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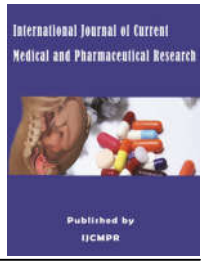

VITAMIN D DEFICIENCY AND ITS ASSOCIATED DISEASES: A CONCISE REVIEW

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ABSTRACT

Vitamin D is a fat-soluble vitamin that act as a hormone precursor that regulates calcium absorption and, in conjunction with the parathyroid hormone, bone mineralization. Vitamin D insufficiency leads to reduced bone mass, which can be manifested as the debilitating diseases of osteoporosis and osteomalacia in adults and rickets in children. Vitamin D deficiency is defined as 25-hydroxy vitamin D serum concentrations below 30 ng/ml. In this review article we tried to shed some light on how vitamin D is synthesized in human body and how vitamin D has connection with not just skeletal diseases but with various autoimmune diseases, metabolic disorders, neurological disorders.

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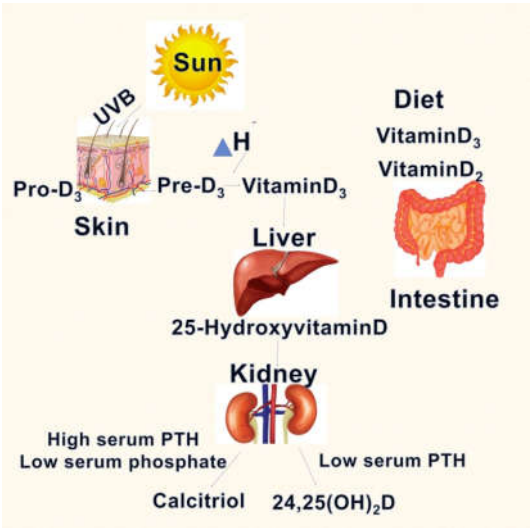
INTRODUCTION

Vitamin D is a fat-soluble vitamin that act as a hormone precursor that regulates calcium absorption and, in conjunction with the parathyroid hormone, bone mineralization. Vitamin D insufficiency leads to reduced bone mass, which can be manifested as the debilitating diseases of osteoporosis and osteomalacia in adults and rickets in children (1). Vitamin D is present in 2 forms (Ergocalciferol or vitamin D2, Cholecalciferol or vitamin D3. Ergocalciferol, or vitamin D2, is present in plants and some fish. Cholecalciferol, or vitamin D3, is synthesized in the skin by sunlight. Humans can fulfill their vitamin D requirements by either ingesting vitamin D through a few dietary sources; primarily fatty fish, cod-liver oil, pork-liver, egg and fortified margarine and butter or being exposed to the sun for enough time to produce adequate amounts (2). It is formed endogenously by the skin after exposure to ultraviolet radiation B (UVR-B) light (wavelength 290–315 nm). In the skin, a plateau of daily vitamin D production is reached after only 30 min of UVR-B irradiation (3). Vitamin D synthesis is highly dependent on the concentration of melanin in the skin (skin tone) , duration of exposure and location as well as surface and atmospheric conditions (4). Vitamin D deficiency is defined as 25- hydroxy vitamin D serum concentrations below 30 ng/ml (5).

Physiology behind Vitamin D



Vitamin D is synthesized in the human body by following metabolic pathway shown in the **Fig. 1**

Fig. 1. The major metabolic pathways of vitamin D. Human sources of vitamin D are skin production of vitamin D3 by UVR-B and oral intake of vitamin D2 and/or vitamin D3. Vitamin D is hydroxylated in the liver into 25-hydroxyvitamin D and in the kidney into the vitamin D hormone (calcitriol). Renal calcitriol synthesis includes activation of 1a-hydroxylase by parathyroid hormone and suppression of the 1a-hydroxylase by high serum levels of ionized Ca. PTH; parathyroid

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hormone; 24,25(OH)2D, 24,25-dihydroxyvitamin D (6).When the human skin comes in contact with the UVR-B the Provitamin D3 (Pro-D3) or 7-dehydrocholesterol (7-DHC) which is present in the human skin is converted to previtamin D3 (Pre-D3) which is then converted into vitamin D3 in a process independently ultraviolet light which thermally isomerizes it into vitamin D3 (Cholecalciferol) and the vitamin D2 (ergocalciferol) taken from the dietary source (7). Both are absorbed via the lymphatic system as part of chylomicrons, which are metabolized to remnant particles that then transport vitamin D to the liver with the help of vitamin D binding protein (DBP) which then metabolises vitamin D into 25-Hydroxyvitamin D (25(0H)D) by the enzyme 25-hydroxylase in the liver (8). la-Hydroxylase (la-OHase) then converts 25(0H)D to the active form of vitamin D, Calcitriol (1,25-dihydroxy vitamin D [l,25(0H)2 D]) in renal tissues. l,25(0H)2D can depress the activity of la-OHase, and the parathyroid hormone (PTH) can stimulate this activity, Calcitrol (1,25 [OH]2D) binds with high affinity to vitamin D receptors (VDRs) (9). The other form compound formed hydroxylations in the body is known as Calcidiol (25-hydroxyvitamin D3). This activated form of vitamin D then binds to vitamin D receptors located throughout the body and that lead to its biologic action (10). Calcitriol (1,25-dihydroxy vitamin D3), the active form of vitamin D, has a half-life of about 15 hours, while calcidiol (25-hydroxyvitamin D3) has a half-life of about 15 days (11).

Adequate Intake of Vitamin D

Recognition of the high incidence of inadequate vitamin D status and reports of the association of low vitamin D status with increased risk of a wide range of diseases has prompted many medical practitioners to recommend vitamin D supplements for their patients (12).

Table 1 Vitamin D Dietary Reference Intakes (DRIs) for Adequacy (amount/day)

Life Stage Group	AI	EAR	RDA
Infants			
0 to 6 months	400 IU (10 µg)	—	—
6 to 12 months	400 IU (10 µg)	—	—
Children			
1–3 y	—	400 IU (10 µg)	600 IU (15 µg)
	—	400 IU (10 µg)	600 IU (15 µg)
Males			
9–13 y	—	400 IU (10 µg)	600 IU (15 µg)
14–18 y	—	400 IU (10 µg)	600 IU (15 µg)
19–30 y	—	400 IU (10 µg)	600 IU (15 µg)
31–50 y	—	400 IU (10 µg)	600 IU (15 µg)
51–70 y	—	400 IU (10 µg)	600 IU (15 µg)
> 70 y	—	400 IU (10 µg)	800 IU (20 µg)
Females			
9–13 y	—	400 IU (10 µg)	600 IU (15 µg)
14–18 y	—	400 IU (10 µg)	600 IU (15 µg)
19–30 y	—	400 IU (10 µg)	600 IU (15 µg)
31–50 y	—	400 IU (10 µg)	600 IU (15 µg)
51–70 y	—	400 IU (10 µg)	600 IU (15 µg)
> 70 y	—	400 IU (10 µg)	800 IU (20 µg)
Pregnancy			
14–18 y	—	400 IU (10 µg)	600 IU (15 µg)
19–30 y	—	400 IU (10 µg)	600 IU (15 µg)
31–50 y	—	400 IU (10 µg)	600 IU (15 µg)
Lactation			
14–18 y	—	400 IU (10 µg)	600 IU (15 µg)
19–30 y	—	400 IU (10 µg)	600 IU (15 µg)
31–50 y	—	400 IU (10 µg)	600 IU (15 µg)

NOTE: AI = Adequate Intake; EAR = Estimated Average Requirement; IU = International Unit; RDA = Recommended Dietary Allowance
SOURCE: Reference (13).

There is high confusion regarding the optimum intake of vitamin D because inadequate intake of vitamin D will lead to various skeletal diseases and high intake can lead to hypervitaminosis D. A more comprehensive dietary reference intake (DRIs) for adequacy is given in the (Fig. 2)

DISCUSSION

Vitamin D and Osteoporosis

Osteoporosis is a systemic skeletal disease characterized by low bone mass, microarchitectural deterioration of bone tissue leading to enhanced bone fragility, and a consequent increase in fracture risk (14). It is a well-established fact that vitamin D deficiency is a factor in the multifactorial causes with are associated, suboptimal bone growth in childhood and adolescence, calcium malabsorption and resultant secondary hyperparathyroidism that enhance age-related bone loss and reduced osteoblast formation that leads to Osteoporosis (15)(16)(17). Osteoporosis is diagnosed on the basis of T-score ≤−2.5 which reflects the bone mineral density (BMD) of a young adult if T-scores equal to or below −2.5 are considered as clear indications for osteoporosis therapy. T-score between −2.5 and −1 is considered as osteopenia (18). Low sunshine exposure and low vitamin D intake leads to low serum 25-hydroxyvitamin D which then leads to low serum Calcitriol (1,25-dihydroxy vitamin D [l,25(0H)2 D]) also decreased renal function can also cause low serum Calcitriol (1,25-dihydroxy vitamin D [l,25(0H)2 D]) due to this Hyperparathyroidism occurs that causes high turnover bone reabsorption (bone loss) which results in osteoporosis (19). Because of low bone mineral density (T-score between −2.5 and −1), first osteopenia is developed which later results in osteoporosis (T-scores equal to or below −2.5).

Vitamin D and Osteomalacia/Rickets

Osteomalacia is a distinctive disorder of adults with bone pain and muscle weakness. It is characterized histologically by broad seams of the uncalcified bone matrix in sections of trabecular bone (20). Osteomalacia is a disorder of mature (adult) bone, whereas rickets occurs in growing bone. In individuals with rickets, defective mineralization occurs in both bones and cartilage of the epiphyseal growth plates and is associated with defects in growth, shaping (modelling) and turnover (remodelling) of bone in accordance with metabolic, structural and repair requirements, and patients exhibit short stature (physical disturbances), growth retardation and skeletal deformities that are not typically seen in adults with osteomalacia (21)(22). It is a well-established fact that Osteomalacia and Rickets are caused by the deficiency of Primary (‘nutritional') vitamin D and Secondary vitamin D deficiency due to malabsorption and also due to other causes such as Genetic factors (22)(23)(24). However they both are developed via a similar pathway, Low sunshine exposure and low Vitamin D intake leads to low serum 25-hydroxy vitamin D which then leads to low serum Calcitriol (1,25-dihydroxy vitamin D [l,25(0H)2 D]) also decreased renal function can also cause low serum Calcitriol (1,25-dihydroxy vitamin D [l,25(0H)2 D]) due to this their is marked decrease in Calcium absorption that causes mineral deficit hyperosteoidosis which results in Osteomalacia(19) while on the other hand in the vitamin D-dependent rickets type I an enzyme a-hydroxylase does not functions properly, causing very low serum levels of Calcitriol (1,25-dihydroxy vitamin D [l,25(0H)2 D] and vitamin D-dependent rickets type II or hereditary vitamin D

resistant rickets do not have a functioning vitamin D receptor (VDRs) leading to the vitamin D deficiency (24).

Vitamin D and Sarcopenia

The term Sarcopenia (Greek, sarx for:"flesh" and penia for "loss") refers to the phenomenon of reduction of both muscle mass and function with aging (25). However many factors are associated with the reduction of both muscle mass and aging but vitamin D deficiency is widely thought to also play a major role in this (26)(27)(28)(29). Sarcopenia is one of the geriatric syndromes that increases with the age and how vitamin D plays a role in this can be understood by that the vitamin D regulates the calcium-mediated functions of muscle, such as contraction, mitochondrial function and insulin sensitivity and also its morphology and vitamin D Receptor (VDRs) expression in human muscle tissue decreases with age (28)(30) this leads to lack of the substrate 25-hydroxyvitamin D for the formation of Calcitriol (1,25-dihydroxyvitamin D [l,25(0H)2 D]) that may contribute to decreased calcium absorption and other actions of Calcitriol (1,25-dihydroxyvitamin D [l,25(0H)2 D]) (31) Cacitriol regulates the skeletol muscle calcium uptake by modulating the activity of calcium pumps in sarcoplasmic reticulum and sarcolemma, Its low levels affects the proper functioning of the skeletal muscles (32) as well as impairment of glucose tolerance (33). Reduced expression of VDR and 1- alpha-hydroxylase results in increased concentrations of IL-6 and TNF-α, which inhibit muscle protein synthesis and leads to skeletal muscle apoptosis (33). Lack of Calcitriol leads to high level of Parathyroid hormone (PTH), a high concentration of PTH causes hypophosphatemia which also leads to muscle weakness this has been found in vitamin D deficient mouse (34). Most of the studies have found vitamin D supplementation beneficial in the prevention of muscle weakness, improvement in muscle strength, physical performance as well (35) (36) (32) (33).

Vitamin D and Multiple Sclerosis

Multiple sclerosis (MS) is an autoimmune disease which is characterized by neurological and cognitive manifestations including visual impairment, tremors, sensory disturbance, ataxia, and sexual dysfunction in young adults (37)(38). Most patients experience bouts of inflammatory demyelination (relapsing-remitting MS) followed years later by treatment-resistant disease progression and brain atrophy (39). In a study, it was found out that among patients with MS treated with interferon beta-1b, higher 25(OH)D levels were associated with lower rates of MS activity (40). Epidemiological data support a potential relationship between vitamin D deficiency and an increased risk of developing MS and its progression (41–43). For individuals predisposed to MS, evidence indicates that maintenance of adequate vitamin D has a protective effect.(44). Both 25(OH)D and 1,25(OH)2D are involved in the regulation of the immune system and have an immunomodulatory effect (45). Due to deficiency of vitamin D and signals delivered through the vitamin D receptor (VDRs), actions through autoreactive T-cells manifest, especially in the presence of insufficient 1,25(OH)2D concentrations and vitamin D receptor activity. Once bound to VDR in immune cells, vitamin D acts as a selective immunosuppressant (46) and decreases the severity of autoimmune diseases, when vitamin D is sufficient, the T-cell response is restored and autoimmunity minimized (47).

Vitamin D and Type 1, type 2 diabetes mellitus

Type 1 diabetes mellitus (T1DM) is a chronic disease of multi-factorial nature resulting from progressive autoimmune destruction of pancreatic islet cells at the early stages of disease (48). Type 2 diabetes mellitus is characterized by insulin resistance and altered insulin secretion, although its precise aetiopathogenesis is unknown. Recent studies in rodent models and humans have suggested that 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) and also that the vitamin D is a potential modifier of diabetes risk (48–53). Vitamin D enhances insulin sensitivity by stimulating the expression of insulin receptors and by activating peroxisome proliferator-activated receptor-δ (PPAR- δ) that results in the rise of intracellular calcium concentration via non-selective voltage-dependent calcium channels. Vitamin D could promote β-cells survival by inactivation of nuclear factor-κB (NF-κb) and effects of cytokines (54).Vitamin D can affect insulin resistance indirectly through the renin-angiotensin-aldosterone system (RAAS). Angiotensin II inhibits the action of insulin in vascular and skeletal muscle tissue leading to impaired glucose uptake that suppresses rennin formation and local pancreatic RAAS. Therefore, vitamin D may be a negative endocrine regulator of RAAS (55). In an open-label randomized trial, it was found out that the calcitriol supplementation resulted in temporarily reducing the required dose of insulin in type-1 diabetes mellitus (56). A meta-analysis data support that supplementation of vitamin D during early infancy, reduces the incidence of type-1 diabetes mellitus (57). The evidence suggests that the vitamin D deficiency may be associated with the incidence of type-1 and type-2 diabetes mellitus and the possible role played by the vitamin D in type-1 and type 2 diabetes mellitus is far from being completely understood and many studies suggest further investigations on this (48,57–60).

Vitamin D and Alzheimer's Disease

Alzheimer's disease (AD) is a neurodegenerative disorder that is the most common form of dementia in elderly individuals and is associated with progressive memory loss and cognitive dysfunction. There is a high prevalence of dementia in patients with low serum 25- hydroxy vitamin D3 (25OHD) levels as a circulating biomarker for vitamin D status (61). A 6-year study found that the low levels of vitamin D were associated with a substantial cognitive decline in the elderly population (62) also another study finds out the same that vitamin D deficiency is associated with a substantially increased risk of all-cause dementia and Alzheimer disease (63). A 7-year cohort study found out that the higher vitamin D dietary intake was associated with a lower risk of developing Alzheimer's disease among older women (64). A Meta-analysis also investigated the association of vitamin D with cognitive function in older adults and conceptualized vitamin D as a ‘neurosteroid hormone' that could be a potential biomarker of the AD (65). It Extracellular amyloid plaques and intracellular neurofibrillary tangles are two major is the most common pathological cause of Alzheimer's disease (AD). Those extracellular cause of cognitive decline in the elderly and intracellular fibrillar aggregations cause disruption characterized by progressive loss of memory and other of axonal transport, interneuronal signal transduction, neurotrophic factor synthesis, alteration of neuronal calcium homeostasis and induction of oxidative stress (66). So the link between the vitamin D and Alzheimer's

disease (AD) is clearly established with these studies (67). How vitamin D plays a role in the AD is not clear but Vitamin D receptor (VDR) along with vitamin D3 seems to be playing a major role in it. Vitamin D3 is known to be involved in neuroprotection and exert its neuroprotective effects by modulating neuronal calcium homeostasis and production of neurotrophins (68). In a study it was found out that vitamin D protected the neurons by down regulating LVSCC A1C expression, up regulating VDR expression and inducing NGF. The neurons which received vitamin D treatment before treatment prevented LVSCCA1C and NGF induction and resisted amyloid-β induced neurodegeneration (69). The vitamin D receptor (VDR) is a ligand-activated transcription factor, belonging to the nuclear hormone receptor super family. It is widely expressed in human brain and both VDR and 1α-hydroxylase, the enzyme responsible for the formulating of active vitamin D in the human brain are widespread in both neurons and glial cells in a regional and layer-specific pattern (70) they exert their effects on AD via CaSR, Aβ, IL-10, MMPs, HO-1, and the reduced form of NADP, suppressing PTH and inflammatory mediators (71). This proves that the vitamin D plays a role in Alzheimer's disease and in cognitive functions as well and it can be beneficial in preventing Alzheimer's disease (62–65,67–69,71-74).

Table 2.3 Diseases, disorders and conditions that are related with or aggravated by vitamin D

Osteomalacia/osteoporosis	Muscle function and falls
Autoimmune disorders	Tuberculosis/infections
Cancer (breast, colon, skin, pancreas, prostate)	Peripheral vascular disease
Chronic pain	Fibromyalgia
Celiac disease	Cystic fibrosis
Multiple sclerosis	Hypertension
Type 2 diabetes	Inflammatory bowel disease
Rheumatoid arthritis	Polymyalgia rheumatic
Depression	Seasonal affective disorder
Parathyroid diseases	Muscle function and falls
Autism	Obesity
Parkinson's disease	Chronic fatigue syndrome
Psoriasis	Incontinence
Macular degeneration (AMD)	Cognitive impairment
Cardiovascular events	Rheumatoid arthritis

CONCLUSION

Vitamin D is an important dietary substance and plays a major role in various diseases and conditions. It is also used in prevention and treatment of many ailments. The role played by vitamin D in many diseases is not well researched and studied, hence their should be more emphasis on experimental studies to find out the new possibilities of treatment and prevention of diseases by vitamin D.

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