



Extra Skeletal Functions of Vitamin D

KEYWORDS

Vitamin D, cholecalciferol, extra skeletal effects, VDR, hypovitaminosis.

Gayathri Keerthivasan

ABSTRACT

Recent research work on 1,25(OH)₂D and its receptor mediated actions in the cells not involved in maintaining mineral homeostasis and bone health in humans has revealed the association of Vitamin D and biologically significant extra skeletal health manifestations. Although India is a sunny country, Vitamin D deficiency is increasing and awareness of the non calcemic functions are inevitable. This review gives an overview about Vitamin D inadequacy and its potential implications beyond skeletal health.

Extra Skeletal Health Benefits of Vitamin D

Recent advances in research involving vitamin D in health has transcended from the concept of prevention of rickets in children to its important role in producing the beneficial effects on extra skeletal tissues which has a major impact on the optimal health and well being of humans. The role of vitamin D in extra skeletal health benefits has been going under recognized by both the treating physicians and the general population. The purpose of this article is to review the implications of vitamin – D on the less focused extra skeletal health benefits.

Prevalence of Vitamin –D inadequacy

Vitamin – D inadequacy is reported worldwide , and it is stated as a under recognized epidemic. Vitamin -D inadequacy is reported as low serum 25(OH)D levels(< 30ng/mL). It is particularly common in patients with osteoporosis and post menopausal women, but several studies have reported inadequate vitamin –D levels in healthy children , young adults middle aged & elderly adults(1). Though sunlight exposure is the primary source of vitamin –D , and India is a sunny country, the prevalence of vitamin–D inadequacy is reported to be widespread vitamin D deficiency(74-96%) among apparently healthy Indians of all age groups and both sexes have been reported from India(2).

Vitamin D– Biochemistry, Metabolism & Functions

Two forms vitamin D are D₂ & D₃. Vitamin D₂ comes from irradiation of the yeast and plant sterol ergosterol and vitamin D₃ is found in only fish , cod liver oil and is made in the skin. Vitamin D obtained from cutaneous synthesis and dietary sources occurs intermittently. Irregular intake may lead to vitamin D inadequacy. (R) UV –B irradiation of skin causes photolysis of 7-dehydrocholesterol (pre vitamin d₃) to pre vitamin D₃ in the plasma membrane of human skin keratinocytes. Pre vitamin D₃ is rapidly converted to vitamin D₃ by the skin temperature. Vitamin D₃ from the skin and vitamin D from the diet undergo 2 sequential hydroxylations, first in the liver to 25(OH) D and then in the kidney to its biologically active form 1,25(OH)₂ D(3,4).

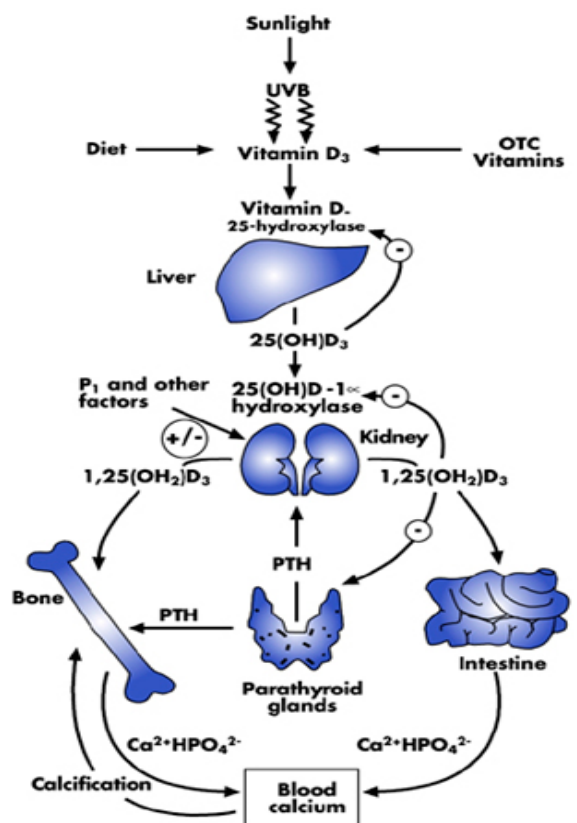


Fig.1:VitaminD metabolism and functions.

Vitamin D and Cell growth: A Potential therapeutic anti cancer agent ?

Vitamin D regulates cell growth; inhibits proliferation and induces differentiation by reducing angiogenesis, metastases, increasing cell differentiation, apoptosis of cancer cells. Understanding the cellular mechanisms involved in the role of vitamin D in cancer will potentially lead to the identification of new targets for treatment. Epidemiological studies have reported higher 25(OH) D levels are associated with reduced cancer incidence and decreased cancer related morbidity. Several in vitro studies have shown that colon, prostate cancer cells, osteosarcomas and melanomas are responsive to the anti proliferative effects of 1,25(OH)₂ D. Several retrospective and prospective observational studies have reported a decrease of 50% or greater in risk of large bowel cancer

and prostate cancer when serum 25(OH) D levels are greater than 20ng/mL or when Vitamin D intake is increased. In one study, women with the highest quartile of serum 1,25(OH)₂ D had one fifth the risk of breast cancer vs those in the lowest quartile. Women in the national health and nutrition examination survey with self reported high intake of Vitamin d from supplements or high life time sun exposure had a significantly reduced risk of breast cancer. Observations have been made in prostate, breast, colon, lung, skin and other organs had the enzymatic machinery 25(OH)D-1alpha hydroxylase; CYP27B to convert 25(OH)D to 1,25(OH)₂ D(5,6). Thus a new autocrine or paracrine function of vitamin D is revealed. Thus the evidence generated indicates the biological responses that result in the inhibition of the disease process of cancer. In the future, well designed, large scale clinical trials are needed to assess whether or not vitamin D analogs have a role as anti cancer agents.

Vitamin D and Heart:

Recent Evidences suggest the progression of hypertension and cardiovascular disease may be due to effect of vitamin D. Vitamin D is involved in controlling the production of rennin, a hormone which controls the blood pressure. African Americans who are at risk of vitamin d deficiency, also have a greater risk of hypertension and cardio vascular disease(7). Though studies do not provide a direct cause and effect relationship, suggest a provocative hypothesis for further research.

Vitamin D and keratinocytes:

Psoriasis can be treated with topically applied 1,25(OH)₂D₃ and 1,25(OH)₂D₃ analogs. Vitamin D causes a marked decrease in proliferation and an increase in differentiation(8).

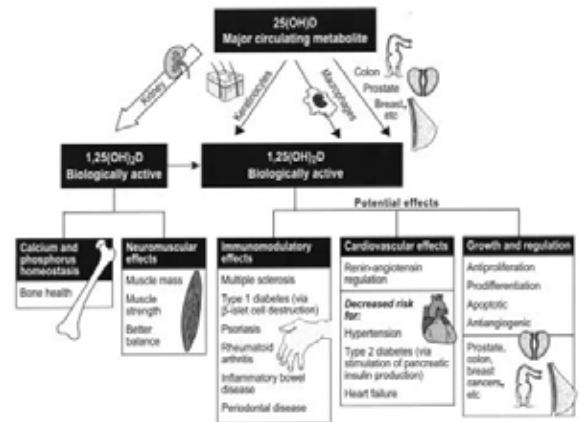
Vitamin D and Immunity:

Vitamin D has the potent ability to act as a modulator of human immune responses. 1,25(OH)₂D₃ inhibits lymphocyte proliferation ,activation and IL2 and interferon gamma are decreased after activated T cells are exposed to 1,25(OH)₂D₃. It also inhibits the differentiation and survival of dendritic cells, resulting in impaired alloreactive T cell activation. These are evidences that studies provide evidence regarding 1,25(OH)₂D₃ is a modulator of Immune system. Vitamin D can protect against auto immune encephalomyelitis, SLE, IBD, auto immune thyroiditis. Vitamin D analysis before the age of 20, suggest that the supplementation in adolescents and young adults may be important with a family history of multiple sclerosis(9).

Vitamin D and type I Diabetes Mellitus:

1,25(OH)₂D₃ acts as an immune modulator by reducing the cytokine production and lymphocyte proliferation which has been implicated in the destruction of insulin secreting β cells in the pancreas and the development of type I Diabetes mellitus. Vitamin D receptors are expressed in islet cells and

respond to 1,25(OH)₂D₃ by increasing insulin production. Zella and Deluca have shown that large doses of Vitamin D were able to suppress the development of insulinitis and diabetes in non obese diabetic mouse, a model of human type I diabetes mellitus. A study has shown that regular supplementation of vitamin D to children during the first year of life had a decreased rate ratio for type I diabetes mellitus than who did not receive Vitamin D(10). Though these data do not support a direct cause and effect relationship but suggest that further studies are needed to substantiate the results.



Endocrine and autocrine or paracrine functions of 1,25-dihydroxyvitamin D (1,25[OH]₂D). www.mayohealthproceedings.com

Vitamin D supplementation and sensible sun exposure:

Several studies have shown that Vitamin D supplementation and exposure to sunlight or simulated sunlight increased its serum levels in elderly patients. It has been suggested that amounts upto 10000IU/day of vitamin D may be needed to maintain a healthy level of more than 30ng/mL. Vitamin D toxicity has not been reported from long term exposure to sunlight has only been observed from dietary intake exceed daily intake of 10,000IU. It has been reported in the general population approximately 98% of Vitamin D deficiency has been prevented by regular supplementation with Vitamin D(3).

Conclusion:

Vitamin D Inadequacy has become a global health issue due to possibility of its role in several disorders including cancer, hypertension, Cardiovascular disease, neuro muscular disease, auto immune disease and Diabetes. Evidences highlights the need for research on prevalence and screening of Vitamin D inadequacy, mechanisms by which it exerts non calcemic effects. Results of future trials may provide ways on how to manage vitamin D status in clinical practice and in non musculoskeletal disorders and its supplementation in general population.

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