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VITAMIN D AND ITS DEFICIENCY – AN UPDATE

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ABSTRACT
Vitamin D is a fat soluble vitamin present as ergocalciferol and cholecalciferol, synthesized in skin by sunlight. The requirement of Vitamin D in humans is achieved either by ingesting vitamin D or being exposed to sun light for enough time to produce adequate amounts. It controls calcium absorption in small intestine and works with parathyroid hormone to mediate skeletal mineralization and maintain calcium homeostasis in the blood stream. It may be a determinant of mortality because of its anti-inflammatory and immune-modulating effects. It is synthesized from 7-dehydrocholesterol in the skin. The hydroxylation in liver forms 25(OH)D, the inactive form of vitamin D and then in the kidneys it is further hydroxylated to 1,25(OH)D, the active form, also known as Calcitriol. This paper is formed on the basis of reviewing and analyzing various research work on Vitamin D as the greater awareness is required among researchers, clinicians and patients due to high prevalence of vitamin D deficiency in the recent days.

KEYWORDS: Ercocalciferol, Cholecalciferol, Calcitriol, Vitamin D, Osteoporosis, Rickets.

INTRODUCTION
Vitamin D is a fat soluble vitamin present as (a) Ergocalciferol or vitamin D_2, present in plants and in some fish (b) Cholecalciferol or vitamin D_3, synthesized in skin by sunlight. Humans get vitamin D by either ingesting vitamin D or being exposed to the sun light for enough time. Vitamin D controls calcium absorption in small intestine and works with parathyroid hormone to mediate skeletal mineralization and maintain calcium homeostasis in the blood stream. In addition, recent epidemiologic studies have observed relationships between low vitamin D levels and multiple disease states, probably caused by its anti-inflammatory and immune-modulating properties and possible affects on cytokine levels. Vitamin D_3 can be synthesized in the skin by ultraviolet B (UVB) rays. Vitamin D_3 is synthesized from 7-dehydrocholesterol in the skin. The vitamin D binding protein transports the vitamin D_3 to the liver where it undergoes hydroxylation to 25(OH)D and then to the kidneys where it is hydroxylated by the enzyme 1 alpha hydroxylase to 1,25(OH)D, its active form.[1] Vitamin D plays an important role in maintaining an adequate level of serum calcium and phosphorus. Without vitamin D, only 10 to 15% of dietary calcium and about 60% of phosphorus are absorbed.[2,3,4] Vitamin D deficiency is widespread in individuals irrespective of their age, gender, race and geography. Vitamin D is photosynthesized in the skin on exposure to UVB rays. Sun exposure alone ought to suffice for vitamin D sufficiency. However, vitamin D deficiency is widely prevalent despite plentiful sunshine even in tropical countries like India.[5,6,7]

Vitamin D_2 versus Vitamin D_3
The Ergocalciferol or Vitamin D_2 is a synthetic product derived by irradiation of plant sterols / ergosterol. The Cholecalciferol or Vitamin D_3 is a natural form of vitamin D in all animals and the form synthesized in human skin on exposure to sunlight. The vitamin D_2 is substantially less potent than vitamin D_3. Both are absorbed in the intestine and to be 25- hydroxylated in the liver with equal efficiency; however, Vitamin D_2 seems to upregulate several 24-hydroxylases, leading to increased metabolic degradation of both the administered D_2 and endogenous D_3. Even though it is certainly possible to treat patients satisfactorily with vitamin D_2, Ergocalciferol seems to have no advantage over Cholecalciferol, which is also less expensive.[8]

The two major biologically inert precursors of vitamin D are vitamin D_3 and vitamin D_2.[9,10] Vitamin D_3 is formed when 7-dehydrocholesterol in the skin is exposed to solar UVB and then converted to provitamin D_3. In a heat-dependent process, provitamin D_3 is immediately converted to vitamin D. Excess UVB rays transform provitamin D_3 into biologically inactive metabolites, tachysterol and lumisterol. Vitamin D_2 is plant derived, produced exogenously by irradiation of ergosterol and enters the circulation through diet.[11]

Sources

The major source of vitamin D for most humans is exposure to sunlight.[12] The foods naturally contain vitamin D, are oily fish such as salmon, mackerel and herring and oils from fish, including cod liver oil.[13,14] Humans obtain vitamin D through dietary intake and exposure to sunlight. Very few foods naturally contain vitamin D. Oily fish such as salmon, mackerel and sardines are rich in vitamin D_3. Egg yolks are reported to contain vitamin D though the amounts are highly variable. The cholesterol content of egg yolks makes it a poor source of vitamin D. Also, a small number of foods are fortified with vitamin D such as milk, orange juice and some bread and cereals.[15,16]

Vitamin D Deficiency

Vitamin D deficiency in children causes growth retardation and classic signs and symptoms of rickets. In adults, vitamin D deficiency will precipitate and exacerbate both osteopenia and osteoporosis and increase the risk of fracture.[16,17,18]

Muscle weakness has long been associated with vitamin D deficiency. A vitamin D receptor is present in skeletal muscle and vitamin D deficiency has been associated with proximal muscle weakness, increase in body sway, and an increased risk of falling.[19]

In adults it causes skeletal mineralization defect. The unmineralized osteoid provides little structural support for the periosteal covering. As a result, patients with osteomalacia often complain of isolated or global bone discomfort along with aches and pains in their joints and muscles. These patients may be misdiagnosed with fibromyalgia, dysthymia, degenerative joint disease, arthritis, chronic fatigue syndrome and other diseases.[20]

The major source of vitamin D for humans is exposure to sunlight. Anything that diminishes the transmission of solar UVB radiation to the earth's surface or anything that interferes with the penetration of UVB radiation into the skin will affect the cutaneous synthesis of vitamin D_3.[21]

Aging is associated with decreased concentrations of 7-dehydrocholesterol, the precursor of vitamin D_3 in the skin. A 70-y-old has 25% of the 7-dehydrocholesterol that a young adult does and thus has a 75% reduced capacity to make vitamin D_3 in the skin. Because vitamin D is fat soluble, it is readily taken up by fat cells. Obesity is associated with vitamin D deficiency. Medications including antiseizure medications and glucocorticoids and fat malabsorption are also common causes of deficiency.[22]

Malabsorption results in vitamin D deficiency. For example, Cystic fibrosis patients have inefficient vitamin D absorption due to pancreatic exocrine insufficiency.[23]

Vitamin D in Various Conditions

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.[24]

Vitamin D and Diabetes

Epidemiologic data has long suggested a link between exposure to vitamin D early in life and the development of type 1 Diabetes Mellitus (DM).[25,26] Vitamin D_3 receptors have strong immune-modulating effects. In some populations the development of type 1 DM is associated with polymorphisms in the vitamin D receptor gene.[27,28] There is also some evidence that increased vitamin D intake by infants may reduce the risk of the development of type 1 DM.[29] 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.[25,28,29] There was also an inverse relationship between type 2 DM and metabolic syndrome incidences and vitamin D and calcium intake.[30]

Vitamin D and Osteoporosis

Osteoporosis is the most common metabolic bone disease. 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[31] 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.[32]

Vitamin D and Falls Among the Elderly

Vitamin D status is increasingly recognized as an important factor in fall status among elderly patients. Several trials have demonstrated that vitamin D supplementation decreases the risk of falling. One proposed mechanism is that higher vitamin D levels are associated with improved muscle function. A randomized, controlled trial from Australia evaluated women with at least one fall in the preceding 12 months and with a plasma 25-hyroxyvitamin D level 24 ng/mL.[33]

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.[34] A population-based randomized, control trial found that postmenopausal women who were supplemented with calcium and vitamin D had a reduced risk of cancer after the first year of treatment.[35]

Autoimmune Diseases

Several studies have shown that vitamin D affects the growth and differentiation of immunemodulator cells such as macrophages, dendritic cells, T cells and B cells.[36,37,38] This immune-modulatory effect has implications for a variety of autoimmune diseases including rheumatoid arthritis, systemic lupus erythematosous, type 1 DM, inflammatory bowel disease, and multiple sclerosis (MS).[37]

CONCLUSION

In earlier days vitamin D intake was associated with the prevention of rickets in children. But recently, its effect in other areas has received little attention and the vitamin D deficiency has also been linked with the pathogenesis and/or progression of several disorders, including cancer, hypertension, MS, diabetes although the evidence for the associations of vitamin D with these conditions is generally weaker than it is for bone-related disease. Vitamin D, particularly its active form Calcitriol is a highly potent molecule, capable of producing serious toxic effects, including death at milligram intake levels. Thus, it was concluded that a daily intake as per physician advice should be considered the tolerable upper intake level.

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