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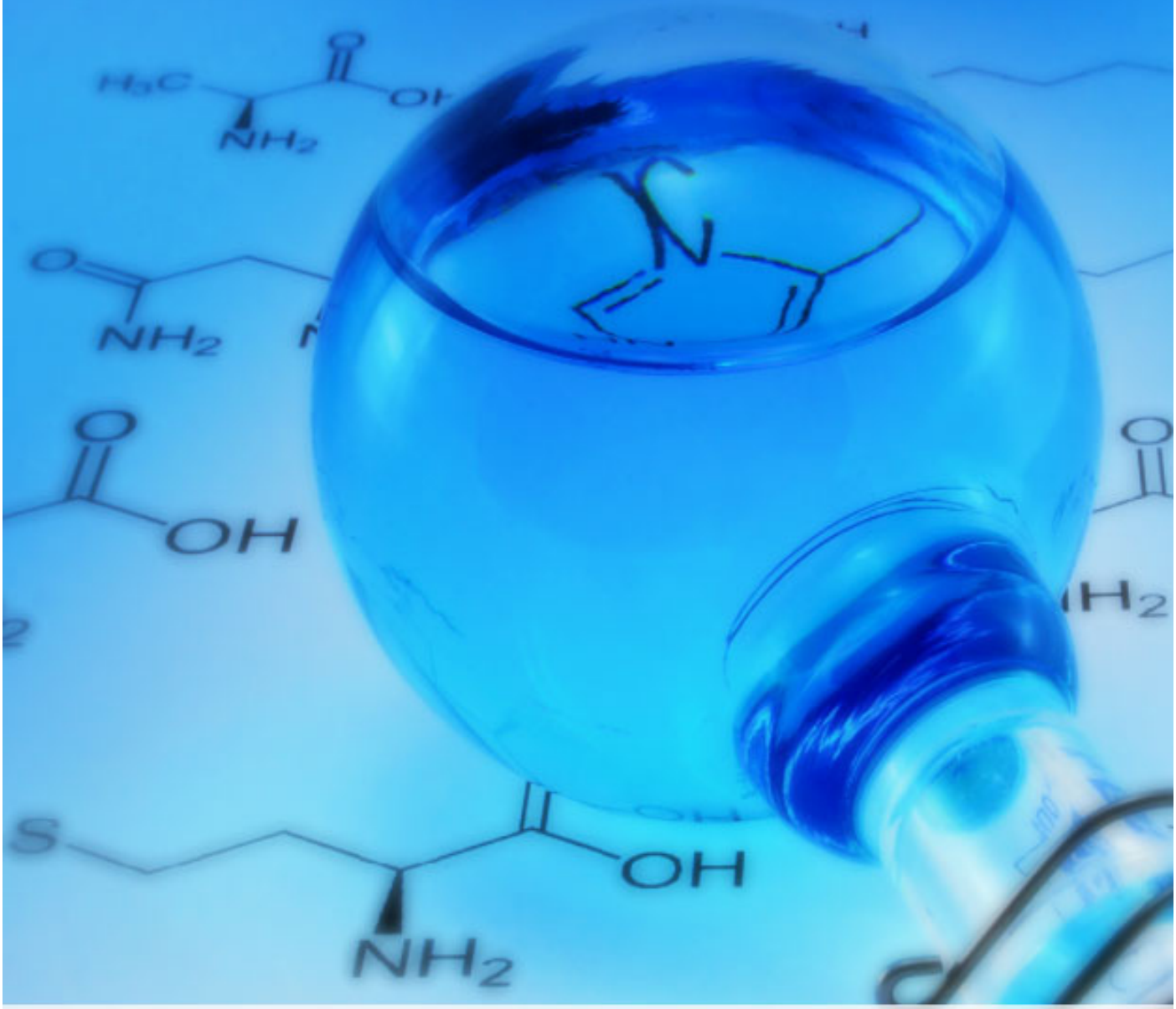

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Vitamin D in Physiological and Pathological Conditions

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Abstract

Vitamin D, one of the fat soluble vitamins, is considered a hormone also owing to its ability to be synthesized in the body and similarity of its mechanism of action with steroid hormones. It is the key hormone, along with parathormone and calcitonin, in calcium homeostasis. Besides regulating calcium levels in plasma, vitamin D plays a significant role in maintaining normal physiological functions and growth and development of the body. Deficiency of vitamin D has been implicated in a number of pathological conditions while high levels may produce toxic features. This chapter is an attempt to throw light on these important aspects of vitamin D in human physiology and pathology.

Keywords: Vitamin D; Normal physiology; Calcium homeostasis; Pathological conditions.

Introduction

Although vitamin D is classified under fat soluble vitamin, it must be considered more accurately as a pro-hormone, and its metabolite 1,25$(OH)_2$ cholecalciferol as the major steroid hormone involved in mineral ion homeostasis in the body. It is because that its mechanism of action is similar to that of the steroid hormone and in normal physiologic setting it can be synthesized in the body and if the body gets adequate exposure to sunlight, then requirement of vitamin D through diet is little or not at all. Apart from its role in calcium homeostasis, it is also involved in cell differentiation and proliferation. Its deficiency may lead to rickets and osteomalacia, particularly in absence of adequate sunlight exposer. Besides this, it has also been reported to reduce the risk of insulin resistance, metabolic syndrome, obesity and different cancers [1].

Physiology of vitamin D

Types and sources

Vitamin D derived from the animal sources is in the form of vitamin D_3 (cholecalciferol) and that from plant sources is vitamin D_2 (ergocalciferol). These two are the principal forms of vitamin D. The sources of former include fish oil (saltwater fishes-especially salmon, sardines and herring), liver and egg yolk and that of the latter includes mainly alfalfa, agaricus etc.Over the last several decades, increasing use of sun-block and decreasing exposure to sunlight seen in North America and Western Europe, people's dependence on food as the source of vitamin D has increased. For this, milk, butter and other dairy products, cereals are being fortified by vitamin D_2 prepared by irradiation of ergosterol from yeast. Vitamin D potency is measured by the

microgram of cholecalciferol (1 microgram of cholecalciferol = 40 IU). Biologic activity and potency are equivalent for the two forms, though in recent times, some controversy have arisen regarding this. But both of these are metabolized in human in similar fashion [1].

Metabolism of vitamin D

In the Skin

In the skin, a photochemical reaction on exposure to Ultraviolet (UV) component of sunlight causes the formation of cholecalciferol from 7-dehydrocholesterol. The latter is an intermediate in synthesis of the cholesterol. It gets accumulated in the skin. UV rays cause non enzymatic conversion of 7-dehydrocholesterol to previtamin D which, on thermal ionization for period of hours, yields cholecalciferol or calciol or vitamin D_3, and this gets absorbed in the blood. The production of cholecalciferol in the skin is affected by availability of sunlight. It is decreased by high amount of melanin in the skin and also by the use of high protection sun-blockade, which impairs the penetration of skin by UV rays. The plasma concentration of vitamin D is highest at the end of summer and lowest at the end of winter. The availability of UV fraction of sunlight declines beyond 40^0 latitude [1].

In the liver

Cholecalciferol, whether produced in the skin or absorbed from the intestine, reaches the circulation where it binds to vitamin D binding protein. Then it reaches the liver where it is hydroxylated at 25-position by acytochrome P450 like enzyme, calciol-25-hydroxylase, in mitochondria and microsomes. It yields 25-hydroxy derivative 25-hydroxycholecalciferol or calcidiol. The latter is released into the circulation. This is the main circulating and storage form of vitamin D. In blood, 88% of it binds to vitamin D binding protein, 0.03% is free and the rest is bound to albumin. Its half-life is 2-3 weeks, which can be reduced in the condition like nephrotic syndrome due to urinary loss of vitamin D binding protein [1].

In the kidney

Next step in the metabolism of vitamin D occurs in the kidney. Here, 25-hydroxyvitamin D-1α hydroxylase causes the second hydroxylation to produce 1,25-dihydroxycholecalciferol or calcitriol, the biologically active form of vitamin D. This reaction occurs in the proximal convoluted tubules in the kidney. This enzyme is cytochrome P450 like mixed function oxidase, which is under tight regulation unlike the calciol 25-hydroxylase in the liver. The former is induced by parathormone (PTH) and hypophosphatemia and downegulated by calcium, fibroblast growth factor (FGF23) and 1,25- dihydroxycholecalciferol. This enzyme is also present in different tissues like brain, colon, breast, prostate, beta cells of pancreas, vascular smooth muscle, macrophage and epidermal keratinocyte. But this does not contribute to the circulating level of active form of vitamin D, rather it has paracrine action in those tissues [1].

In kidney there is also another enzyme, vitamin D-24-hydroxylase which hydroxylates at 24^{th} position of 25-hydroxycholecalciferol yielding 24,25-dihydroxycholecalciferol, an inactive metabolite. This is the principal pathway of inactivation of vitamin D, which is present in almost every tissue. Interestingly, 1,25-dihydroxycholecalciferol increases the action of vitamin D-24-hydroxylase leading to inactivation and diminished biological activity of vitamin D. Besides these, there are various polar metabolites of vitamin D, which are secreted in bile and reabsorbed by enterohepatic circulation. So, if the latter is hampered due to any reason like diseases of terminal ileum, it causes the increased loss of vitamin D metabolites [1].

Metabolic role of vitamin D in body

How vitamin D exerts its effects at molecular level

Vitamin D acts through Vitamin D Receptor (VDR), a member of nuclear receptor superfamily. This receptor belongs to a subfamily that also includes the thyroid receptors, retinoid receptors and the peroxisome proliferator-activated receptor. Among these, VDR has only one isoform. From previous discussions, it is evident that vitamin D acts like a steroid hormone and exerts its effects by binding to VDR. The latter binds to Retinoid X Receptors (RXR-which can bind to 9-cis-retinoic acid) and forming a heterodimer, which binds to DNA sequence, stimulates recruitment of necessary molecules and thus initiates the expression of the target gene. The RXRs also form heterodimer with thyroid and other nuclear acting receptors. Deficiency and excess of vitamin A can decrease the action of vitamin D. In deficiency, there is decreased level of 9-cis retinoic acid to form heterodimers, while in excess, there is formation of RXR homodimers what make the RXR receptors unavailable to form heterodimer with VDR. For some target genes, VDR exerts its inhibitory action by interfering the very action of the transcription factors or by recruiting novel proteins to VDR complex. 1,25-dihydroxycholecalciferol has three times more affinity than other vitamin D metabolites and so in physiologic condition the latter do not directly interact with the receptors. But in case of vitamin D toxicity, 25-hydroxycholecalciferol can directly interact with VDR, resulting in hypercalcemia and also can displace 1,25-dihydroxycholecalciferol from vitamin D binding protein leading to rise of its bioavailability [1].

Functions of vitamin D

Role in mineral ion homeostasis

Vitamin D plays an important role in calcium homeostasis. It exerts its effects in three ways:

a) Vitamin D induces the synthesis of calcium binding protein calbindin 9K which is present in the intestinal mucosal cells and is involved in active transport of calcium. Apart from this, there are two major calcium transporter, TRPV5 and TRPV6 (transient receptor potential vanilloid), in the intestinal mucosa, which are also induced by 1,25-dihydroxycholecalciferol. By inducing the expression of these proteins in the intestinal epithelial cells, the latter increases the intestinal absorption of calcium [1].

b) This vitamin is also important for mobilization of calcium from bone. Here, it acts synergistically with PTH. Vitamin D affects osteoblast through its receptor, VDR and increases the expression of different genes encoding bone matrix proteins, osteocalcin and osteopontin and decreases that of type I collagen. Besides this, 1,25-dihydroxycholecalciferol and PTH both induce the synthesis of Receptor Activator of Nuclear Factor k B (RANK) ligand, which binds to RANK present on osteoclast progenitors and mature osteoclasts. This is how they increase the osteoclast differentiation and their activity and thereby bone resorption. Though it was previously thought that 24,25-dihydroxycholecalciferol was an inactive metabolite but recent studies on knock out mouse have showed its ill-defined role in

bone metabolism [1].

c) 1,25-dihydroxycholecalciferol and PTH together increase the reabsorption of calcium from distal convoluted tubules of kidney and thereby decreasing the renal excretion of kidney [1].

In these three ways, vitamin D helps to maintain the serum calcium levels in the body [1].

Role in cell proliferation

Vitamin D is thought to have a regulatory effect on cell proliferation. It has been shown to have anti-proliferative effect on different cells like keratinocyte, breast cancer cells, prostate cancer cells [1].

Effect on endocrine system

1,25-dihydroxycholecalciferol acts through VDR receptors expressed on parathyroid gland and exerts an anti-proliferative effect and decreases the transcription of PTH, thereby decreasing its action. This is the background knowledge for strategy to prevent and treat the hyperparathyroidism in renal insufficiency [1].

It may have role in secretion of insulin from pancreatic beta cells and also in synthesis and secretion of thyroid hormone [1].

Other functions assigned to vitamin D include

a) Regulation of normal functioning of innate and adaptive system- It has effect in inhibition of production of interleukins by activated T lymphocytes, and of immunoglobulins by activated B lymphocytes and also in differentiation of monocyte precursor cells [1].

b) Normal functioning of neuromuscular activity[1].

c) Regulation of blood pressure [1].

Pathology associated with vitamin D metabolism

Alteration of vitamin D metabolism can be seen in various pathological conditions like rickets, osteomalacia, renal dystrophy, essential hypertension, multiple sclerosis, rheumatoid arthritis, different cancers etc. Out of them, few worth mentioning disorders have been described here.

Vitamin D deficiency

Vitamin D deficiency is major global public health problem reported from both sunshine deficient and sunshine sufficient countries. In spite of this, it is the most underdiagnosed and undertreated nutritional deficiency in the world. Almost 1 billion people are reported to suffer from vitamin D deficiency and 50% of the population from vitamin D insufficiency [2]. The prevalence of vitamin D deficiency is more in elderly and obese patients and also in hospitalized patients and nursing home residents. It is 35% higher in obese individual irrespective of latitude and age [3]. In United States (US), 50% to 60% of hospitalized and nursing home resident patients were reported to have vitamin D deficiency [4,5]. The condition may be related to decreased sun exposure resulting from higher skin content of melanin and also the practice of higher skin coverage especially in Middle Eastern countries. In United States, 47% of African American infants and 56% of Caucasian infants, while 90% of infants in Iran, Turkey and India have vitamin D deficiency. Among the adults, it has been observed that 35% in US have vitamin D deficiency, on the other hand, in India, Pakistan and Bangladesh more than 80% are vitamin D deficient. When it comes to elderly population (>60 years), 61% in US, 90% in Turkey, 96% in India, 72% in Pakistan and 67% in Iran are vitamin D deficient [6].

Causes of vitamin D deficiency

The deficiency of vitamin D mainly results from decreased production in skin, lack of dietary intake, increased loss, impaired vitamin D activation and resistance to biologic action of 1,25-dihydroxycholecalciferol.

a) Vitamin D deficiency due to decreased production or intake:

1) In case of aged and hospitalized patients, there is reduced exposure to sunlight as well as reduced absorption in intestine with age, leading to deficiency.

2) Reduced intake through diet may be a cause in various populations.

3) Intestinal malabsorption, particularly of dietary fats, specially in terminal illeal disease where there is decreased enterohepatic circulation of vitamin D metabolites resulting in increased loss of those compounds.

b) Increased loss of vitamin D:

1) Due to increased catabolism resulting from induction of hepatic cytochrome P-450 by various drugs like barbiturates, phenytoin, rifampin.

2) Decreased enterohepatic circulation leading to increased loss of vitamin D metabolites.

3) Nephrotic syndrome

c) Decreased 25-hydroxylation:

1) In severe liver disease

2) Use of isoniazid

d) Reduced 1α hydroxylation:

1) Renal failure

2) 1α hydroxylase mutation like in genetic disorder pseudovitamin D deficiency.

3) Hypoparathyroidism

4) Oncogenic osteomalacia

5) X-linked hypophosphatemic rickets

6) Use of ketoconazole

e) Resistance in the target organ :

Mutation in the vitamin D receptor like hereditary vitamin D resistant rickets which is more difficult to treat [7].

Clinical features

The clinical features mainly result from the impaired calcium absorption. Mild to moderate deficiency may be asymptomatic but longstanding one may be manifested with secondary hyperparathyroidism, impaired mineralization of bone characterized by osteopenia on X-ray and proximal myopathy. The latter rarely may show the features of acute hypocalcemia as numbness tingling seizures [7].

Rickets and osteomalacia

Vitamin D is manifested as rickets in children before epiphyseal fusion. There is continued formation of osteoid matrix and cartilage but there is improper mineralization of it resulting in soft, pliable bones, growth retardation with expansion of growth plate. In normal cases, three layers of chondrocytes are present in growth plate- the reserve zone, the proliferative zone, and hypertrophic zone. Rickets is characterized by expansion of hypertrophic layer as the result of impaired apoptosis of late hypertrophic chondrocytes. Moreover, in murine models, it is seen that hypophosphatemia is important etiologic factor for the development of rachitic growth plate. [8] Clinical features include:

1) Craniotabes: In this feature, pressure over soft membranous skull bone will give feeling of ping-pong ball being compressed.

2) Bossing of the skull: Bossing of frontal and parietal bone, mainly seen after 6 months of age.

3) Broadening of the end of the long bones, mainly around wrists and knees, seen about 6-9 months of age.

4) Delayed teeth eruption.

5) Harrison's sulcus: Horizontal depression along the lower part of chest corresponding to insertion of the diaphragm.

6) Pigeon chest: Sternum is prominent.

7) Rachitic rosary: The costo-chondral junctions of anterior chest wall become prominent.

8) Muscular hypotonia: The child's abdomen is protruberant (pot belly), and visceroptosis and lumbar lordosis are also seen.

9) Deformities: A variety of deformities like knock knees or bowed legs which become evident as the child starts to walk [9].

Osteomalacia occurs due to vitamin D deficiency in adults resulting in demineralization of preexisting bone leading to more susceptibility to fracture. Unlike osteoporosis, osteoid matrix remains intact here. It may be a feature of long-standing hypophosphatemia due to either renal phosphate wasting or chronic use of etidronate or phosphate-binding antacid. [8] Clinical features include:

1) Bone pains: It may range from skeletal discomfort to diffuse pain, even tenderness is common.

2) Muscular weakness: Difficulty in climbing up and down stairs. Waddling gait may be seen. Tetany may manifest at carpopedal spasm and facial twitching.

3) Spontaneous fracture: Mainly in spine leading to kyphosis [9].

Diagnosis of vitamin D deficiency, rickets and osteomalacia

1) The most specific screening test for vitamin deficiency is estimation of serum 25-hydroxycholecalciferol. The different criteria are stated in **Table 1** [10].

Table 1: Recommended serum levels of 25-(OH) vitamin D.

Condition	Serum levels of 25-(OH) vitamin D
Sufficiency	More than or equal to 30 ng/mL
Relative Insufficiency	21-29 ng/Ml
Deficiency	Less than or equal to 20 ng/mL
Toxicity	>150 ng/mL

2) There may be decreased serum total and ionized calcium [8].

3) Due to PTH induced bone turn over there may be increased alkaline phosphatase. It is also associated with phosphaturia and hypophosphatemia as PTH induces the urinary calcium retention and phosphate excretion [8].

4) As PTH is an important stimulus for renal 1α hydroxylase, paradoxically level of 1,25-dihydroxycholecalciferol may be increased some times. This is the reason why the latter does not reflect the status of vitamin D in body and should not be used to diagnose the vitamin D deficiency [8].

5) **Radiologic findings:**

For rickets: Delayed appearances of epiphysis, widening of epiphyseal plate, cupping and splaying of metaphysis, bone deformities and in late cases rarefaction of diaphyseal cortex [9].

For osteomalacia: Diffuse rarefaction of bones, looser's zone or pseudofracture (radiolucent zone at sites of stress; common sites include pubic rami, axillary border of scapula, ribs, the medial cortex of the neck of femur; it is due to rapid resorption and slow mineralization and the zone may be surrounded by collar of callus), triradiate pelvis in females, protrusio-acetabuli (protruding acetabulum into pelvis) [9].

Treatment of vitamin D deficiency

The condition is treated with vitamin D supplementation. Based on observation that 400IU supplementation is often insufficient to prevent deficiency, and 800IU along with calcium supplementation reduces the risk of hip fractures in elderly women, the high doses are preferred. Vitamin D should always be supplemented along with calcium because most of the features of deficiency are due to hypocalcemia. Toxicity occurs with the dose 40000IU daily. Patients having impaired 1α-hydroxylation, are treated by metabolites not requiring this activation step like 1,25-dihydroxyvitaminD_3 (calcitriol,0.25-0.5 μg/d) and 1α-hydroxyvitaminD_2 (hectotrol,2.5-5μg/d). Severe deficiency is treated by initially 50000IU weekly for 3-12 weeks, followed by 800IU daily. Calcium supplementation should be 1.5-2 g/d of elemental calcium [8].

In response to treatment, normocalcemia occurs within one week, though, increased PTH and alkaline phosphatase levels persist for 3-6 months. Treatment monitoring is done by measuring serum and urinary calcium. If the treatment is adequate then, 24-hour urinary calcium excretion wiil be in the range of 100-250mg/24-hours, if less, it means any problem regarding patient's compliance to treatment regimen or absorption of calcium or vitamin D supplement. The levels of >250mg/24-

hours are associated with nephrolithiasis requiring a reduction of doses [8].

Vitamin D toxicity

The increased level of plasma concentration leads to toxicity characterized by contraction of blood vessels, resulting in increased blood pressure and calcinosis i.e. deposition of calcium in the soft tissues. With increased level of vitamin D, there will also be increased bone resorption and calcium absorption resulting in hypercalcemia and hypercalciuria, and the latter will increase the predisposition of renal stone formation. Some infants may be sensitive to dose of vitamin D as low as 50µg/day. Toxicity is seen in excessive dietary intake but not in excessive exposure to sunlight. It is because that our body has limited capacity to synthesize precursor, 7-dehydrocholesterol and excessive exposure results in formation of inactive metabolites [10].

Vitamin D and other diseases

Besides playing a crucial role in calcium homeostasis, vitamin D exerts a variety of functions in the body. On account of this fact, altered levels of vitamin D have been found to be associated with a number of clinical disorders. A few of them have been discussed here in a bit detail:

Renal osteodystrophy

One of the complications of the chronic renal failure is renal osteodystrophy. There is inability of body to produce 1,25-dihydroxycholecalciferol and so the bone calcium becomes the source to maintain the serum level. Besides, the condition is associated with renal retention of phosphate and hyperphosphataemia. This leads to formation of calcium phosphate resulting in deposition of the latter in soft tissues, metastatic calcification, reducing the level of calcium further. Thus the combination of hypocalcemia and hypophosphatemia increases the secretion of parathyroid hormones resulting in bone resorption. Therefore, in this case treatment with only vitamin D or its metabolites will not help because it will rather increase metastatic calcification due to hypercalcemia resulting from the treatment and already existing hypophosphatemia. So, important is to reduce the phosphate level alongside the high calcium diets/vitamin D supplements. As it is difficult to reduce phosphate component in diet, vegetable proteins are preferred over animal ones, for, in them phosphates are in the form of phytates which are not readily absorbed. The patients are also asked to avoid processed food as phosphates are added to them. For all the above reasons, phosphate binders are used. They are calcium acetate and cationic polymer called sevalamer hydrochloride. If orally administered 1,25-dihydroxyvitamin D is not sufficient to raise serum calcium level, as in severe hyperparathyroidism, intravenous form may be given. Lot of research is going on to develop calcimimetic agents which can bind to calcium sensor on the parathyroid gland, thereby decreasing its secretion [11].

Cystic fibrosis

This is the disease caused by the mutation of the gene encoding Cystic Fibrosis Transmembrane Conductance Regulator (CFTR), a cAMP regulated chloride channel. It is the most common lethal inherited disease among caucassians. This defect leads to problem in the activity of exocrine glands affecting mainly the lungs and the pancreas. In the lungs, there is viscid secretion in bronchi and bronchioles blocking the lumen and it also results in frequent infections. On the other hand, dysfunction of exocrine cells of pancreas results in deficiency of pancreatic enzymes and also partial obstruction of common bile duct. Consequently, deficiency of pancreatic amylase, proteases and lipase will lead to severe malabsorption. Due to fat malabsorption resulting from lipase and bile deficiency, there will be associated fat soluble vitamin deficiency. Calcium binds with long chain fatty acids to form insoluble salts. Partially digested food bolus too hinders the absorption of starch and proteins by physical entrapment of those molecules. Besides these, increased mucus secretion in the intestinal lumen also reduces the absorption of several micronutrients like iron [11].

Patients are treated with preparation of pancreatic enzymes. Although, with this, the absorption of protein and carbohydrates approximates to normal, that of fat does not. It is due to the fact that there remains the persistent deficiency of bile acid and excessive mucus secretion. Moreover, for some patients calorie demand is increased due to chronic infection. The recommendation is high energy, high protein diet without restriction of dietary fats (50% carbohydrate, 15% protein, 35% fat). If diet fails to supply the need of the body, then supplementary feed or enteral feeding comes into the picture. Sometimes, medium chain fatty acids may be advised because they get absorbed directly in the intestinal mucosa. Children of age 2-8 years are treated with multivitamin preparation containing 400IU of vitamin D and 5000IU of vitamin A, though, older children, adolescent and adults need 1-2 dose per day. Vitamin K is only recommended when patient is on antibiotics or suffering from cholestatic liver disease. In spite of the fact that iron deficiency is commonly associated with this condition, it is not recommended because of chance of high level of iron to enhance probability of systemic bacterial infection. Although calcium level is normal in these patients, it is noteworthy to maintain its recommended level in diet [11].

Vitamin D and cancer

Alteration of vitamin D level has been implicated in the risk and progression of various cancers. Different research works have supported this fact. It goes long back to 1915 when Hoffman first noticed the association of sun exposure and latitude with cancer mortality. Peller and Stephenson found that people who were exposed to sunlight sufficient to induce nonlethal, non-melanoma skin cancer, had lower incidence of more malignant tumors. In 1980s to 90s, Garland et al and Gorham et al conducted a number of epidemiologic studies and concluded that there was a strong negative correlation between latitude, sun exposure and poor vitamin D status and the risk of developing many deadly cancers like that of colon, breast, ovarian and melanoma. Age adjusted death rates among the patients of colon cancer have been found to be high in areas with low levels of winter sunlight. A study showed that the individuals with 25-hydroxyvitamin D level <30ng/mL had higher incidence of colonic adenomas. The association of 25-hydroxyvitamin D with risk of colon cancer was present both early and late in follow-up, suggesting that vitamin D metabolites may have effects at all stages of carcinogenesis. There are 7 epidemiological studies indicating the higher risk of colon cancer in individuals taking lower amounts of vitamin D including Western Electric Cohort Study, the Nurses' Health Study, the Male Health Professionals' Follow-Up Study, the Iowa Women's Health Study, and the American Cancer Society Cancer Prevention Study II (CPS II) Cohort Study and 2 case control study. There are also studies reporting that breast cancer death rates are higher in areas with low winter sunlight levels. Women who are exposed to sufficient sunlight on regular basis, seem to have significantly lower

incidence of breast cancer. Low levels of 25-hydroxy vitamin D may be attributed to faster progression of breast cancer. Moreover, mortality rates of perimenopausal ovarian cancer have also been found lower in sunny regions. The same effect can be seen in case of prostate cancer. In a study of 19000 men, those with levels of 25-hydroxyvitamin D <16ng/mL had a higher incidence of prostate cancer than those having more than this value. Although, there are few studies showing no association between vitamin D and cancer, making the topic controversial [12,13].

We know that vitamin D is involved in regulation of cellular proliferation and maturation. Nevertheless, the exact mechanism is not fully understood. A number of genes controlling proliferation, differentiation, apoptosis and angiogenesis, are directly or indirectly affected by vitamin D. The active form of the latter increases inhibitors and decreased activators of cyclin-cyclin dependent kinase complexes in addition to increasing levels of cyclin dependent kinase inhibitors Cip/Kip proteins P21 and P27. These proteins are known to keep the cell cycle in the G1/S phase, preventing DNA synthesis and so, the cell proliferation [12].

Vitamin D and autoimmune diseases

Vitamin D is known to have important immunomodulatory effects in body. Dendritic cells are primary targets for this activity of 1,25-dihydroxycholecalciferol, the active form of vitamin D. It is indicated by inhibited dendritic cells differentiation and maturation leading to down regulated expression of MHC-II, co-stimulatory molecules like CD40, CD80, CD86 and decreased production of IL-12. Besides these, 1,25-dihydroxycholecalciferol increases IL-10 production and thereby, promotes dendritic cell apoptosis. In this way, vitamin D inhibits dendritic cell dependent T-cell activation. Apart from these, vitamin D receptor agonists seem to inhibit pathogenic pro-inflammatory T-cells like Th1 and Th17 and under appropriate conditions they tend to favor a deviation to Th2 pathway [14].

These types of immunomodulatory and anti-inflammatory effects are particularly efficient for the rheumatoid arthritis patients to support a therapeutic role of 1,25-dihydroxycholecalciferol in this disease. From different studies, it is also seen that vitamin D may play an important role in maintenance of B-cell homeostasis and correction of vitamin D deficient state may affect the treatment of B-cell mediated autoimmune disorders such as systemic lupus erythematosus (SLE) [14].

Conclusion

It is obvious from the above discussion that vitamin D is important in the body to maintain physiologic homeostasis. Besides this, alteration of vitamin D status in the body, underlies different pathologic conditions. Therefore, vitamin D is gaining great interest in recent biomedical research works.

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