Vitamin D

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Over 1 billion people worldwide have low vitamin D levels, which appears to constitute an actual "pandemic" of hypovitaminosis D, with a myriad of health consequences. Antirachitic effects of Vitamin D were identified in the 1920s. This sunshine vitamin was for many years only seen in relation to its function in calcium and bone metabolism. As Vitamin A, B and C, which had been discovered earlier, the vitamin found in cod liver oil was, nominated as "D".

More recently, it has become clear that bioactive vitamin D or calcitriol is a steroid hormone. It has long been known for its important role in regulating body levels of calcium and phosphorus, and in mineralization of bone. But now it has become clear that receptors for vitamin D are present in a wide variety of cells, and that this hormone has biologic effects which extend far beyond control of mineral metabolism.

Homeostasis

Humans derive vitamin D from

- Ultraviolet B sunlight exposure >90% of humankind's vitamin D supply is derived from ultraviolet B light
- Oily fish including trout, salmon, mackerel, herring, • sardines, anchovies, pilchards, and fresh tuna Amount will depend on preparation, with smoked herring containing approximately 4 µg (160 IU) per 100 g and raw herring 40 µg (1600 IU) per 100 g
- Cod liver oil and other fish oils
- Egg yolk 0.5 µg (20 IU) per yolk)
- Mushrooms Small quantities

Cholecalciferol or vitamin D3	Ergocalciferol or vitamin D2	Calcifediol or calcidiol or 25-hydroxyvitamin-D3 or 25(OH)D3	Calcitriol or 1,25-dihydroxyvitamin-D3 or 1,25(2OH)D3
Present in foods of animal origin and vitamin supplements	Present in liver oil of cod and other fish (salmon, mackerel and herring), as well as vegetables sources and mushrooms	Form usually measured in the human body, has a half-life of two to three weeks	Active form in the human body, has a half-life of four hours, and can be measured in specific clinical conditions

Risk factors for vitamin D insufficiency and deficiency

- Pigmented skin (non-white ethnicity)
- Lack of sunlight exposure or atmospheric pollution
- Skin concealing garments or strict sunscreen use
- Exclusively breast fed
- Multiple, short interval pregnancies
- Elderly, obese, or institutionalised
- Vegetarian (or other non-fish eating) diet
- Malabsorption, short bowel, or cholestatic liver disease
- Use of anticonvulsants, rifampicin, cholestyramine, highly active antiretroviral treatment (HAART), or glucocorticoids

Vitamin D—formation

7-dehydrocholesterol of skin reacts to uv rays of sunlight

Leads to formation of pre-vitamin D3

Pre vitamin D3 converted to vitamin D3 in a heat-dependent process. [cholecalciferol]

Liver converts vitamin D3 into 25-hydroxyvitamin D (25OH D) or calcidol z

25(OH)D is converted by kidneyinto active vitamin D hormone [1α,25(OH)2D]

On exposure to ultra violet B radiation (UVB), 7-dehydrocholesterol in the skin is converted to pre-vitamin D3, which is immediately converted to vitamin D3 in a heat-dependent process.

Vitamin D3 can be ingested in the form of diet by consuming fish and meat.

Once vitamin D enters the circulation it is rapidly converted to 25-hydroxy vitamin D3 by liver.

25(OH)D is converted in the kidney by 25(OH)D-1ahydroxylase (CYP27B1), to its bioactive hormonal metabolite 1,25 dihydroxy-vitamin D (1,25(OH)2D or calcitriol). It is the most potent form of vitamin D. Most of the physiological effects of vitamin D in the body are related to the activity of 1,25-dihydroxyvitamin D.

The Vitamin D Receptor and Mechanism of Action

The **calcitriol receptor**, also known as the vitamin D receptor (**VDR**) and also known as **NR1I1** (nuclear receptor subfamily 1, group I, member 1), is a member of the nuclear receptor family of transcription factors.

- The active form of vitamin D binds to intracellular receptors. This also functions as transcription factors to modulate gene expression.
- The vitamin D receptor has hormone-binding and DNA-binding domains like the receptor of other steroid hormones.
- 1,25-dihydroxyvitamin D on entering the nucleus of a cell, associates with the VDR and promotes its association with the retinoic acid X receptor (RXR).
- The VDR/RXR complex binds small sequences of DNA known as vitamin D response elements (VDREs) and initiates a cascade of molecular interactions that modulate the transcription of specific genes.
- In most cases the effect is to activate transcription, but situations are also known in which vitamin D suppresses transcription.
- The vitamin D receptor binds several forms of cholecalciferol. Its affinity for 1,25-ihydroxycholecalciferol is roughly 1000 times that for 25-hydroxycholecalciferol, which explains their relative biological potencies.

Functions of Vitamin D

Calcium Balance

Serum calcium levels maintenance within a narrow range is vital for normal functioning of the nervous system, as well as for bone growth and maintenance of bone density. Vitamin D is essential for the efficient utilization of calcium by the body. The activation of parathyroid gland take place by low serum calcium levels and it secrete parathyroid hormone (PTH). Elevations in PTH increase the activity of the 25-hydroxyvitamin D_3-1-hydroxylase enzyme in the kidney, resulting in increased production of 1,25-dihydroxyvitamin D. Increasing 1,25-dihydroxyvitamin D production results in changes in gene expression that normalize serum calcium by

(1) Increasing the intestinal absorption of dietary calcium,

(2) Increasing the reabsorption of calcium filtered by the kidneys, and

(3) Mobilizing calcium from bone when there is insufficient dietary calcium to maintain normal serum calcium levels. Parathyroid hormone and 1,25-dihydroxyvitamin D are required for these latter two effects.

Cell Differentiation

Rapid division of cell s is proliferation. Differentiation of cells is specialization of cells for specific functions. In general, differentiation of cells leads to a decrease in proliferation. Cellular proliferation is essential for growth and wound healing but uncontrolled proliferation of cells with certain mutation may lead to diseases like cancer. The active form of vitamin D, 1,25-dihydroxyvitamin D, inhibits proliferation and stimulates the differentiation of cells.

Immunity

Vitamin D in the form of 1,25-dihydroxyvitamin D is a potent immune system modulator. The vitamin D receptor (VDR) is expressed by most cells of the immune system, including T cells and antigen-presenting cells, such as dendritic cells and macrophages. There is considerable scientific evidence that 1,25-dihydroxyvitamin D has a variety of effects on immune system function, which may enhance innate immunity and inhibit the development of autoimmune disease.

There is increasing evidence that the incidence and severity of autoimmune diseases, including rheumatoid arthritis, type 1 diabetes, inflammatory bowel disease, and Multiple Sclerosis may be reduced by increasing vitamin D levels from.

The placenta regulates communication and transport between mother and fetus during pregnancy. For allowing proper trophoblast invasion of the uterus the immunosuppressive effects of 1,25(OH)2D3 are crucial. Impaired vitamin D status may also lead to aberrant response to infection.

Vitamin D and Diabetes and Insulin Secretion

The VDR is also expressed by insulin -secreting beta cells of the pancreas. The results of animal studies suggest that 1,25-dihydroxyvitamin D plays a role in insulin secretion under conditions of increased insulin demand.
From the Recent studies in animal models and humans following association of vitamin D and diabetes is observed.

- Vitamin D may also play a role in the homeostasis of glucose metabolism and the development of type 1 and type 2 diabetes mellitus (DM).
- In some populations the development of type 1 DM is associated with polymorphisms in the vitamin D receptor gene.
- There is also some evidence that increased vitamin D intake by infants may reduce the risk of the development of type 1 DM.
- Vitamin D has recently been associated with several of the contributing factors known to be linked to the development of type 2 DM, including defects in pancreatic cell function, insulin sensitivity, and systemic inflammation.
- Several physiologic mechanisms have been proposed, including the effect of vitamin D on insulin secretion, the direct effect of calcium and vitamin D on insulin action, and the role of this hormone in cytokine regulation.

Blood Pressure Regulation

The renin-angiotensin system plays an important role in the regulation of blood pressure. Renin is catalyzes the cleavage angiotensinogen to produce a small peptide Angiotensin I.Angiotensin converting enzyme (ACE) catalyzes the cleavage of angiotensin I to form angiotensin II, a peptide that can increase blood pressure by inducing the constriction of small arteries and by increasing sodium and water retention. The rate of angiotensin II synthesis is dependent on renin. Research in mice lacking the gene encoding the VDR indicates that 1,25-dihydroxyvitamin D decreases the expression of the gene encoding renin through its interaction with the VDR . Since inappropriate activation of the renin-angiotensin system is thought to play a role in some forms of human hypertension, adequate vitamin D levels may be important for decreasing the risk of high blood pressure.

Deficiency
In vitamin D deficiency, calcium absorption cannot be increased enough to satisfy the body's calcium needs. Consequently, PTH production by the parathyroid glands is increased and calcium is mobilized from the skeleton to maintain normal serum calcium levels—a condition known as secondary hyperparathyroidism. Although it has long been known that severe vitamin D deficiency has serious consequences for bone health, recent research suggests that less obvious states of vitamin D deficiency are common and increase the risk of osteoporosis and other health problems .
Severe Vitamin D Deficiency
Rickets
In infants and children, severe vitamin D deficiency results in the failure of bone to mineralize. Rapidly growing bones are most severely affected by rickets. The growth plates of bones continue to enlarge,

but in the absence of adequate mineralization, weight-bearing limbs (arms and legs) become bowed. In infants, rickets may result in delayed closure of the fontanels (soft spots) in the skull, and the rib cage may become deformed due to the

Vitamin D and Cardiovascular Disease

Vitamin D receptors are present in vascular smooth muscle, endothelium, and cardiomyocytes and may have an impact on cardiovascular disease. Observational studies have shown a relationship between low vitamin D levels and blood pressure, coronary artery calcification, and existing cardiovascular disease.

- Vitamin D deficiency activates the renin-angiotensin-aldosterone system, which can lead to systemic arterial hypertension (SAH) and left ventricular (LV) hypertrophy.
- Another consequence of deficiency is the increase in PTH, which leads to increased insulin resistance, diabetes mellitus type 2, SAH, and inflammation.
- Vitamin D inhibits the proliferation of cardiomyoblasts by promoting cell cycle arrest, and increases cardiomyotubule formation, without inducing apoptosis.
- It has also been observed that vitamin D attenuates LV dysfunction in animal models and humans.

Vitamin D and Osteoporosis It is a multifactorial disease; vitamin D insufficiency can be an important contributing factor. Intestinal calcium absorption cannot be maximized without adequate vitamin D. This triggers PTH secretion by the parathyroid glands. The elevated PTH results in increased resorption of bone, which may lead to osteoporotic fracture.

(1) It is the only hormone known to induce the proteins involved in active intestinal calcium absorption. Furthermore, it stimulates active intestinal absorption of phosphate.
(2) In the absence of intestinal calcium absorption two mechanisms play a role in increasing blood calcium concentrations. Vitamin D hormone stimulates osteoblasts to produce receptor activator nuclear factor-κB ligand (RANKL). RANKL then stimulates osteoclastogenesis and activates resting osteoclasts for bone resorption. Therefore, the vitamin D hormone plays an important role in mobilizing calcium from bone when it is absent from the diet. However, in vivo both vitamin D and parathyroid hormone are required for this mobilization event.
(3) The distal renal tubule is responsible for reabsorption of the last 1% of the filtered load of calcium. here also both vitamin D and PTH interact to stimulate the reabsorption of this last 1% of the filtered load. Because 7 g of calcium are filtered every day among humans, this represents a major contribution to the calcium pool.

Osteoporosis is the most common metabolic bone disease in the world. A low vitamin D level is an established risk factor for osteoporosis. Inadequate serum vitamin D levels will decrease the active transcellular absorption of calcium. Although combination calcium and vitamin D supplementation is associated with higher bone mineral density and decreased incidence of hip fractures, the evidence for vitamin D supplementation alone is less clear. A recent evidence summary found that vitamin D supplementation at doses of more than 700 IU daily (plus calcium) prevented bone loss compared with placebo. However, vitamin D supplementation (300 to 400 IU daily) without calcium did not affect fractures

Vitamin D and Chronic Pain: Because of the important role vitamin D plays in bone homeostasis, it is only logical to think that vitamin D deficiency may correlate with chronic pain syndromes, including chronic low back pain. Most of the times Vitamin D deficiency occurs without any symptoms, if at all any

symptoms present it indicates severe deficiency (<5ng/ml). Severe vitamin D deficiency leads to osteomalacic myopathy, as characterized in a case series demonstrating severe myalgia and muscle weakness in individuals with low serum concentration of vitamin D, with prompt resolution of symptoms following vitamin D replacement.

Vitamin D and Falls among the Elderly

Vitamin D status is increasingly recognized as an important factor in fall status among elderly patients. The possible association between falls and vitamin D deficiency is based on some findings:

- There are receptors for 1,25(2OH)D3 in muscles25,26;
- Vitamin D is associated with muscle protein synthesis27,28;
- and some studies demonstrated that vitamin D improves muscle function and may reduce falls, especially when associated with calcium.29,30

There are also studies that show that PTH induces muscle catabolism, that is, when there is vitamin D deficiency, the increase in this hormone would damage muscle. Another hypothesis is decreased reflexes in individuals with vitamin D deficiency, explaining falls regardless of muscle injury.

Vitamin D and Cancer

Both observational studies in humans and animal models support that vitamin D has a beneficial role in cancer prevention and survival. The mechanism of action is probably related to its role in the regulation of cell growth and differentiation.23

Vitamin D status should be monitored in all cancer patients and treated by adequate vitamin D supplementation [25(OH)D target value: 40–60 ng/mL or 100–150 nmol/L). This applies in particular to cancer patients with poor nutritional status, treatment with aromatase inhibitors, bisphosphonates, and CTX containing anthracycline taxane as well as in cases of muscular or mucocutaneous disorders, fatigue and tumor cachexia.

Neurology and Vitamin D

- activates receptors on neurons in regions implicated in the regulation of behaviour,
- stimulates neurotrophin release,
- and protects the brain by buffering anti-oxidant and anti-inflammatory defence against vascular injury.

  There is growing evidence for a relationship between vitamin D receptors in the brain, hypovitaminosis D and abnormal cognitive executive functions, major depression bipolar disorder, and schizophrenia.[17] Hypovitaminosis D has previously been connected to the autoimmune effects of multiple sclerosis.[13]

DEFINITION OF VITAMIN D DEFICIENCY

Recently, the Institute of Medicine (IOM) and the Endocrine Society released separate guidelines for vitamin D requirements.

The revised guidelines by the IOM stress that the daily requirements for vitamin D are generally met by most of the population and are appropriate to reach the “sufficient” level of 20 ng/mL (to convert to nmol/L, multiply by 2.496). The IOM guidelines used a population model to prevent vitamin D deficiency in 97.5% of the general population. Also, note that the IOM report focuses only on bone health (calcium absorption, bone mineral density, and osteomalacia/rickets) and found no evidence that a serum 25(OH)D concentration greater than 20 ng/mL had beneficial effects at a population level. However, considering the available evidence on skeletal and extraskeletal effects of vitamin D, the few negative studies, and the lack of toxicity potential of vitamin D supplementation at

VITAMIN D STATUS IN RELATION TO 25 (OH) D LEVELS

US IOM classification

- Severe deficiency <5 ng/mL
- Deficiency <15 ng/mL
- Sufficiency >20 ng/mL
- Risk of toxicity >50 ng/mL

US Endocrine Society classification

- Deficiency <20 ng/mL (50 nmol/L)
- Insufficiency 21-29 ng/mL (52.5–72.5) nmol/liter
- Sufficiency >30 ng/mL
- Toxicity >150 ng/mL

Laboratory investigations rickets

Alkaline phosphatase: It is a marker of disease activity. In X-linked hypophosphatemic rickets (XLH), the serum alkaline phosphatase activity is moderately elevated (400-800 international units per liter (IU/L)) whereas in calcipenic rickets, values often reach greater levels (>1,500IU/L).

Serum calcium: is usually decreased in calcipenic rickets (nutritional, vitamin D dependent rickets (VDDR) or renal tubular acidosis (RTA) and renal failure rickets), while it is normal in phosphopenic rickets.

Serum phosphorus concentration: usually are low in both calcipenic and phosphopenic rickets. The total reabsorption of phosphorus (TRP) and the maximal tubular reabsorption of phosphorus per glomerular filtration rate (TmP/GFR) usually are decreased in both calcipenic and phosphopenic rickets, but decrease is severe in renal phosphate wasting type of rickets. These values are quite elevated in the setting of nutritional phosphate deprivation. In rickets due to renal failure there is high serum phosphorus.

Serum creatinine: Elevated in renal failure rickets.

Arterial blood gas (ABG): In rickets due to RTA there is normal anion gap (hyperchloremic metabolic acidosis. In renal failure rickets there is high anion gap metabolic acidosis. In all other varieties the ABG is normal.

Urine pH is >5.5 in distal RTA (DRTA) while it is <5.5 in proximal RTA (PRTA). Acid load test are the other tests done in RTA (discussed below).

A generalized aminoaciduria occurs from hyperparathyroidism. However, aminoaciduria does not occur in XLH.

Glycosuria and bicarbonaturia is seen in Fanconi's syndrome.

Serum concentration of parathyroid hormone (PTH): is elevated in calcipenic rickets. In contrast, PTH concentrations are usually normal or modestly elevated in phosphopenic rickets. Elevated PTH levels may also be seen in X-linked hypophosphatemia (XLH). Therefore, if calcipenic rickets is diagnosed, it is mandatory to observe appropriate healing during therapy, and if predicted response does not occur, XLH should be considered.

Serum concentrations of 25-hydroxyvitamin D (25OHD) and 1,25-dihydroxyvitamin D ($1,25(OH)_2$ D)-25 OHD reflects body's vitamin D stores, and consequently, is low in nutritional rickets due to vitamin D deficiency; but it may be normal if there is associated calcium deficiency. In extremely severe liver disease or in intestinal disorders such as celiac disease, vitamin D levels may be low due to defective absorption or metabolism. Anticonvulsants may interfere with vitamin D metabolism leading to low levels. In type I VDDR 25OHD levels are high while $1,25(OH)_2$ D levels are low while in type II VDDR, 25OHD levels are normal and $1,25(OH)_2$ D levels are high. In some forms of phosphopenic rickets (XLH, tumor-induced osteomalacia (TIO)), serum concentrations of $1,25(OH)_2$ D may be low or inappropriately normal (despite hypophosphatemia). In other forms of phosphopenic rickets (hereditary hypophosphatemic rickets with hypercalcuria (HHRH)), the serum concentration of $1,25(OH)_2$ D may be elevated.

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ARTICLE HIGHLIGHTS

- **Vitamin D deficiency is a common underdiagnosed condition.**
- Recent evidence from hundreds of studies suggests that vitamin D is important for reducing the risk of type 1 diabetes mellitus, cardiovascular disease, certain cancers, cognitive decline, depression, pregnancy complications, autoimmunity, allergy, and even frailty.
- The blood level of 25(OH)D is the best method to determine vitamin D status.
- Vitamin D deficiency during pregnancy may influence fetal “imprinting” that may affect chronic disease susceptibility soon after birth as well as later in life.
- An effective strategy to prevent vitamin D deficiency and insufficiency is to obtain some sensible sun exposure, ingest foods that contain vitamin D, and take a vitamin D supplement.