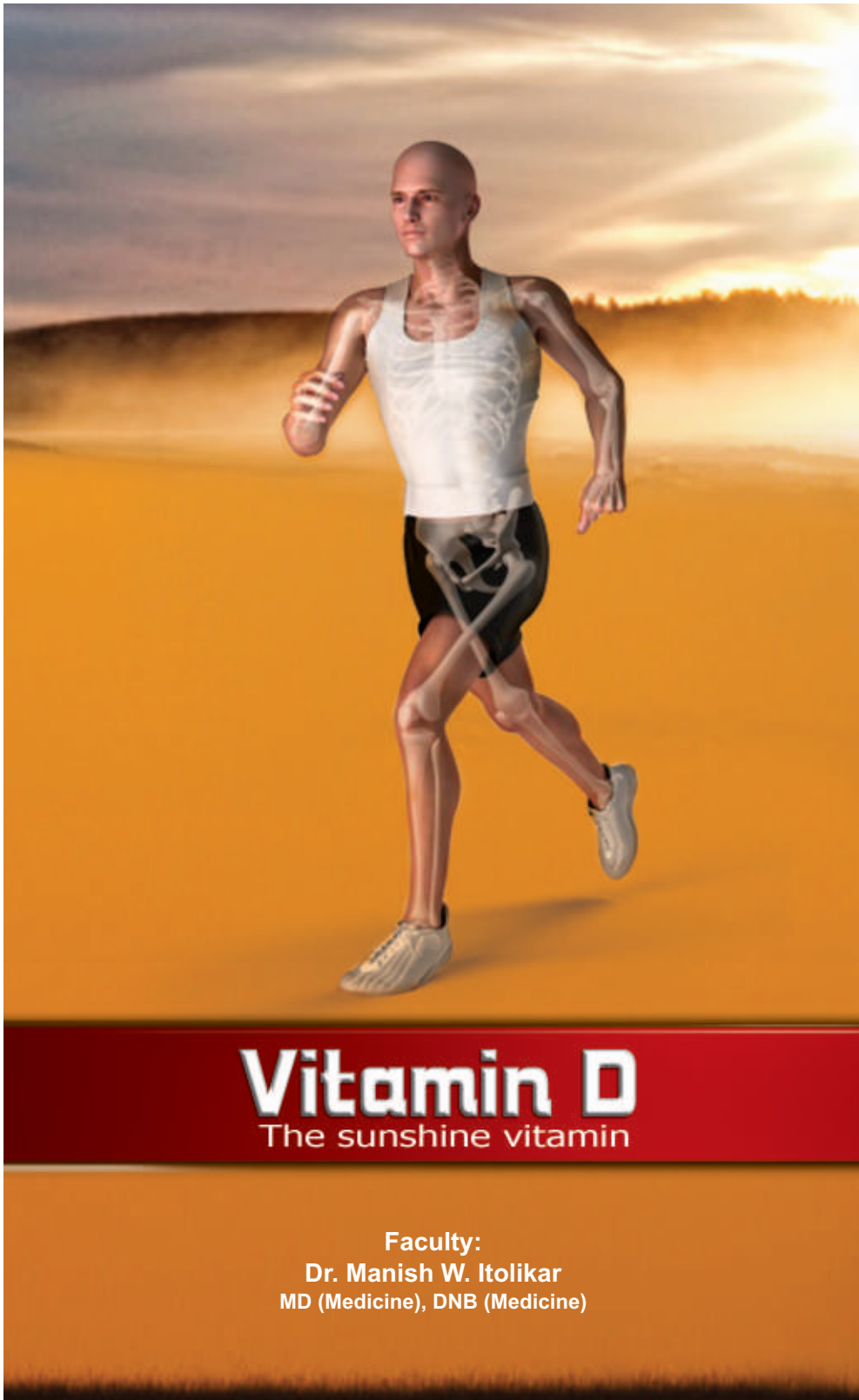

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Editor: Dr. Milind Nadkar **RNI No. MAHENG/2011/37223**

Editorial

Vitamin D_3: The 'sunshine' vitamin

Today, vitamin D has become the talk of the town since reports came that more than 90% of Indian population is vitamin D deficient. And it is not just worrisome due to ill-effects of vitamin D on the bone health but probably also on most of the body systems like muscles, immunity, cardiovascular systems, insulin secretion, mental health, etc. Now it is being understood how vital is this vitamin.

Since Indian subcontinent gets more than adequate sunshine for synthesis of vitamin D, it is surprising to find many Indians deficient in vitamin D without even realising it. The effects of its deficiency are not catastrophic and hence go unnoticed. They only manifest as other symptoms when various systems are being affected. It is difficult to demonstrate the role of vitamin D deficiency when different systems are affected.

It is important to determine whether vitamin D levels should be tested before giving supplements to population, 'not to say patients'. In overenthusiasm, hypervitaminosis should not result which is also worrisome. At the same time, it is not feasible to test each and every patient for vitamin D levels. Hence, unless specifically indicated, laboratory tests should not be encouraged. Judicious use of vitamin D should be advocated in clinical practice.

This CME Digest will certainly help you in understanding therapeutics of vitamin D in clinical practice.

Dr. Milind Nadkar

Editor

Asian Society of Continuing Medical Education

"Asian Society of Continuing Medical Education" is a registered charitable society and not for profit forum of doctors engaged in updating the skills and knowledge of practicing doctors by providing Continuing Medical Education (CME) activities.

Asian Society has worked with many renowned senior faculty in the medical fraternity to create Continuing Medical Education programmes in Live and Home Study formats, leveraging the evidence based knowledge and skills of the thought leaders drawn from various medical specialties and reaching out to a large number of practicing doctors across the country. The Distance Education mode has enabled practicing doctors even from the remotest parts of India to easily and conveniently participate in the programmes without any sacrifice to their practice.

CME Digest is a new and unique initiative from Asian Society of Continuing Medical Education. It is India's first fortnightly Journal dedicated to CME. It will be published from Mumbai under the Editorship of Dr. Milind Nadkar.

The objective of the Journal is to update the knowledge and enhance the skills of physicians in managing both commonly and not so commonly encountered disease conditions in the clinic. Asian Society of Continuing Medical Education through this Journal aims to provide quality CME to doctors in every nook and corner of India.

Each issue of the Journal would dwell in depth on a disease condition and would be authored by a leading nationally renowned Key Opinion Leader.

The CME will be structured for easy and quick assimilation of knowledge. The CME would be supported by Case Studies and Clinical Challenges. The Case Studies would serve the purpose of demonstrating the application of the knowledge while the Clinical Challenges would serve the role of self evaluation.

In addition to the CME, each issue would have columns on News & Notes and Medicolegal.

Editorial Board

Printed for the proprietor

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News & Notes

1. Synergistic effect of vitamin D and omega-3 fats in interrupting Alzheimer's plaque formation

Scientists have determined the combined effect of vitamin D_3 and omega-3 fatty acids in building up the immune system's ability to clear off the amyloid plaques which are found in the brains of patients suffering from Alzheimer's disease. Key genes and signaling pathways controlled by vitamin D_3 and the omega-3 fatty acid docosahexaenoic acid (DHA) were identified by researchers which possibly aided in controlling inflammation and promoting plaque clearance.

Enhancement of immune response by vitamin D_3 and DHA in preventing development of amyloid protein tangles

In the study conducted, blood samples were collected from Alzheimer's patients and healthy individuals and macrophages which are important immune cells were isolated from the blood. Macrophages bring about splicing of amyloid proteins before they accumulate around the nerve synapse, thereby efficiently restraining electrical and chemical transmissions throughout the brain. Immune cells were incubated with amyloid-beta to which either an active form of vitamin D_3 or omega-3 fatty acid DHA was added to estimate the effectiveness on inflammation and amyloid-beta absorption. Vitamin D_3 and DHA significantly improved the clearance of amyloid-beta by macrophages in patients with Alzheimer's disease. There was found to be precision in the effects of vitamin D_3 and DHA on expression of inflammatory genes. It was concluded that for efficient clearing of amyloid plaques, supplementation with vitamin D_3 and omega-3 fatty acids should be cautiously balanced depending on each patient. Vitamin D and DHA were found to make use of different receptors and common signaling networks to inhibit the aggregation of amyloid protein. Optimisation of vitamin D saturation levels along with addition of molecularly distilled DHA omega-3 formulation can play a crucial role in clearance of amyloid metabolic by-products, thereby preventing Alzheimer's disease.

Source – Journal of Alzheimer's disease; 2013

2. Depression linked to vitamin D deficiency

Canadian researchers have found a possible association between depression and vitamin D deficiency from a systematised review and meta-analysis of 14 studies involving 31,424 subjects. Decreased levels of vitamin D were found to correspond to depression and lower levels of vitamin D increased odds for depression. Women with moderate-to-severe depression showed a remarkable improvement in their depression symptoms following intervention for vitamin D deficiency. It was concluded that overcoming vitamin D deficiency could have been possibly responsible for improvement in symptoms of depression as women had not adjusted or altered antidepressant medications or other environmental factors linked to depression. In another study conducted that included 3 women in the age range of 42 to 66, all of whom were diagnosed with major depressive disorder, and were on treatment with anti-depressants, along with intervention for either type II diabetes or hypothyroidism, a 25-hydroxyvitamin D blood test was done owing to the presence of risk factors for vitamin D deficiency, such as reduced vitamin D intake and a lack of exposure to the sun that revealed decreased levels of vitamin D in all 3, from 8.9 to 14.5 ng/mL. The women were given oral vitamin D replacement therapy over a period of 8 to 12 weeks, following which the vitamin D levels were brought back to normal (32 to 38 ng/mL). There was also found to be a significant improvement in the depressive state of the women, which was measured by Beck Depression Inventory (BDI). Following their treatment, all three women reported a significant improvement in their depressive state, as measured by the BDI. As per BDI, a score of 0 to 9 indicates minimal depression; 10 to 18, mild depression; 19 to 29 moderate depression; and 30 to 63 indicates severe depression. Scores of one woman improved from 32 before vitamin D therapy to 12 after therapy; another from 26 to 8; and the third fell from 21 to 16. Evaluation of patients for vitamin D deficiency who are at risk of depression and their appropriate treatment could pave a way for identifying other easy and cost-effective alternatives for treating depression.

Source – Natural News; 2013

CME - Pre test

Vitamin D_3 – The 'sunshine' vitamin

1. _____ is also called the 'sunshine' vitamin.

a) Vitamin A

b) Vitamin C

c) Vitamin D

d) Vitamin K

2. The best source of vitamin D among the following is _____.

a) Chicken

b) Green leafy vegetables

c) Salmon

d) Milk

3. Body stores vitamin D in the_____.

a) Spleen

b) Kidneys

c) Blood

d) Fat cells

4. The precursor of vitamin D in skin is _____.

a) 1,25-dihydroxyvitamin D

b) 7- dehydrocholesterol

c) 25-hydroxyvitamin D

d) D-25 hydroxylase

5. The active form of vitamin D is _____.

a) 1,25-dihydroxyvitamin D

b) 7- dehydrocholesterol

c) 25-hydroxyvitamin D

d) D-25 hydroxylase

6. Calcium and phosphorous levels are maintained through vitamin D receptors present in _____.

a) Intestines

b) Kidneys

c) Parathyroid glands and bones

d) All of the above

7. All the statement are true except…

a) Parathormone mobilises calcium from the skeleton

b) Parathormone conserves renal loss of calcium

c) Parathormone reduces renal excretion of phosphorus

d) All of the above

8. Regular daily allowance (RDA) as recommended by ICMR and NIN for vitamin D is _____.

a) 600 IU/day

b) 800 IU/day

c) 200 IU/day

d) 400 IU/day

9. Laboratory findings that suggest vitamin D deficiency include all except...

a) ↓ 24-hour urine calcium excretion

b) ↓ Parathyroid hormone level

c) ↑ Total or bone alkaline phosphatase level

d) ↓ Serum calcium and/or serum phosphorus level

10. Adults who are vitamin D deficient should be treated with 50,000 IU of vitamin D3 once a week for 8 weeks followed by _____IU/d as maintenance therapy.

a) 400

b) 600 to 800

c) 1500 to 2000

d) 600 to 1000

Ans: 1-c; 2-c; 3-d; 4-b; 5-a; 6-d; 7-c; 8-d; 9-b; 10-c

Vitamin D_3 - The 'sunshine' vitamin

Introduction

Vitamin D (calciferol) is a fat soluble vitamin present naturally in very few food sources. Most of it is synthesised in the skin by the action of ultraviolet B (UVB) rays of sunlight. It is not a true vitamin but a steroid hormone acting on specific cell receptor to regulate various tissue processes. The two major physiologically relevant forms of vitamin D are vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol) shown in Fig 1. Vitamin D_2 (D_2), also known as ergocalciferol, is obtained from dietary vegetable sources and oral supplements. Vitamin D_3 (D_3), also known as cholecalciferol, is obtained primarily from skin exposure to UVB radiation in sunlight, ingestion of food sources such as oily fish, fortified foods and oral supplements.

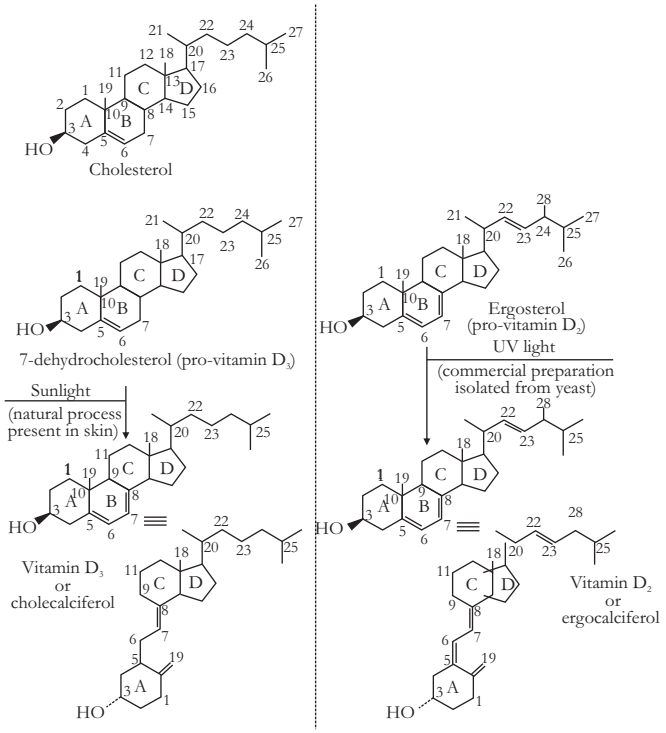

Fig. 1: Physiolgically relevant forms of vitamin D – D_2 and D_3

The use of the term vitamin D is interchangeable with D_2 or D_3 since these are the physiologically relevant forms.

Vitamin D obtained from sun exposure, food and supplements is biologically inert and must undergo two hydroxylations in the body for activation. The first hydroxylation takes place in the liver and converts vitamin D to 25-hydroxyvitamin D [25(OH)D], also known as calcidiol. The second occurs primarily in the kidney and forms the physiologically active 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], also known as calcitriol. The function of vitamin D, recognised since its identification in 1921 is to maintain serum calcium and phosphorus concentrations within the normal range by increasing the efficiency of the small intestine to absorb these minerals from the diet.

In recent years, vitamin D deficiency has become a problem of pandemic proportions. It has been estimated that 1 billion people worldwide have vitamin D deficiency. As per published studies, there is a widespread prevalence of varying degrees (50 to 90%) of vitamin D deficiency with low dietary calcium intake in Indian population. The lack of appreciation of the fact that sun exposure is the major source of vitamin D has contributed to vitamin D deficiency. Very few natural dietary sources contain vitamin D and, therefore, it is difficult to maintain vitamin D levels through dietary sources alone. Food that are fortified with vitamin D are often inadequate to meet daily vitamin D requirements.

To maximise vitamin D's beneficial effects for health, a circulating level of [25(OH)D] of >75 nmol/L or 30 ng/mL is needed. In the absence of adequate sun exposure, at least 800 to 1000 IU vitamin D_3/day may be required to obtain these levels in children and adults. Studies have demonstrated that that vitamin D_3 may be more effective than vitamin D_2 in establishing normal vitamin D stores.

Vitamin D deficiency is known to cause rickets in children; osteopaenia, osteoporosis and fractures in adults. Also in recent years, vitamin D deficiency has been associated with increased risk of common cancers, autoimmune diseases, hypertension and infectious diseases.

Conversions used in reference to vitamin D and its metabolites

Conversions for vitamin D_3:

Sources : 40 IU = 1 µg

Serum: 2.5 nmol/L = 1 ng/mL

Biosynthesis of vitamin D

The production of vitamin D_3 in the skin involves a series of reactions. 7-dehydrocholesterol in the skin is converted to previtamin D_3 on exposure to sun's UVB rays. Pre-vitamin D_3 is then immediately converted to vitamin D_3 in a heat-dependent process. Newly formed vitamin D_3 enters the circulation from the skin by binding to vitamin D binding protein (DBP). Vitamin D_2 and vitamin D_3 from dietary sources are fat soluble, they are incorporated into chylomicrons and absorbed through the lymphatic system into the venous circulation and transported to the liver (Fig. 2).

Both vitamin D_2 and D_3 are biologically inert and require 2 sequential hydroxylations to form (1,25$[OH]_2$D), which is the biologically active form.

Vitamin D is initially hydroxylated in the liver by the hepatic microsomal and/or mitochondrial enzyme vitamin D 25-hydroxylase into [25(OH)D]. This is the major circulating form of vitamin D that is used by clinicians to determine vitamin D status. This form of vitamin D is biologically inactive and must be converted in the kidneys by 1α-hydroxylase enzyme to the biologically active form – [1,25$(OH)_2$D] (Fig. 1). This metabolic step is very tightly regulated by blood calcium and phosphate levels through parathyroid hormone (PTH) and the phosphaturic hormone, fibroblast growth factor 23 (FGF23), and constitutes the basis of the vitamin D endocrine system that is central to maintaining calcium and phosphate homeostasis. FGF23 acts by reducing the expression of renal sodium-phosphate transporters and reducing serum calcitriol levels.

Calcitriol is transported to various target organs by binding to vitamin D-binding protein (DBP), a carrier protein in the plasma. Calcitriol is also synthesised by monocyte-macrophages in the immune system. Calcitriol synthesised by monocyte-macrophages acts locally as a cytokine by stimulating the innate immune system.

Calcitriol mediates its biological effects by binding to the vitamin D receptor (VDR), located in the nuclei of target cells. The binding of calcitriol to VDR modulates the gene expression of transport proteins, which are involved in calcium absorption in the intestine. VDRs are expressed by cells in most organs, including the brain, heart, skin, gonads, prostate and breast. VDR activation in the intestine, bone, kidney and parathyroid gland cells along with the help of of PTH and calcitonin assists in maintenance of calcium and phosphorus levels in the blood and bone.

Key Insights

- Vitamin D also known as calciferol is a fat soluble vitamin present naturally in very few food sources.
- The two major physiologically relevant forms of vitamin D are vitamin D_2 also known as ergocalciferol and vitamin D_3 also known as cholecalciferol.
- Vitamin D that is obtained from sun exposure, food and supplements is biologically inert and must undergo two hydroxylations in the body for activation.
- Vitamin D deficiency is found to cause rickets in children; osteopaenia, osteoporosis and fractures in adults.

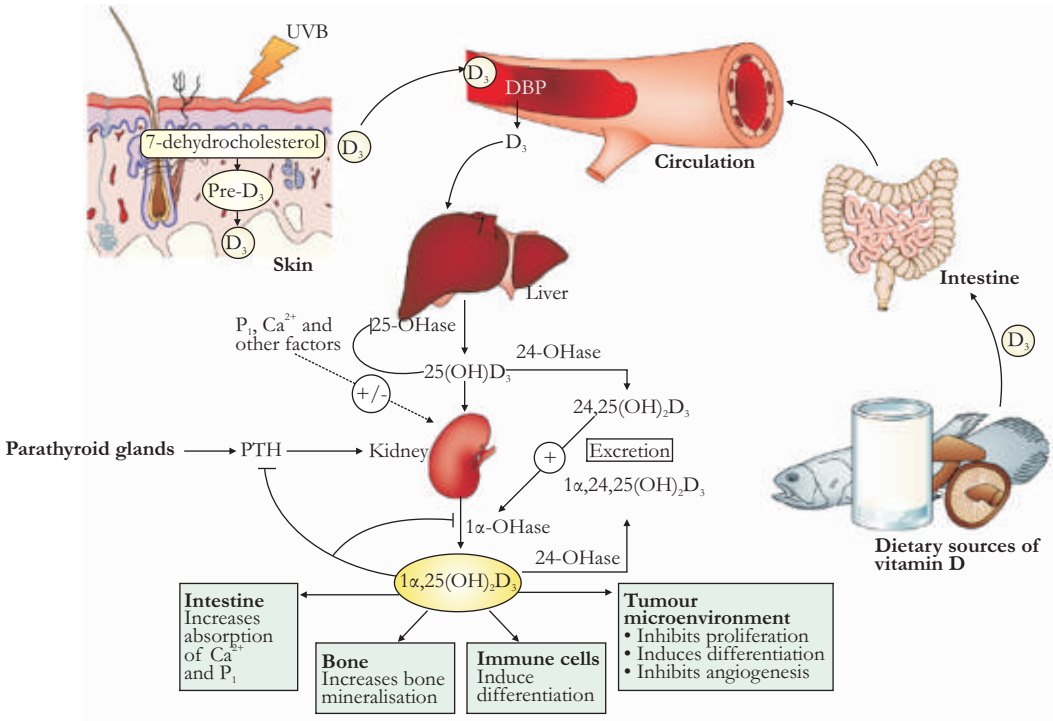

Fig. 2: Vitamin D metabolism

Serum phosphorus, calcium, FGF-23 and other factors can either increase or decrease the renal production of $1,25(OH)_2D$. Moreover, $1,25(OH)_2D$ can reduce its own production through negative feedback and inhibit the synthesis and secretion of PTH by the parathyroid glands. $1,25(OH)_2D$ increases the secretion of 24-hydroxylase (24-OHase) to catabolise $1,25(OH)_2D$ to water-soluble, biologically inactive calcitroic acid, which is excreted in the bile.

Sources of vitamin D

Vitamin D intake from food and nutrient supplements is expressed in international units (IU) or micrograms (μg). One IU of vitamin D is defined as the activity of 0.025 μg of cholecalciferol, therefore, the biological activity of 1 μg of vitamin D is 40 IU.

Food

Very few natural foods contain vitamin D. The flesh of fatty fish (such as salmon, tuna and mackerel) and fish liver oils are among the best sources. Fish oils approximately have Vitamin D_3 concentrations of 50 mcg/g but cod, tuna, mackerel oils contain 20 times that level. Small amounts of vitamin D are found in beef liver, cheese and egg yolks. Vitamin D in these foods is primarily in the form of vitamin D_3 and its metabolite $25(OH)D_3$. Some mushrooms provide vitamin D_2 in variable amounts (Table 1).

Table 1: Food sources of vitamin D

Food	Vitamin D (IU[a]/100 g)
Animal products	
Milk	
Cow	0.3 to 54
Human	0 to 10
Dairy products	
Butter	35
Cheese	12
Cream	50
Eggs	28
Fish products	
Cod	85
Cod liver oil	10000
Herring	330

Table 1: Food sources of vitamin D (table contd...)	
Food	**Vitamin D (IU[a]/100 g)**
Herring liver oil	140,000
Mackerel	120
Salmon	220 to 440
Sardines	1500
Shrimp	150
[a]1 IU = 0.025 mg of vitamin D_2 or vitamin D_3	

Dietary supplements

Vitamin D is available in 2 forms, D_2 and D_3 in dietary supplements and fortified foods. Research suggests that at nutritional doses vitamin D_2 and D_3 are equivalent, but at high doses vitamin D_2 is less potent. Most of the intake of vitamin D comes from fortified milk products and other fortified foods such as breakfast cereals.

Sunlight

Throughout the world, the major source of vitamin D for humans is the exposure of the skin to sunlight. During sun exposure, UVB rays between the wavelength of 290 and 320 nm penetrate uncovered skin and convert cutaneous 7-dehydrocholesterol to previtamin D_3 which in turn becomes vitamin D_3.

However, a number of factors can limit the cutaneous production of vitamin D_3. Excessive exposure to sunlight causes photo-degradation of previtamin D_3 and vitamin D_3. An increase in skin melanin pigmentation or the topical application of a sunscreen can significantly reduce production of vitamin D_3 in the skin. Sunscreens with a sun protection factor (SPF) of 8 or more appear to block vitamin D-producing UV rays. Latitude, season, time of day, length of day, cloud cover and smog are some other factors that influence the cutaneous production of vitamin D_3. Complete cloud cover reduces UV energy by 50% where as shade or smog reduces it by 60%. UVB radiation does not penetrate through glass, therefore, exposure to sunlight through a windowpane does not produce vitamin D.

Research suggests that approximately 5 to 30 minutes of sun exposure between 10 a.m. and 3 p.m. at least twice a week to the face, arms, legs or back without sunscreen usually lead to sufficient vitamin D synthesis.

Normal functions of vitamin D

VDRs are present on many tissues and organs in the body and as such vitamin D has been identified as playing a role or a potential role, in many human diseases.

Bone health

Other than increasing calcium absorption through the intestine, $1,25(OH)_2D$ plays an important role in bone health as it also stimulates bone maturation, matrix formation, renal reabsorption of Ca, bone remodelling and osteoclast cell activity.

Muscle strength

The effects of vitamin D on de novo protein synthesis mediates its effects on muscle through receptors for $1,25(OH)_2D$ in muscle tissue. Calcitriol binds to a specific VDR in the muscle tissue. Vitamin D deficiency is reported to cause proximal muscle weakness with a reduction in type 2 muscle fibres. Type 2 fibres are fast twitch and are recruited in activities of high intensity but short duration. Type 2 muscle fibres are the first to be recruited in balance and preventing a fall which may explain the inverse association between 25(OH)D levels and falls. Studies have shown that vitamin D supplementation in older individuals receiving calcium improved hip muscle strength and mobility in participants with low baseline values.

Immunity

The identification of VDRs in peripheral blood mononuclear cells sparked interest in vitamin D as an immune system regulator. Helper T (Th) cells are central to all antigen-specific immune responses. Th1 cell activation is essential for strong cell-mediated immune responses, including host responses to tumours and intracellular pathogens e.g., viruses. Th2 cells secrete IL-4 and IL-5, both of which are important for strong antibody-mediated immunity. Th1 and Th2 cells are direct targets of $1,25(OH)_2D_3$. $1,25(OH)_2D_3$ decreases the proliferation of purified Th cells and production of IFN-γ, IL-2 and IL-5

whereas it increases the production of IL-4 in Th2 cells. Evidence suggests a role of vitamin D in inhibiting the development of autoimmune diseases such as type I diabetes, asthma, multiple sclerosis, rheumatoid arthritis, and inflammatory bowel disease. Both the type of immune response and the calcium status of the host determine the effects of vitamin D status and $1,25(OH)_2D_3$ on immunity.

Anti-carcinogenic activity

In vitro and *in vivo* studies have demonstrated the potential of vitamin D in prevention and regression of colorectal, prostate and breast cancers. It has been found to interfere with the transduction pathways of various growth factor-activated receptors which modulate transcription and alter genomic functions resulting in inhibition of cell proliferation and angiogenesis and facilitates cell differentiation and apoptosis. Moreover, it enhances the level of cystatin D, an endogenous protein with anti-tumour and anti-metastatic property. Thus, it may be used for the prevention of cancer and can be included as an adjuvant in combination chemotherapy for the treatment of cancer.

Cardiovascular health

Evidence suggests that vitamin D can improve cardiovascular health through multiple mechanisms. Its deficiency is now recognised as a potential risk factor for several cardiovascular disease processes.

Potential mechanisms through which vitamin D deficiency may affect cardiovascular disease are listed as under–

- **Hypertensive vascular disease** – Increased intracellular calcium leading to decreased renin activity; calcitriol suppression of rennin promoter gene; alteration of the sensitivity of vascular smooth muscle cells
- **Peripheral vascular disease** – Increased calcification
- **Diabetes mellitus** – Immunomodulatory effects by reducing tumour necrosis factor α (TNF-α), PTH and interleukin-10; decreased insulin receptor expression, leading to peripheral resistance of insulin ; effect on intracellular calcium levels leading to decreased insulin secretion
- **Lipid metabolism** – Increase in peripheral insulin resistance, contributing to high lipid profile; statins may increase vitamin D levels by increasing 7-dehydrocholesterol; increased vessel free radicals lead to oxidation of low-density lipoprotein and increased engulfment by macrophages, an early sign of atherosclerosis
- **Coronary artery disease** – Indirect effect through risk factor modification; alteration in endothelial function; increased coronary artery calcification
- **Heart failure** – Direct effect on myocardial contractility; regulation of brain natriuretic peptide secretion; reduction of left ventricular hypertrophy with effects on extracellular remodeling; regulation of inflammatory cytokines; secondar hyperparathyroidism, which leads to vasodilatation and positive inotropic stimulation
- **Arrhythmias** – Direct myocardial substrate modification; indirectly via calcium levels and metabolism at a cellular level

Mental health

Various studies confirm a link between low vitamin D and mental illness. These studies provide evidence that optimising vitamin D levels may improve psychological well-being. Many studies support the role of vitamin D in the pathophysiology of depression and as a potential treatment for depression. Schizophrenia has also been linked with abnormal levels of vitamin D.

Relationship between vitamin D, calcium, phosphorus and parathhormone

Maintaining the level of circulating ionised calcium within a narrow physiological range is critical for the body to function normally, and control of serum calcium levels is maintained through an endocrine system that includes a major role for vitamin D metabolites, principally calcitriol and PTH. Calcium balance within the body is closely linked to the hormonal actions of calcitriol.

The vitamin D metabolic system forms the basis of the calcium homeostatic mechanism in humans. Total calcium concentration in serum is tightly regulated so that the level is

between 8.5 and 10.5 mg/dL. If this level deviates slightly, the calcium sensing receptor of the parathyroid gland signals the secretion of PTH, which functions as a calcium sensor. PTH then stimulates the kidney to produce calcitriol, the hormonal form of vitamin D, as well as to activate bone resorption, which will increase extracellular calcium levels. Calcitriol acts in an endocrine manner on the intestine, bone, and kidney to raise serum calcium levels; it also acts on the intestine and, to some extent, the kidneys to raise serum phosphorus levels. As the serum calcium level rises, the feedback mechanism causes the calcium sensing receptor to be turned off and PTH secretion to drop.

If there is an overshoot in serum calcium levels, the "C" cells (parafollicular) cells of the thyroid gland secrete calcitonin, which can block bone calcium resorption, helping to keep serum calcium levels in the normal range. Calcitriol, through its receptor, also provides feedback relative to suppressing the production and release of PTH, commonly referred to as PTH suppression. Calcitriol is also directly controlled by the serum phosphorus level; a high serum phosphorus level suppresses the formation of calcitriol, whereas a low level stimulates it.

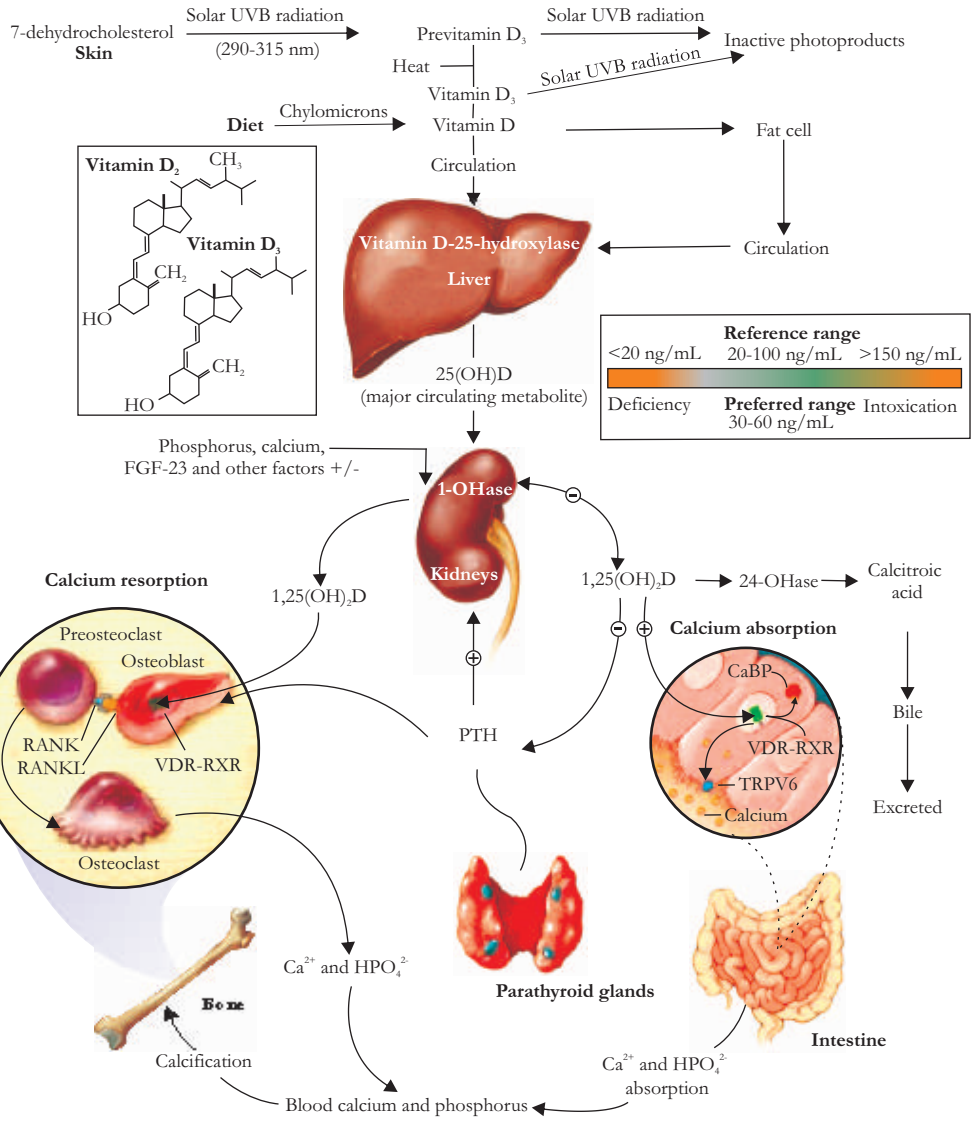

Fig. 3: Calcium homeostasis involving $1,25(OH)_2D_3$ and PTH

Calcitriol facilitates the formation of osteoclasts by stimulating the secretion of a protein called receptor activator for nuclear factor κ B (RANK) ligand, which in turn is responsible for osteoclastogenesis and bone resorption. Also, calcitriol together with PTH stimulates the renal distal tubule reabsorption of calcium, ensuring retention of calcium by the kidney when calcium is needed (Fig. 3).

Without vitamin D, only 10 to 15% of dietary calcium and about 60% of phosphorus is absorbed. The interaction of $1,25(OH)_2D$ with the VDR increases the efficiency of intestinal calcium absorption to 30 to 40% and phosphorus absorption to approximately 80%. Deficiencies of calcium and vitamin D *in utero* and in childhood may prevent the maximum deposition of calcium in the skeleton. PTH also causes phosphaturia, resulting in a low-normal or low serum phosphorus level. Without an adequate calcium–phosphorus product, mineralisation of the collagen matrix is diminished, leading to classic signs of rickets in children and osteomalacia in adults.

Recommended dietary allowances (RDA)

The American Academy of Pediatrics recommends 400 IU/d. However, Institute Of Medicine (IOM) has specified estimated average requirements (EARs) and RDAs on the basis of serum 25(OH)D levels of 16 and 20 ng/mL, respectively. EAR and RDA for vitamin D, as per IOM review are 400 IU/day and 600 IU/day respectively, while tolerable upper level of intake are 1000 IU/day for infants <6 months old, 1500 IU/day for 6 to 12 months old, 2500 IU/day for 1 to 3 years old, 3000 IU/day for 4 to 8 years old and 4000 IU/day for 9 years and above including pregnant and lactating mothers. The RDA and tolerable upper intake level of vitamin D as suggested by IOM is tabulated below in Table 2.

Table 2: RDA for vitamin D

Life stage	RDA per day	Tolerable upper intake level per day
0 to 6 months	400 IU*	1000 IU
6 to 12 months	400 IU*	1500 IU
1 to 3 years	600 IU	2500 IU
4 to 8 years	600 IU	3000 IU
9 to 70 years	600 IU	4000 IU
Pregnant or lactating	600 IU	4000 IU
>70 years	800 IU	4000 IU

*The listed RDA values for infants from 0 to 12 months are actually adequate intake values, based on lack of sufficient evidence to generate RDA values.

In India, RDA as recommended by ICMR and NIN for vitamin D is 400 IU (10 mcg).

Vitamin D_3 deficiency (Hypovitaminosis)

Prevalence of vitamin D_3 deficiency is on the rise and approximately a billion people suffer from it worldwide. The primary reason is that naturally occurring dietary sources of vitamin D are limited, and food fortification is inconsistent or inadequate. Therefore, most people depend on cutaneous production from sun exposure. Surprisingly, hypovitaminosis of vitamin D is highly prevalent even in areas with adequate sunshine like India. Factors involved in this paradox include duration and timing of sun exposure, amount of skin exposed, atmospheric pollution, skin pigmentation, sunscreen use, dietary and genetic factors. Exposure of only face, hands and arms due to clothing versus whole body is associated with marked differences in vitamin D synthesis. Vitamin D synthesis is maximum

between 10 a.m. to 3 p.m., the time when most of the people are indoors. Cloud cover, increasing water vapour and industrial pollution can also alter the amount of UVB rays reaching the earth's surface.

Epidermal melanin has a protective action of reducing skin cancer, however, it also reduces cutaneous vitamin D synthesis. Indians require 3 times the sun exposure than light-skinned people to produce equivalent amount of vitamin D. Sunscreens block UVB rays more than UVA and those with SPF of 8 and 15 reduce vitamin D synthesis by 95 and 98%, respectively vitamin D stores may be depleted due to dietary factors like very low calcium intake and high fibre diet. Genetic factors such as increased activity of 25(OH)D-24-hydroxylase in South Asians causing excessive breakdown of vitamin D is among the plausible explanations of high rates of hypovitaminosis D in sunny countries. Vitamin D crosses the placenta and poor vitamin D content of breast milk even in vitamin D replete mothers, maternal vitamin D deficiency and exclusive breastfeeding without vitamin D supplements or adequate sunlight exposure are important risk factors for vitamin D deficiency in infants.

Risk factors for vitamin D deficiency include–

- Age older than 65 years
- Breastfed exclusively without vitamin D supplementation
- Dark skin
- Insufficient exposure to sunlight
- Medication use that alters vitamin D metabolism (e.g., anti-convulsants, glucocorticoids)
- Obesity (body mass index greater than 30 kg per m^2)
- Sedentary lifestyle
- Malnutrition (poor oral intake)
- Gastrointestinal malabsorption (e.g., short bowel syndrome, pancreatitis, inflammatory bowel disease, amyloidosis, celiac sprue and malabsorptive bariatric surgery procedures)
- Severe liver disease or failure (decreased 25-hydroxylase activity)
- Renal ageing (decreased 1-a hydroxylase activity); renal insufficiency-glomerular filtration rate <60% (decreased 1-α hydroxylase activity); nephrotic syndrome (decreased levels of vitamin D-binding protein) (Fig. 4)

Pathophysiology of vitamin D_3 deficiency

In the presence of sufficient vitamin D, net intestinal calcium absorption is between 30 to 80%, which reduces to 10 to 15% in vitamin D deficient state. Decrease in ionised calcium in blood, in turn leads to increased production and secretion of PTH. PTH stimulates the mobilisation of calcium from the skeleton, conserves renal loss of calcium, and causes increased renal excretion of phosphorus leading to a normal fasting serum calcium with a low or low-normal serum phosphorus. Thus, vitamin D deficiency is characterised biochemically by either a normal or low-normal serum calcium with a low-normal or low-fasting serum phosphorus and an elevated serum PTH. Serum alkaline phosphatase is usually elevated in vitamin D deficiency states. The elevated PTH leads to an increase in the destruction of the skeletal tissue in order to release calcium into the blood. Decreased calcium phosphorus product (CaXP) leads to reduced bone mineralisation. In addition, low phosphorus levels cause a failure of the apoptosis of hypertrophied chondrocytes, with cellular ballooning and disorganisation of the growth plate. Failure or delay of calcification of osteoid leads to osteomalacia in mature bones and rickets in immature bones. The term rickets also refers to the abnormal organisation of the cartilaginous growth plate and the impairment of cartilage mineralisation.

Key Insights

- Vitamin D deficiency has been linked to a rise in risk of common cancers, autoimmune diseases, hypertension and infectious diseases.
- 25-hydroxyvitamin D levels are used by the clinicians to assess the vitamin D status.

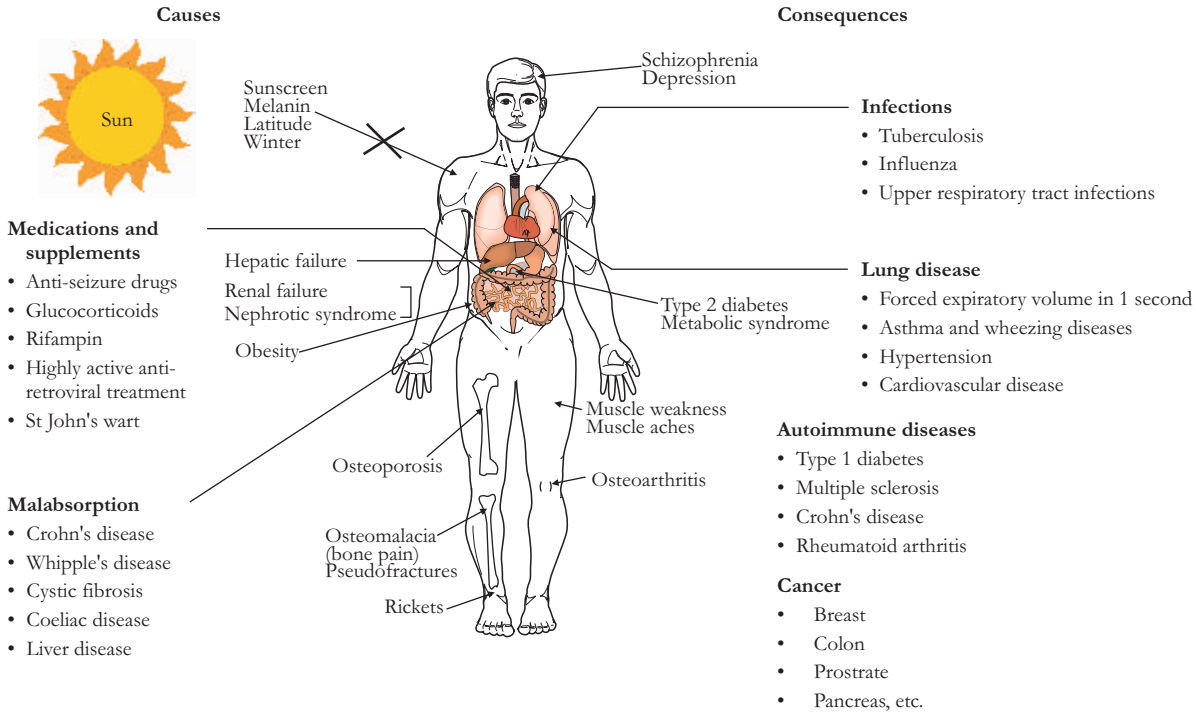

Fig. 4: Causes and consequences of vitamin D deficiency

Clinical features of vitamin D deficiency

In adults

- Vitamin D insufficiency can be asymptomatic or may be present insidiously as non-specific musculoskeletal aches. Most patients present with muscle weakness or muscle aches and pains. Muscle weakness is most noticeable in the quadriceps and gluteus muscles resulting in difficulty in getting up from a chair and waddling gait
- May present as localised or generalised bone pain and local bone tenderness. Less commonly, swelling and redness at pseudo-fracture sites may occur. If osteoporosis is co-existent, then the risk of fractures increases

Osteomalacia

Osteomalacia may be asymptomatic and is presented radiologically as osteopaenia. It can also produce characteristic symptoms, including diffuse bone and joint pain, muscle weakness and difficulty walking.

- *Bone tenderness and fractures* – Dull aching bone pain aggravated by activity and weight bearing. Most pronounced in the lower spine, pelvis and lower extremities and often tender to palpation. Fractures may occur with little or no trauma, typically involving the ribs, vertebrae and long bones. Spinal curvature abnormality or deformity of the thorax or pelvis may appear in severe osteomalacia of long duration (Fig. 5)

Key Insights

- Around the globe, the major source of vitamin D for humans is the exposure of the skin to sunlight .
- *In vitro* and *in vivo* studies have demonstrated the ability of vitamin D in prevention and regression of colorectal, prostate and breast cancers.
- A number of studies have confirmed an association between low vitamin D levels and mental illness.

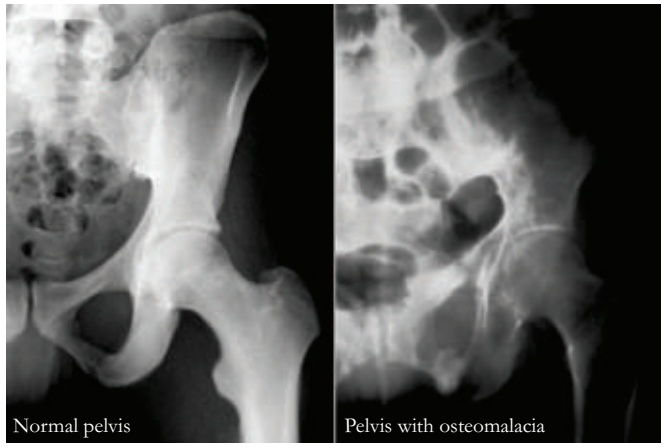

Fig. 5: Bony changes in pelvis in osteomalacia

- Difficulty in walking and waddling gait
- Muscle spasms, cramps, positive Chvostek's sign, tingling/numbness and difficult ambulation

Rickets in children

Rickets is the consequence of poor bone mineralisation. It is the childhood equivalent of osteomalacia. Defective mineralisation of cartilage in the epiphyseal growth plate leads to widening of the long ends of bones, growth retardation and skeletal deformities in children. The most common cause of rickets is vitamin D deficiency caused by low endogenous vitamin D. The other forms include vitamin D dependent rickets caused by reduced activity of 25-hydroxylase and vitamin D resistant rickets due to defect in tubular reabsorption of phosphate.

Clinical features of vitamin D deficient rickets

The site and type of deformity of the extremities in children depends upon the child's age and weight bearing patterns in the limbs. For example, in toddlers, exaggeration of bowing of legs is common in a child who has started walking. In older children, valgus deformity of one leg and varus deformity of the other leg (windswept deformity) may be present (Fig. 6).

Skeletal findings:

- Flaring of bones at the distal forearm, knee and costochondral junctions is observed initially as they are the site of rapid bone growth, where significant quantities of both calcium and phosphorus are required for mineralisation
- Delay in closure of fontanelles, parietal and frontal bossing, craniotabes, enlargement of the costochondral junction continues, enlargement of the wrist and bowing of the distal radius and ulna and progressive lateral bowing of the femur and tibia is seen as the disease progresses

Extraskeletal findings:

Hypoplasia of dental enamel, reduced muscle tone, delay in developmental milestones, seizures in case of severe hypocalcaemia are associated features.

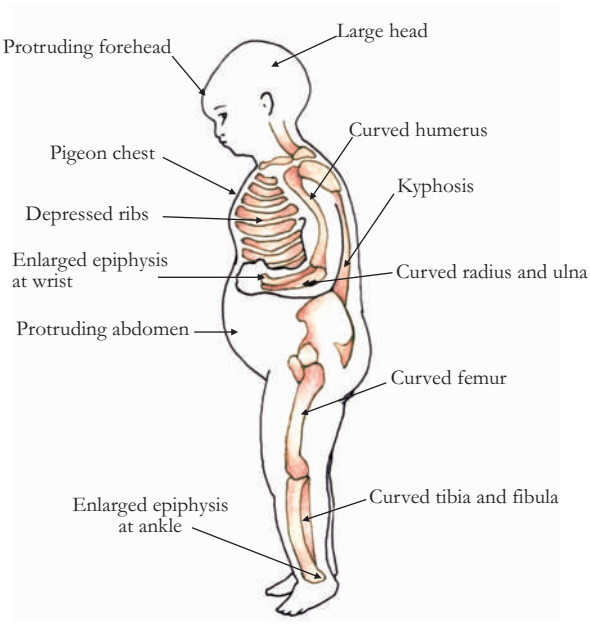

Fig. 6: Clinical features of vitamin D deficiency rickets

Radiographic findings:

- *Craniotabes:* In the first few months of life, the head is most affected. During this period, the skull must accommodate the rapidly growing brain. The rapid accommodation results in excess osteoid formation, particularly at the central margins and outer table, while resorption at the inner table continues. The thin calvarium is less rigid and results in posterior flattening. As osteoid continues to accumulatein the frontal and parietal regions, it results in the squared configuration known as craniotabes
- *Long bone findings:* The long bones show the greatest deformity during infancy and early childhood. The metaphyseal end is widened, cupped and has a ragged edge. A wide gap appears between the metaphysis and the epiphysis which corresponds to the area of disordered mineralisation. The first radiological sign is a widening of the gap between the epiphysis and the metaphysis. The characteristic bowing deformities of the arms and legs are related to the sitting position assumed by the child. The shafts of long bones may also become less dense caused by the loss of mineral content
- *Rachitic rosary:* Prominent knobs develop at the costochondral junctions, particularly those of the middle ribs forming the characteristic rachitic rosary. The costochondral junctions are the most active growth plates
- *Harrison's groove:* A semicoronal impression is found at the costal attachment of the diaphragm as the distal end of the ribs are weak and may be pressed by the negative intrathoracic pressure developed during respiration
- *Scoliosis:* As age increases, the effects of weight bearing become prominent and scoliosis often develops.
- *Looser's zones (pseudofractures):* Rickets, later in childhood, may present as pseudofractures. Focal accumulations of uncalcified bone matrix is known as Looser's zone. They are usually are seen at sites where major arteries cross the bone
- *Fractures:* Greenstick fractures of the cortex are commonly seen

Extraskeletal manifestations of vitamin D deficiency

Vitamin D deficiency has been reported to be associated with higher risk of metabolic syndrome, hypertension and adverse cardiovascular events. Severe vitamin D deficiency not only enhances the risk of developing cardiovascular disease but also increases risk of sudden cardiac death. Vitamin D supplementation in infancy might be protective against the development of type I diabetes mellitus and a temporary reduction in insulin dose is apparent following supplementation with calcitriol in adult patients with type I diabetes. Studies suggest that vitamin D may play a role in the prevention and treatment of type I and II diabetes mellitus through its action on systemic inflammation, insulin secretion and resistance.

Vitamin D plays a physiological role in cell differentiation in normal and tumour cells. Pre-clinical and epidemiological data suggest a role for vitamin D in the prevention and treatment of cancer. Polymorphism of VDR gene has been associated with high risk of cancer. $1,25(OH)_2D$ is capable of regulating genes that control proliferation, differentiation, apoptosis and angiogenesis. It is said to play a protective role in prostatic, breast and colorectal cancer. Evidence suggests a role of vitamin D in inhibiting the development of autoimmune diseases such as asthma, multiple sclerosis, rheumatoid arthritis and inflammatory bowel disease.

Investigation of vitamin D deficiency

Laboratory findings

Dietary and cutaneously produced vitamin D is rapidly converted to 25(OH)D, but only a fraction of 25(OH)D is converted in serum to its active metabolite $1,25(OH)_2D$. Thus for assessing body stores of vitamin D, the best test is to measure the total 25(OH)D level. The total 25(OH)D level allows for the diagnosis and monitoring of vitamin D deficiency, whereas quantification of $25(OH)D_2$ and

Note: Contd. on page 25

QUICK REFERENCE PULL OUT

Detach & file for future reference

Introduction

Vitamin D (calciferol) is a fat soluble vitamin present naturally in very few food sources. Most of it is synthesised in the skin by the action of ultraviolet B (UVB) rays of sunlight. It is not a true vitamin but a steroid hormone acting on specific cell receptor to regulate various tissue processes. The 2 major physiologically relevant forms of vitamin D are vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol). Vitamin D_2 (D_2) is obtained from dietary vegetable sources and oral supplements. Vitamin D_3 (D_3) is obtained primarily from skin exposure to UVB radiation in sunlight, ingestion of food sources such as oily fish, fortified foods and oral supplements.

Vitamin D obtained from sun exposure, food and supplements is biologically inert and must undergo 2 hydroxylations in the body for activation. The first hydroxylation takes place in the liver and converts vitamin D to 25-hydroxyvitamin D [25(OH)D], also known as calcidiol. The second occurs primarily in the kidney and forms the physiologically active 1,25-dihydroxyvitamin D [1,25(OH)2D], also known as calcitriol. The function of vitamin D, recognised since its identification in 1921 is to maintain serum calcium and phosphorus concentrations within the normal range by increasing the efficiency of the small intestine to absorb these minerals from the diet.

To maximise vitamin D's beneficial effects for health, a circulating level of 25-hydroxyvitamin D of >75 nmol/L or 30 ng/mL is needed. In recent years, vitamin D deficiency has become a problem of pandemic proportions. It has been estimated that 1 billion people worldwide have vitamin D deficiency. Vitamin D deficiency is known to cause rickets in children; osteopaenia, osteoporosis and fractures in adults. Also in recent years, vitamin D deficiency has been associated with increased risk of common cancers, autoimmune diseases, hypertension and infectious diseases.

Biosynthesis

7-dehydrocholesterol in the skin is converted to previtamin D_3 on exposure to sun's UVB rays. Pre-vitamin D_3 is then immediately converted to vitamin D_3 in a heat-dependent process. Newly formed vitamin D_3 enters the circulation from the skin by binding to vitamin D binding protein (DBP). Vitamin D_2 and vitamin D_3 from dietary sources are fat soluble, they are incorporated into chylomicrons and absorbed through the lymphatic system into the venous circulation and transported to the liver.

Both vitamin D_2 and D_3 are biologically inert and require 2 sequential hydroxylations to form 1,25-dihydroxyvitamin D (1,25$[OH]_2$D), which is the biologically active form.

Vitamin D is initially hydroxylated in the liver by the hepatic microsomal and/or mitochondrial enzyme vitamin D 25-hydroxylase into 25-hydroxyvitamin D. This is the major circulating form of vitamin D that is used by clinicians to determine vitamin D status. This form of vitamin D is biologically inactive and must be converted in the kidneys by 1α-hydroxylase enzyme to the biologically active form – 1,25-dihydroxyvitamin D. This metabolic step is very tightly regulated by blood calcium and phosphate levels through PTH and the phosphaturic hormone, fibroblast growth factor 23(FGF23) and constitutes the basis of the vitamin D endocrine system that is central to maintaining calcium and phosphate homeostasis. FGF23 acts by reducing the expression of renal sodium-phosphate transporters and reducing serum calcitriol levels.

Serum phosphorus, calcium, FGF-23 and other factors can either increase or decrease the renal production of $1,25(OH)_2D$. Moreover, $1,25(OH)_2D$ can reduce its own production through negative feedback and inhibit the synthesis and secretion of PTH by the parathyroid glands.

Sources of vitamin D

Very few natural foods contain vitamin D. The flesh of fatty fish (such as salmon, tuna, and mackerel) and fish liver oils are among the best sources. Fish oils approximately have vitamin D_3 concentrations of 50 mcg/ g but cod, tuna, mackerel oils contain 20 times that level. Small amounts of vitamin D are found in beef liver, cheese and egg yolks. Vitamin D in these foods is primarily in the form of vitamin D_3 and its metabolite $25(OH)D_3$. Some mushrooms provide vitamin D_2 in variable amounts.

Normal functions of vitamin D

Vitamin D receptors (VDR) are present on many tissues and organs in the body and as such vitamin D has been identified as playing a role, or a potential role, in many human diseases.

Bone health – Other than increasing calcium absorption through the intestine, $1,25(OH)_2D$ plays an important role in bone health as it also stimulates bone maturation, matrix formation, renal reabsorption of Ca, bone remodelling and osteoclast cell activity.

Muscle strength – The effects of vitamin D on de novo protein synthesis mediates its effects on muscle through receptors for $1,25(OH)_2D$ in muscle tissue. Calcitriol binds to a specific VDR in the muscle tissue. Vitamin D deficiency is reported to cause proximal muscle weakness with a reduction in type 2 muscle fibres.

It has a positive effect on cardiovascular and the immune system. Also, optimising vitamin D levels has been seen to improve psychological well-being. *In vitro* and *in vivo* studies have demonstrated the potential of vitamin D in prevention and regression of colorectal, prostate and breast cancers.

Relationship between vitamin D, calcium, phosphorus and PTH

Maintaining the level of circulating ionised calcium within a narrow physiological range is critical for the body to function normally, and control of serum calcium levels is maintained through an endocrine system that includes a major role for vitamin D metabolites, principally calcitriol and PTH. Calcium balance within the body is closely linked to the hormonal actions of calcitriol. The vitamin D metabolic system forms the basis of the calcium homeostatic mechanism in humans.

Calcitriol acts in an endocrine manner on the intestine, bone and kidney to raise serum calcium levels; it also acts on the intestine and, to some extent, the kidneys to raise serum phosphorus levels. As the serum calcium level rises, the feedback mechanism causes the calcium sensing receptor to be turned off and PTH secretion to drop.

Without vitamin D, only 10 to 15% of dietary calcium and about 60% of phosphorus is absorbed. The interaction of 1,25-dihydroxyvitamin D with the vitamin D receptor increases the efficiency of intestinal calcium absorption to 30 to 40% and phosphorus absorption to approximately 80%

Recommended dietary allowance (RDA)

The American Academy of Pediatrics recommends 400 IU /d. However, Institute Of Medicine (IOM) has specified estimated average requirements (EARs) and RDAs on the basis of serum 25(OH)D levels of 16 and 20 ng/mL respectively. EAR and RDA for vitamin D, as per IOM review, are 400 IU/day and 600 IU/day respectively, while tolerable upper level of intake are 1000 IU/day for infants <6 months old, 1500 IU/day for 6 to 12 months old, 2500 IU/day for 1 to 3 years old, 3000 IU/day for 4 to 8 years old and 4000 IU/day for 9 years and above including pregnant and lactating mothers.

In India, RDA as recommended by ICMR and NIN for vitamin D is 400 IU (10 mcg).

Vitamin D_3 deficiency (Hypovitaminosis)

Prevalence of vitamin D_3 deficiency is on the rise and approximately a billion people suffer from it worldwide. The primary reason is that naturally occurring dietary sources of vitamin D are limited, and food fortification is inconsistent or inadequate. Therefore, most people depend on cutaneous production from sun exposure.

Risk factors for vitamin D deficiency include–

- Age older than 65 years
- Breastfed exclusively without vitamin D supplementation
- Dark skin
- Insufficient exposure to sunlight
- Medication use that alters vitamin D metabolism (e.g., anti-convulsants, glucocorticoids)
- Obesity (body mass index greater than 30 kg per m^2)
- Sedentary lifestyle
- Malnutrition (poor oral intake)
- Gastrointestinal malabsorption (e.g., short bowel syndrome, pancreatitis, inflammatory bowel disease, amyloidosis, celiac sprue, and malabsorptive bariatric surgery procedures)
- Severe liver disease or failure (decreased 25-hydroxylase activity)
- Renal ageing (decreased 1-α hydroxylase activity); renal insufficiency- glomerular filtration rate <60% (decreased 1-α hydroxylase activity); nephrotic syndrome (decreased levels of vitamin D-binding protein)

Pathophysiology of vitamin D_3 deficiency

Decrease in ionised calcium in blood, in turn leads to increased production and secretion of PTH. PTH stimulates the mobilisation of calcium from the skeleton, conserves renal loss of calcium and causes increased renal excretion of phosphorus leading to a normal fasting serum calcium with a low or low-normal serum phosphorus. Thus, vitamin D deficiency is characterised biochemically by either a normal or low-normal serum calcium with a low-normal or low-fasting serum phosphorus and an elevated serum PTH. Serum alkaline phosphatase is usually elevated in vitamin D deficiency states. The elevated PTH leads to an increase in the destruction of the skeletal tissue in order to release calcium into the blood. Decreased calcium phosphorus product (CaXP) leads to reduced bone mineralisation. Failure or delay of calcification of osteoid leads to osteomalacia in mature bones and rickets in immature bones

Clinical features of vitamin D deficiency

Osteomalacia in adults

Osteomalacia may be asymptomatic and present radiologically as osteopaenia. It can also produce characteristic symptoms, including diffuse bone and joint pain, muscle weakness, and difficulty walking.

- Bone tenderness and fractures – Dull aching bone pain dull and aching aggravated by activity and weight bearing
- Difficulty in walking and waddling gait
- Muscle spasms, cramps, positive Chvostek's sign, tingling/numbness and difficult ambulation

Rickets in children

Bowing of legs is common in a child who has started walking. In older children, valgus deformity of one leg and varus deformity of the other leg (windswept deformity) may be present.

On radiography, the metaphyseal ends of long bones are widened, cupped and have a ragged edge. A wide gap appears between the metaphysis and the epiphysis which corresponds to the area of disordered mineralisation. The first radiological sign is a widening of the gap between the epiphysis and the metaphysis.

Investigation of vitamin D deficiency

For assessing body stores of vitamin D, the best test is to measure the total 25(OH)D level. The total 25(OH)D level allows for the diagnosis and monitoring of vitamin D deficiency, whereas quantification of $25(OH)D_2$ and $25(OH)D_3$ fractions may facilitate treatment monitoring (Box 1).

Box 1: Summary of laboratory findings in vitamin D deficiency
• ↓24-hour urine calcium excretion
• ↓Serum total 25(OH)D level
• ↑PTH level
• ↑Total or bone alkaline phosphatase level
• ↓Serum calcium and/or serum phosphorus level

Radiological findings in D_3 deficiency–

- ↓ Bone mineral density (osteopaenia or osteoporosis)
- Non-traumatic fracture
- Skeletal pseudofracture

Table 1 given below shows vitamin D status in relation to serum 25(OH)D level as per the Endocrine Society Clinical Practice Guideline, 2011.

Table 1: Vitamin D status in relation to serum 25(OH)D level

Vitamin D status	Serum 25(OH)D level (ng/mL)
Deficiency	< 20
Insufficiency	21 to 29
Sufficiency	30 to 100

Treatment of vitamin D_3 deficiency

- For infants and toddlers aged 0 to 1 year who are vitamin D deficient, treat with 2000 IU/d of vitamin D_2 or vitamin D_3 or with 50,000 IU of vitamin D_2 or vitamin D_3 once weekly for 6 weeks to achieve a blood level of 25(OH)D above 30 ng/mL, followed by maintenance therapy of 400 to 1000 IU/d
- For children aged 1 to 18 years who are vitamin D deficient, treat with 2000 IU/d of vitamin D_2 or vitamin D_3 for at least 6 wk or with 50,000 IU of vitamin D_2/D_3 once a week for at least 6 weeks to achieve a blood level of 25(OH)D above 30 ng/mL, followed by maintenance therapy of 600 to 1000 IU/d
- All adults who are vitamin D deficient, should be treated with 50,000 IU of vitamin D_2 or vitamin D_3 once a week for 8 weeks or its equivalent of 6000 IU of vitamin D_2 or vitamin D_3 daily to achieve a blood level of 25(OH)D above 30 ng/mL, followed by maintenance therapy of 1500 to 2000 IU/d

Vitamin D toxicity

Most patients with vitamin D toxicity have 25(OH)D levels greater than 150 ng/mL and the lowest reported level associated with toxicity in patients without primary HPT with normal renal function is 80 ng/mL.

Symptoms and signs of vitamin D toxicity include –

- Headache
- Metallic taste
- Nephrocalcinosis or vascular calcinosis
- Pancreatitis
- Nausea
- Vomiting

Despite widespread concern, a comfortable safety margin exists between the intake required for optimisation of vitamin D status and those associated with toxicity.

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25(OH)D_3 fractions may facilitate treatment monitoring. For e.g., in patients without clinical improvement after D_2 or D_3 supplementation, lack of increase in the corresponding 25(OH)D_2 or 25(OH)D_3 and total 25(OH)D levels may indicate inadequate dosing, nonadherence or malabsorption.

Vitamin D deficiency is usually accompanied by normal blood levels for calcium and phosphorus, high-normal or elevated levels of PTH, normal-to-elevated levels of total alkaline phosphatase, a low 24-hour urine calcium excretion rate and low levels of total 25(OH)D (Box 1).

Box 1: Summary of laboratory findings in vitamin D deficiency

- ↓ 24-hour urine calcium excretion
- ↓ Serum total 25(OH)D level
- ↑ Parathyroid hormone level
- ↑ Total or bone alkaline phosphatase level
- ↓ Serum calcium and/or serum phosphorus level

It is important not to consider 1,25$(OH)_2$D levels for diagnosis of hypovitaminosis of vitamin D. It can lead to wrong interpretation of vitamin D status because calcitriol levels are often normal or even elevated in patients with vitamin D deficiency due to elevated PTH levels.

Optimal 25(OH)D level

A wide "optimal" range for 25(OH)D is reported (25 to 80 ng/mL) and differences of opinion exist as to the definitions of vitamin D insufficiency (sometimes reported as <30 ng/mL) and deficiency (<20 ng/mL). Mild-to-modest deficiency can be associated with osteoporosis and/or secondary hyperparathyroidism (HPT). Severe deficiency may lead to failure to mineralise newly formed osteoid in bone, resulting in rickets in children and osteomalacia in adults.

As per 2010 review published by IOM, the benefits for most in the population is associated with levels of approximately 20 ng/mL, and use of higher cut-offs artificially increase the estimates of prevalence of vitamin D deficiency. Table 3 shows vitamin D status in relation to serum 25(OH)D level as per the Endocrine Society Clinical Practice Guideline, 2011.

Table 3: Vitamin D status in relation to serum 25(OH)D level

Vitamin D status	Serum 25(OH)D level (ng/mL)
Deficiency	< 20
Insufficiency	21 to 29
Sufficiency	30 to 100

Radiological findings

- ↓ Bone mineral density (osteopaenia or osteoporosis)
- Non-traumatic fracture
- Skeletal pseudofracture

Treatment of vitamin D_3 deficiency

Most clinicians believe that adequate vitamin D intake can be obtained from diet alone. This assumption is false. The vitamin D content of most foods, other than fatty fish, is relatively low to non-existent. Even fortified foods often fall short of providing adequate amounts of vitamin D.

Both D_2 and D_3 are available as dietary supplements. There exists no consensus on the relative efficacy of D_2 versus D_3 in humans. Although both appear to be effective for preventing or treating disease, the longer half life of D_3 makes it an effective treatment strategy. 1 mcg of either provides 40 IU, although D_3 raises serum 25(OH)D levels up to three-fold higher than D_2. D_2 and D_3 should be taken with a meal containing fat to ensure maximum absorption.

In a study, 1600 IU of D_2 daily/ 50,000 IU of D_2 once monthly was compared with similar doses of D_3 in the treatment of vitamin D deficiency. Results showed that treatment with D_3 resulted in higher levels of 25(OH)D_3 at the end of 1 year.

As per Endocrine Society Clinical Practice Guideline, 2011, the following treatment is recommended–

- For infants and toddlers aged 0 to 1 year who are vitamin D deficient, treat with 2000 IU/d of vitamin D_2 or vitamin D_3 or with 50,000 IU of vitamin D_2 or vitamin D_3 once weekly for 6 weeks to achieve a blood level of 25(OH)D above 30 ng/mL, followed by maintenance therapy of 400 to 1000 IU/d
- For children aged 1 to 18 years who are vitamin D deficient, treat with 2000 IU/d of vitamin D_2 or vitamin D_3 for at least 6 weeks or with 50,000 IU of vitamin D_2/D_3 once a week for at least 6 wk to achieve a blood level of 25(OH)D above 30 ng/mL, followed by maintenance therapy of 600 to 1000 IU/d
- All adults who are vitamin D deficient should be treated with 50,000 IU of vitamin D_2 or vitamin D_3 once a week for 8 weeks or its equivalent of 6000 IU of vitamin D_2 or vitamin D_3 daily to achieve a blood level of 25(OH)D above 30 ng/mL, followed by maintenance therapy of 1500 to 2000 IU/d
- In obese patients, in patients with malabsorption syndromes and in patients on medications that affect vitamin D metabolism, a higher dose (at least 6000 to 10,000 IU/d) should be used, followed by maintenance therapy of 3000 to 6000 IU/d)
- In patients with extrarenal production of $1,25(OH)_2D$, serial monitoring of 25(OH)D levels and serum calcium levels during treatment is needed to prevent hypercalcaemia. For patients with primary hyperparathyroidism and vitamin D deficiency, treat with vitamin D as needed. Serum calcium levels should be monitored

Vitamin D supplementation is contraindicated in the following conditions–

- Granulomatous diseases
- Metastatic bone disease
- Sarcoidosis
- Williams syndrome

Vitamin D_2 versus D_3 in the treatment of vitamin D deficiency

D_2 is made from UV irradiation of ergosterol in yeast whereas D_3 is made from irradiation of 7-dehydrocholesterol from lanolin and the chemical conversion of cholesterol. Oral formulations of vitamin D_2 and D_3 have traditionally been regarded as equivalent, however, clinical studies prove otherwise. Studies indicate that vitamin D_3 is more potent and has a longer duration of action than D_2.

In the past, D_2 had been used instead of D_3 for severe vitamin D deficiency. This is possibly due to high-dose D_2 being more widely available in doses of up to 50,000 IU per softgel capsule. As per various studies, It is often difficult to raise 25-hydroxyvitamin D levels with D_2 in patients with severe vitamin D deficiency.

In a study conducted by Armas *et al.*, after administration of single oral doses of 50,000 IU of the vitamin D_2 and D_3 preparations to 20 healthy male volunteers, 25-hydroxyvitamin D levels were measured over a period of 28 days. Both D_2 and D_3 produced similar initial increases in serum levels of 25-hydroxyvitamin D over the first 3 days, indicating equivalent absorption. However, levels continued to increase with D_3 and peaked at day 14, whereas levels decreased rapidly with D_2 and were no different from baseline at day 14. The investigators concluded that D_2 potency is less than 30% of that of D_3 and that it has a markedly shorter duration of action.

The results of this study are consistent with other single, high-dose studies that indicate the mean time to peak concentration of D_2 to be about 3 days compared with 14 days for D_3.

In another study by Houghton and Vieth, D_3 was found to be more than 3 times as effective as D_2 in elevating 25-hydroxyvitamin D and maintaining those levels for a longer time. These authors also note that D_3 metabolites have superior affinity for vitamin D-binding proteins in plasma, relative to D_2.

Therefore, D_2 and D_3 are not bioequivalent and should not be considered interchangeable. Based on pharmacokinetic studies and limited clinical evidence, D_3 is preferred over D_2.

The need for supplemental calcium

Calcium homeostasis depends on a range of interrelated processes, including intestinal calcium absorption, calcium uptake and release from the skeleton and renal calcium handling. Vitamin D plays a critical role in each of these processes. Vitamin D deficiency reduces intestinal calcium absorption leading to secondary HPT and risk of bone loss.

However, even in the presence of vitamin D sufficiency, inadequate oral calcium intake may cause secondary HPT. It is recommended that men and women younger than 50 years should be administered 1000 mg/d of elemental calcium, whereas those older than 50 years should be supplemented with 1200 mg/d. 24-hour urine calcium excretion is an effective test to assess adequacy of both calcium and vitamin D intake.

Vitamin D toxicity

Vitamin D, particularly its active hormonal form, calcitriol, is capable of producing serious toxic effects. Despite widespread concern, a comfortable safety margin exists between the intake required for optimisation of vitamin D status and those associated with toxicity. It is worth noting, for example, that a single minimum erythema dosage of UV radiation can produce upto 10,000 to 20,000 IU of vitamin D. If repeated day after day, this can add up to substantial vitamin D inputs, however, not a single case of vitamin D intoxication from sun exposure has been reported to date.

In a review of toxicity data, no cases of intoxication were reported for daily intakes of <30,000 IU/d for extended periods and no cases of vitamin D intoxication for serum 25(OH)D levels <200 ng/mL (500 nmol/L). Thus, it was concluded that a daily intake of 10,000 IU should be considered the tolerable upper intake level. As this high dosage is not usually recommended for any medical reason, there is a comfortable margin of safety between therapeutic and toxic intakes (Table 4) .

Table 4: Tolerable upper intake levels for vitamin D

Age	Male	Female	Pregnancy	Lactation
0 to 6 months	1000 IU (25 mcg)	1000 IU (25 mcg)	–	–
7 to 12 months	1500 IU (38 mcg)	1500 IU (38 mcg)	–	–
1 to 3 years	2500 IU (63 mcg)	2500 IU (63 mcg)	–	–
4 to 8 years	3000 IU (75 mcg)	3000 IU (75 mcg)	–	–
≥ 9 years	4000 IU (100 mcg)	4000 IU (100 mcg)	4000 IU (100 mcg)	4000 IU (100 mcg)

For diagnosing vitamin D toxicity, considering elevated 25(OH)D level alone is not enough. It should be recognised as a clinical syndrome of both hypervitaminosis D and hypercalcaemia, in which hyperphosphataemia and hypercalciuria also commonly occur. Patients may present with clinical symptoms and signs suggestive of hypercalcaemia and hypercalciuria.

Symptoms and signs of vitamin D toxicity include –

- Headache
- Metallic taste
- Nephrocalcinosis or vascular calcinosis
- Pancreatitis
- Nausea
- Vomiting

Hypervitaminosis of vitamin D in the absence of hypercalcaemia may prompt further investigation to evaluate the aetiology of increased vitamin D levels; however, unlike hypercalcaemia, it is not a medical emergency. Most patients with vitamin D toxicity have 25(OH)D levels greater than 150 ng/mL and the lowest reported level associated with toxicity in patients without primary HPT with normal renal function is 80 ng/mL.

Drug- vitamin D interactions

Atorvastatin has been found to increase 25(OH)D concentrations, whereas concurrent vitamin D supplementation decreases concentrations of atorvastatin. Use of thiazide diuretics in combination with calcium and vitamin D supplements may cause hypercalcaemia in the elderly or those with compromised renal function or hyperparathyroidism.

Corticosteroids e.g., prednisone can reduce calcium absorption and retard vitamin D metabolism. Orlistat and cholestyramine can reduce absorption of vitamin D and other fat soluble vitamins.

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Case study 1

Case presentation

A 62-year-old female patient presented with history of sudden onset acute pain in her right hip. She did not report any history of trauma, fever or weight loss. She also complained of muscle aches and pains since past 2 months.

Past history

Patient is a known hypertensive on treatment with Lisinopril plus hydrochlorthiazide combination.

Family history

Sister is a known case of osteoporosis on treatment with vitamin D_3 and calcium supplementation.

Personal history

No addictions.

On examination

The right leg was externally rotated and shortened. Movements elicited pain in the area of right hip.

Investigation

- Serum 25(OH) level – 10 ng/mL (↓)
- Serum PO_4 – 0.68 mmol/L (↓)
- Serum calcium – 8.5 mg/dL (↓)
- Serum alkaline phosphatase – 640 U/L (↑)
- PTH – 65 pg/mL (↑)
- Radiographs of the pelvis revealed a displaced transverse fracture in the subtrochanteric region of right femur
- Reduced bone density seen in femoral head and neck with thinning of trabeculae and loss of trabecular contiguity
- T score more than 2.5 standard deviations below normal on Dual-energy X-ray absorptiometry

Diagnosis: Non-traumatic fracture of osteoporotic femur secondary to vitamin D_3 deficiency

Treatment

The subtrochanteric fracture was reduced and fixed with cortical screws. Post-operatively, patient underwent supervised physiotherapy for a period of 6 weeks. Patient was treated with 50,000IU vitamin D_3 once weekly for 6 weeks daily followed by maintenance therapy of 1500 to 2000 IU/d along with oral calcium citrate 1 gm daily. Biochemical abnormalities normalised at 6 weeks. The fracture healed at 12 weeks and the patient was allowed full weight bearing.

Take home message

Suboptimal calcium absorption, secondary hyperparathyroidism, increased bone resorption, decreased muscle strength and increased risk of falling all indicate vitamin D deficiency/insufficiency disorders that can increase fracture risk. In osteoporotic fracture, vitamin D deficiency is the rule, not the exception. Current data suggests that vitamin D is more important than calcium for fracture prevention. Vitamin D sufficiency can ensure ideal PTH values even when the calcium intake level is less than 800 mg/day. The Osteoporosis Education Project estimates that supplementation with therapeutic levels of vitamin D could result in an overall 50 to 60% reduction in low-trauma osteoporotic fractures.

Case study 2

Case presntation

A 2-year-old dark skinned girl, brought by parents with complaints of knock knees and widening of wrists. The child has not started schooling and spends most of the time indoors.

Past history

- No h/o renal or hepatic disease
- No history suggestive of malabsorption
- No h/o any drug intake
- Pre-natal, natal and post-natal periods were uneventful
- Child was exclusively breastfed for the first 8 months of life

Family history

- Parents were of normal stature and built
- Single child from a non- consanguinous marriage

On examination

- Hearing, vision, mental and motor development were normal
- The patient had a bilateral genus varum, widened wrists and short stature
- There was no rachitic rosary or Harrison's sulcus
- The eruption of teeth was normal and the anterior fontanelle had fused
- Systemic examination – NAD

Investigations

- Hb – 10.8 gm/dL
- Se calcium – 7.6 mg/dL
- Se phosphorous – 4.4 mg/dL
- Alkaline phosphatase – 580 U/L
- Se 25(OH)D – 12 ng/mL
- X-ray of both knees and wrists showed widening, cupping and slight fraying of the metaphyseal regions
- Bowing of both legs evident
- No craniotabes, rachitic rosary seen

Diagnosis: Vitamin D deficiency rickets

Treatment

Patient was treated with 50,000 IU of vitamin D_3 once a week for 6 weeks followed by maintenance therapy of 800U/d. Also diet rich in calcium was advised. Patient responded well to treatment and biochemical abnormalities returned to normal in 6 weeks. Bowing deformity improved with the use of splints.

Take home message

Rickets represents the failure of mineralisation of growing bones. Nutritional rickets can be caused by inadequate intake of vitamin D in particular, however, it is not uncommon in dark-skinned children who have limited sun exposure and in infants, exclusively breast fed infants. The aim of early diagnosis and treatment is to resolve biochemical derangements and prevent complications such as severe deformities that may require surgical intervention. Vitamin D and supplements of calcium and phosphorus are used to treat nutritional rickets.

CME – Post test

1. **The 2 physiologically relevant form vitamin D are ergocalciferol and _____.**

   a) Cholesterol

   b) 7-dehydrocholesterol

   c) Cholecalciferol

   d) Ergosterol

2. **The biologically active form of vitamin D is _____.**

   a) Calcidiol

   b) Calcitriol

   c) Calciferol

   d) Cholecalciferol

3. **UVB rays between the wavelength of _____ nm penetrate uncovered skin and convert cutaneous 7- dehydrocholesterol to previtamin D_3.**

   a) 290 to 320

   b) 160 to 200

   c) 340 to 370

   d) 260 to 280

4. **25(OH)D is converted to the biological active form 1,25$(OH)_2$D by _____ enzyme in the kidneys.**

   a) 25-hydroxylase

   b) 24, 25 hydroxylase

   c) 1-hydroxylase

   d) 1α-hydroxylase

5. **Vitamin D_3 plays the following role in bone health except...**

   a) Stimulating bone maturation

   b) Stimulating matrix formation

   c) Reducing renal reabsorption of Ca

   d) Stimulating bone remodelling

6. Interaction of 1,25-dihydroxyvitamin D with the vitamin D receptor increases the efficiency of intestinal calcium absorption by _____.

a) 10 to 15%

b) 5 to 10%

c) 20 to 30%

d) 30 to 40%

7. Which one of the following tests gives the best assessment of vitamin D status?

a) Serum parathyroid hormone

b) Serum 25-hydroxyvitamin D (calcidiol)

c) Serum 1,25-dihydroxyvitamin D (calcitriol)

d) Serum bone alkaline phosphatase

8. Radiographic findings of vitamin D deficiency includes all, except…

a) Increased bone mineral density

b) Osteopaenia or osteoporosis

c) Non- traumatic fracture

d) Skeletal pseudofracture

9. Which one of the following treatment strategies would be most effective to achieve optimal vitamin D levels in a vitamin D deficient toddler?

a) Daily supplementation with 400 IU of D_3

b) Daily supplementation with 800 to 1000 IU of D_2 or D_3

c) 50,000 IU of D_3 once weekly for 6 weeks followed by maintenance therapy

d) Monthly supplementation with 50,000 IU of D_2

10. Signs of vitamin D toxicity include…

a) Metallic taste

b) Nephrocalcinosis or vascular calcinosis

c) Pancreatitis

d) All of the above

Ans: 1-c; 2-b; 3-a; 4-d; 5-c; 6-d; 7-b; 8-a; 9-c; 10-d

Clinical challenges – Vitamin D_3: The 'sunshine' vitamin

Case 1: A case of dietary and sunlight deficient osteomalacia

Case presentation

A 75 year-old woman was admitted with bilateral thigh pain and pain in both shoulders. The pain and weakness progressed to the point that she had difficulties in rising from a chair, holding her arms up and walking, and was unable to climb stairs.

The patient was homebound at most times.

Past history

Patient is a known diabetic, well controlled on metformin therapy.

Family history

Nil significant

Personal history

- No addictions
- Consumes a strict vegetarian diet

On examination

- Clinical examination showed evidence of bilateral, proximal muscle atrophy and weakness in the lower extremities more than the upper extremity
- Patient had a waddling gait

Investigation

- Se 25(OH)D –14ng/mL (↓)
- Se PO_4 – 0.78 mmol/L (↓)
- Se calcium and PTH were normal
- X-ray revealed marked femoral bowing with cortical thickening
- Bone mineral density using dual energy X-ray absorptiometry (DEXA) scan was done and T score measurements were low (3.0 SD below the mean at the femoral neck)

Diagnosis: Dietary and sunlight deficient osteomalacia

Treatment

The patient was treated with vitamin D and calcium supplementation, and her femur was regularly monitored by X-rays. Patient recovered well with treatment.

Questions

1. What is the differential diagnosis for this case and how would you reach the diagnosis of osteomalacia?

2. What is the best treatment strategy in this patient?

Case 2: A case of osteomalacia in a case of chronic liver disease (hepatitis B)

Case presentation

A 62-year-old woman presented with severe acute pain in left elbow. She gave history of dull ache over the ribs since 1 month. She also complained of progressive bilateral lower limb weakness and hip pain since 6 months. She found it progressively difficult to walk without support and had difficulty in getting up from sitting position.

Past history

She is a known case of mild chronic hepatitis B on regular monitoring.

Family history

Husband is a case of chronic hepatitis B on treatment with adefovir.

Personal history

- Patient is a non-vegeterian.
- No addictions.

On examination

- No overt signs of liver disease
- Tenderness and restriction of movement around the left elbow joint and tenderness present bilaterally over lower ribs
- Rest systemic – NAD

Investigations

- ALT – 55IU/L; Alkaline phosphatase – 650 U/L

- HbsAg – Positive
- Serum HBV DNA– Undetectablable
- 25-hydroxyvitamin D –14 ng/mL
- Se PO_4 – 0.70 mmol/L
- X ray showed supracondylar fracture of the Lt distal humerus
- Para-articular osteopaenia with lucent areas in proximal phalanges of left big toe, left distal fibula and tibia
- A bone scan revealed multiple hot spots bilaterally over the rib cage, left elbow, iliac bones, left distal tibia and fibula

Diagnosis: Osteomalacia in a case of chronic liver disease (hepatitis B)

Treatment

Open reduction and internal fixation was performed and the patient was treated with vitamin D_3 and calcium supplementation.

The fracture healed uneventfully and biochemical parameters normalised at 05 weeks.

Questions

1. What role does vitamin D deficiency play in development of osteomalacia in patients with chronic liver disease?

2. What is the treatment of hepatic osteomalacia?

Answers to clinical challenges – Vitamin D_3: The 'sunshine' vitamin

Case 1: A case of dietary and sunlight deficient osteomalacia

Questions

1. What is the differential diagnosis for this case and how would you reach the diagnosis of osteomalacia?

Fibromyalgia, polymyalgia, early rheumatoid arthritis or psychosomatism would be the differential diagnosis in this case. Clinical manifestations of osteomalacia are usually insidious. Bone pain described by patients is characteristically diffuse and may affect several body parts, for example back, knee and rib cage. Therefore, it closely resembles the aforementioned conditions. Skeletal deformities such as kyphoscoliosis, or limb bowing occur very late in the disease. Biochemistry evaluation can provide important clues for early diagnosis (Box 1).

Box 1: Laboratory findings in vitamin D deficiency

- ↓ 24-hour urine calcium excretion
- ↓ Serum total 25(OH)D level
- ↑ Parathyroid hormone level
- ↑ Total or bone alkaline phosphatase level
- ↓ Serum calcium and/or serum phosphorus level

2. What is the best treatment strategy in this patient?

For osteomalacia patients with deficient vitamin D intake, treatment involves 50,000 IU of vitamin D_3 once or twice per week, plus 1 g of elemental calcium per day until blood biochemistry returns to normal. This usually occurs within 6 months.

Case 2: A case of osteomalacia in a case of chronic liver disease (hepatitis B)

1. What role does vitamin D deficiency play in development of osteomalacia in patients with chronic liver disease?

The central role of vitamin D deficiency in the pathogenesis of osteomalacia associated with chronic liver disease is evidenced by the presence of low serum 25(0H)D levels in these patients and by by the therapeutic response to vitamin D. Further indirect evidence for the pathogenetic role of vitamin D deficiency comes from the demonstration of secondary hyperparathyroidism in osteomalacic patients, as evidenced by raised serum parathyroid hormone levels. Vitamin D undergoes 25 hydroxylation in the liver which is impaired in the presence of chronic liver disease. Vitamin D insufficiency is associated with secondary hyperparathyroidism, increased bone turnover and accelerated bone loss. As vitamin D deficiency becomes more severe, impaired bone mineralisation leads to accumulation of osteoid which is a feature of osteomalacia. Many studies have shown low serum levels of 25(0H)D in patients with chronic liver disease and levels fall with disease progression in cirrhosis. It is likely that both reduced exposure to UV light and dietary insufficiency account for vitamin D deficiency in themajority of cases.

2. What is the treatment of hepatic osteomalacia?

About two thirds of patients with cirrhosis and 96% of those awaiting liver transplantation have low vitamin D levels, in which abnormality is also associated with decreased bone mineral density, high bone turnover, and increased risk of osteoporotic fracture.

Patients with liver disease and impaired 1,25 dihydroxy-vitamin D synthesis can be treated with daily oral doses of 1,25 dihydroxy-vitamin D supplement (0.25 to 1 mg/day). The prognosis is good if treatment is appropriately directed at the underlying aetiology.

Medicolegal

IS CONSENT MANDATORY FOR HIV TESTING?

Dr. Gopinath N. Shenoy
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Dr. Gayatri G. Shenoy
MD, DA

Is it necessary to take a written consent from the patient for the HIV testfi In case the test is found to be positive can the doctor inform the spouse without the permission of the patientfi These are two very important issues that come up in one day-to-day practice.

When HIV testing is done with patient's express consent, the doctor is saved of a lot of headaches later on. What is absolutely necessary before an HIV test is pre-test counselling. When a HIV test is undertaken after counselling, wherein the patient is supposed to have asked all sorts of questions, law considers that an implied consent is present even in situations where an express consent is absent. However, a written consent in all such cases will be an additional safe-guard against litigation.

Spouse of an HIV positive patient must be informed about the status of his/her partner. All persons who are at risk of infection should also be informed as the right to a healthy life supersedes the right to confidentiality.

The law in this regard has been settled by none other than the Supreme Court of India in Mr. 'X' Appellant v. Hospital 'Z' Respondents Civil Appeal No. 4641 of 1998, decided on 21st September, 1998

The fact that the appellant - Mr. X was HIV (+) was disclosed by Hospital Z to the relatives of the person with whom X was to be married. Due to this fact, the marriage was cancelled. Since the marriage had been settled but was subsequently called off, several people including members of the appellant's family and persons belonging to his community became aware of the appellant's HIV (+) status. This resulted in severe criticism of the appellant and he was ostracised by the community. The appellant left Kohima (Nagaland) and started working and residing at Madras. The appellant then approached the National Consumer Disputes Redressal Commission for damages against the respondents - Hospital Z, on the ground that the information which was required to be kept secret under Medical Ethics was disclosed illegally and, therefore, the respondents were liable to pay damages. The Commission dismissed the petition as also the application for interim relief summarily on the ground that the appellant may seek his remedy in the civil court. Appeal was filed in the Supreme Court. Appellant vehemently contended that the principle of "duty of care", as applicable to persons in medical profession includes the “duty to maintain confidentiality” and since the respondents violated this duty, they were liable to pay damages to the appellant. The Supreme Court held that the Code of Medical Ethics also carves out an exception to the rule of confidentiality and permits the disclosure in the certain circumstances under which public interest would override the duty of confidentiality, particularly where there was an immediate or future health risk to others.

The Supreme Court further observed Ms. 'Y', with whom the marriage of the appellant was settled, was saved in time by the disclosure of the vital information that the appellant was HIV (+). The disease which is communicable would have been positively communicated to her immediately on the consummation of marriage. As a human being, Ms. 'Y' must also enjoy, as she, obviously, is entitled to, all the Human Rights available to any other human being. This is apart from, and, in addition to, the Fundamental Rights available to her under Article 21, which guarantees "Right to Life" to every citizen of this country. This right would positively include the right to be told that a person, with whom she was proposed to be married, was the victim of a deadly disease, which was sexually communicable. Since right to life includes right to lead a healthy life so as to enjoy all faculties of the human body in their prime

Medicolegal

condition, the respondents, by their disclosure that the appellant was HIV (+), could not be said to have either violated the rule of confidentiality or the right of privacy. Moreover, where there is a clash of two Fundamental Rights, as in the instant case, namely, the appellant's right to privacy as part of right to life and Ms. Y's right to lead a healthy life which is her Fundamental Right under Article 21, the right which would advance the public morality or public interest, would alone be enforced through the process of the Court, for the reason that moral considerations cannot be kept at bay and the Judges are not expected to sit as mute structures of clay, in the Hall, known as Court Room, but have to be sensitive, in the sense that they must keep their fingers firmly upon the pulse of the accepted morality of the day. The appeal was thus dismissed.

Dr. Gopinath N. Shenoy is an Obstetrician and a Gynaecologist and a medico legal consultant who exclusively defends the doctors in the Consumer Courts and the Medical Councils all over India. He was a Judge of the Consumer Court in Mumbai.

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NOTES

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