Vitamin D: Pathophysiology of its Deficiency

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Abstract: Current Perspective Vitamin D deficiency is now recognized as a pandemic. The major cause of Vitamin D deficiency is the lack of exposure to sunlight in modern life, very few foods contribute to Vitamin D and foods that are fortified with Vitamin D are hardly available in India (are inadequate to satisfy the daily requirement). Vitamin D deficiency causes rickets in children and will precipitate osteoporosis in adults. Vitamin D deficiency has been associated with increased risk of autoimmune disease, hypertension and infectious disease. Optimal serum 25(OH)D levels are greater than 32 ng/mL (80 nmol/L). The safest and the most economical way to ensure adequate Vitamin D status is to use oral formulation of Vitamin D. Recent data indicate that cholecalciferol (Vitamin D₃) is substantially potent than ergocalciferol (Vitamin D₂).

Vitamin D, a fat soluble vitamin, is required for the maintenance of adequate plasma levels of calcium and phosphorous to support the metabolic functions, bone mineralization and neuromuscular transmission. The deficiency of Vitamin D leads to bone disease known as rickets (in children whose epiphysis have not been closed), osteomalacia (in adults), and hypocalcemic tetany. Tetany is a convulsive state caused by an insufficient extracellular concentration of ionized calcium, which is required for normal neural excitation and the relaxation of muscles. Rickets was rampant at the end of the nineteenth century although cod liver oil was recognized for its anti-rachitic properties in the early part of that century, it took a long time for the medical professionals to accept it as an effective preventive agent. Over the time, role of Vitamin D had been recognized in autoimmune diseases, hypertension and other cardiovascular diseases, reproductive health, cancers, immunity, in response to infections in addition to its importance in bone density and fractures.

Pathophysiology of defect in vitamin D metabolism (with special reference vitamin D deficient states)

The major source of Vitamin D for humans is its endogenous synthesis from a precursor in skin 7-dehydrocholesterol in skin in presence of UV light in the range of 290 to 315 nm (UVM radiation). This leads to formation of cholecalciferol, known as D₃. Under normal conditions of sun exposure about 90% of the required Vitamin D is endogenously synthesized in the skin. Individuals with dark skin generally have a low level of Vitamin D production because of melanin pigmentation. Rich dietary sources are mainly deep sea fish and plants. Vitamin D is present in a precursor form as ergosterol which is converted to Vitamin D in the body.

Today we can be independent of sun for Vitamin D because of adequate dietary sources. In growing children 400 IU of Vitamin D per day and 100 IU per day in adults will prevent deficiency. Though vitamin D₃ is naturally found in butter, eggs, cod liver oil and some foods like bread and milk (400 IU per quart) are fortified with D₃ (ergocalciferol). This compound is easily manufactured by ultraviolet radiation of ergosterol from yeast and fungi. Vitamin D₂ and D₃ are essentially of equal potency and from this point the terms are used interchangeably.

VITAMIN D METABOLISM

The main steps of Vitamin D metabolism include firstly, there is photochemical synthesis of Vitamin D from 7-dehydrocholesterol in the skin and absorption of vitamin D from food supplements in the gut. Vitamin D from both these sources bind to plasma á₂, globulin (D-binding protein or DBP) and thus it gets transported to liver. In the liver there is conversion of Vitamin D into 25-hydroxycholecalciferol through the action of series of enzymes like CYP27A1 and other CYPs which are present in the liver. This is followed by conversion of 25-OH-D into 1,25-dihydroxyvitamin D, [1α, 25 (OH), D₃], the most active form of Vitamin D, by the action of the enzyme 1α-hydroxylase in the kidney. 1, 25 (OH), D₃ stimulates the expression of RANKL (Receptor activator of nuclear factor kappa B ligand), an important regulator of osteoclast maturation, and enhances the intestinal absorption of calcium and phosphorous.

MECHANISM OF PRODUCTION

There are three main mechanisms which regulate the production of 1,
25-dihydroxy Vitamin D in the kidney.

I. Hypocalcemia facilitates the parathyroid glands to secrete parathyroid hormone, which stimulates the 1-a-hydroxylase to synthesize 1, 25-(OH)2D3 and which in turn suppresses the alternate 25-hydroxylase pathway. 1, 25-(OH)2D3 increases intestinal calcium absorption and in concert with PTH, it enhances calcium reclamation in the kidney and mobilization of calcium from bone. As serum calcium normalizes, PTH falls and 25-hydroxylation of 25-OH-D3 is stimulated.

II. Hypophosphatemia directly stimulates the synthesis of 1, 25-(OH)2D3, which increase intestinal phosphate absorption and in the absence of PTH, enhances renal phosphate reabsorption through a feedback mechanism where increased levels of 1, 25-dihydroxyvitamin D downregulate its own synthesis through inhibition of 1-a-hydroxylase activity.

III. Steroid Mode of Action: Vitamin D, 1,25-(OH)2D3, structurally resembles other steroid hormones with its complex ring structure separating key hydroxyl groups. In the intestine, 1, 25-(OH)2D3 enters the intestinal cell and binds to a specific cytosol receptor. This hormone–receptor complex migrates to the nucleus where it interacts with nuclear chromatin, activates the expression of a part of deoxyribonucleic acid (DNA) and directs the synthesis of a new calcium binding protein which is known to participate in the intestinal uptake of calcium.

The main effects of Vitamin D on calcium and phosphorus homeostasis

STIMULATION OF INTESTINAL CALCIUM ABSORPTION

This is carried out in the duodenum through the interaction of 1, 25-dihydroxy vitamin D with nuclear vitamin D receptor. This leads to the formation of a complex with RXR (Retinoid X receptor). This complex activates the transcription of TR PV 6 (a member of the transient receptor potential vanilloid family) which encodes a critical calcium transport channel.

STIMULATION OF CALCIUM REABSORPTION IN THE KIDNEY

1, 25-dihydroxy vitamin D increases calcium influx in distal tubules of the kidney through the increased expression of TR PV5, which is also regulated by PTH in response to hypocalcemia.

ROLE OF PTH IN REGULATING BLOOD CALCIUM

An important role of Vitamin D is that it maintains calcium and phosphorus at supersaturated levels in the plasma. It is known that the parathyroid gland play an important role in the regulation of extracellular calcium concentrations. The calcium receptors which are present in the parathyroid gland sense the smallest changes in blood calcium concentrations. PTH and 1, 25-dihydroxy vitamin D enhances the expression of RANKL on osteoblasts. RANK (receptor activator of Nuclear Factor Kappa B) binds to its receptor (RANKL) which is located in preosteoclasts. This leads to the differentiation of preosteoclasts into mature osteoclasts. There is secretion of hydrochloric acid and activation of proteases which act on the osteoclasts, which in turn dissolve bone and release calcium and phosphorus into the circulation.

BONE MINERALIZATION

Vitamin D stimulates osteoblasts to synthesize the calcium–binding protein, osteocalcin which is involved in the deposition of calcium during bone development. (Figure 1).

CONSEQUENCES OF VITAMIN D DEFICIENCY

Osteomalacia is seen which is due to inadequate concentration of calcium and phosphate at mineralization site. Also hypocalcemia and negative calcium balance secondary to intestinal malabsorption is present. There is secondary hyperparathyroidism with hypophosphatemia. Proximal muscle weakness may be seen secondary to elevated PTH, hypophosphatemia or lack of direct effect of Vitamin D. Long standing deficiency causes bone under mineralization and softening which leads to skeletal deformities. Associated laboratory findings depend on the stage of disease. In stage-I, there are slightly low levels of 25-OH-D3, low serum calcium, normal serum phosphorous and elevated PTH (mild rickets). In stage-II, the 25-OH-D3 levels are moderately low, and PTH returns serum calcium to normal through stimulation of 1, 25-(OH)2D3 formation, but increases renal phosphate excretion. As serum calcium levels return to normal, the PTH levels fall (mild rickets). In stage-III there is very low 25-OH-D3, levels and low 1,25-(OH)2D3, levels, intestinal calcium malabsorption and bone resistance to PTH, hypocalcemia, hypophosphatemia and elevated PTH (severe rickets). Elevation of bone alkaline phosphatase and low urinary calcium may also be found.

NON-SKELETAL EFFECTS OF VITAMIN D

Vitamin D receptor is present in various cells and tissues which do not participate in calcium and phosphorous homeostasis. Also macrophages, keratinocytes and various tissues like colon, breast and prostate can produce 1, 25-dihydroxy vitamin D. It is believed that the toll like receptors in macrophages lead to increased expression of vitamin D receptor and CYP27 B, this leads to local synthesis of 1, 25-dihydroxy vitamin D and activation of vitamin D dependent gene expression in macrophages and other neighboring immune cells.

In a recent study in patients with tuberculosis, it has been shown that vitamin D supplements leads to an increase in lymphocyte counts, also altered circulating levels of multiple cytokines and chemokines, which in turn leads to the clearance of mycobacterium tuberculosis from the sputum. It has also been reported that low levels of 1, 25-dihydroxy vitamin D (< 20 ng/ml) are associated with a 30 % to 50 % increase in the incidence of colon, prostate and breast cancers. The risk of common cancers has been shown to be reduced in the presence of normal 25-hydroxy vitamin D levels, this is probably due to production of 1, 25-dihydroxy vitamin D in almost all tissues, maintaining normal cell proliferation and differentiation. The effect of Vitamin D on the reduction of type 2 diabetes is thought to be due to 1, 25-dihydroxy vitamin D (produced in the kidneys) entering the circulation and producing an effect on renal rennin production and stimulating insulin secretion in the pancreas.

REFERENCES