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VITAMIN D: AN EVIDENCE BASED REVIEW

Mili Verma
Research Scholar
Department of Physics
C.M.J.University, Shillong,
Meghalaya

ABSTRACT:
Vitamin-D is a fat-soluble vitamin that plays an important role in bone metabolism and seems to have some anti-inflammatory and immune-modulating properties. In addition, recent epidemiologic studies have observed relationships between low vitamin-D levels and multiple disease states. Low vitamin-D levels are associated with increased overall and cardiovascular mortality, cancer incidence and mortality, and autoimmune diseases such as multiple sclerosis. Although it is well known that the combination of vitamin-D and calcium is necessary to maintain bone density as people age, vitamin-D may also be an independent risk factor for falls among the elderly
Key Words-Vitamin-D, Evidences

BACKGROUND:

Vitamin is a hormone precursor that is present in two forms. Ergocalciferol, or vitamin-D_2, is present in plants and some fish. Cholecalciferol, or vitamin-D_3, is synthesized in the skin by sunlight. Humans can fulfil their vitamin-D requirements by either ingesting vitamin-D or being exposed to the sun for enough time to produce adequate amounts. Vitamin-D controls calcium absorption in the 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 manufactured in the skin by way of ultraviolet-B rays. Ultraviolet-B rays are present only during midday at higher latitudes and do not penetrate clouds. The time needed to produce adequate vitamin-D from the skin depends on the strength of the ultraviolet-B rays the length of time spent in the sun, and the amount of pigment in the skin. Tanning beds provide variable levels of ultraviolet-A and ultraviolet-B rays and are therefore not a reliable source of vitamin-D.

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 (optimal health) D and then to the kidneys where it is hydroxylated by the enzyme 1 α hydroxylase to 1, 25 (optimal health) D, its active form. This enzyme is also present in a variety of extrarenal sites, including osteoclasts, skin, colon, brain, and macrophages, which may be the cause of its broad-ranging effects. The half-life of vitamin-D in the liver is approximately 3 weeks, which underscores the need for frequent replenishment of the body's supply.

VITAMIN-D AND MORTALITY:

Vitamin-D may be a determinant of mortality because of its anti-inflammatory and immune-modulating effects. It has been used to treat secondary hyperparathyroidism in people on dialysis. Retrospective trials show that vitamin-D supplementation is associated with decreased mortality in people on dialysis. Low serum vitamin-D levels are also related to increased mortality in most

patients with chronic kidney disease before dialysis. However, there have been no randomized prospective trials examining this relationship.

In patients not on dialysis, low vitamin-D levels are associated with increased levels of inflammation and oxidative load. A prospective study of more than 3000 male and female patients scheduled for coronary angiography found a positive association between low vitamin D levels and cardiovascular as well as all-cause mortality. Data analysis from the National Health and Nutrition Examination Survey III showed that people with vitamin -levels in the lowest quartile had a mortality rate ratio of 1.26. A recent meta-analysis demonstrated that intake of a vitamin-D supplement at normal doses also was associated with decreased all-cause mortality rates. These data suggest that vitamin-D may play a part in multiple causes of death, although causality has not been determined.

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. A large cohort study that included more than 1700 participants from the Framingham offspring study looked at vitamin-D levels and incident cardiovascular events.**8** During a period of 5 years, participants who had 25-(optimal health) D levels of <15 were more likely to experience cardiovascular events. The relationship remained significant among people with hypertension but not among those without hypertension.

VITAMIN-D AND DIABETES:

Recent studies in animal 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. Epidemiologic data has long suggested a link between exposure to vitamin-D early in life and the development of type 1 DM. 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. 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 β 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.

VITAMIN-D AND OSTEOPOROSIS:

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 international unit daily prevented bone loss compared with placebo. However, vitamin-D supplementation without calcium did not affect fractures. A Cochrane review found unclear evidence that vitamin-D alone affected hip, vertebral, or other fracture rates but supported the use of vitamin-D with calcium in frail, elderly nursing home residents. A subsequent meta-analysis of trials looking at vitamin-D and fracture rates concurred that calcium was also necessary to affect a significant difference.

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.

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. In the Health Professionals Follow-Up study each increment in 25(optimal health) D level of 25mmol/L was associated with a 17% reduction of total cancer cases. However, the National Health and Nutrition Examination Survey of 16,818 men and women did not find a relationship between total cancer mortality and vitamin-D level. There was an inverse relationship between vitamin-D level and colorectal cancer, however. In this study, serum 25(optimal health) D levels of ≥ 80 nmol/L conferred a 72% reduction in risk of colorectal cancer compared with a level lower than 50 nmol/L.

VITAMIN-D AND MULTIPLE SCLEROSIS:
Multiple sclerosis is a neurodegenerative, T-lymphocyte-mediated, autoimmune disease of uncertain etiology. Although genetic susceptibility may be involved, epidemiologic studies suggest environmental influence because the development of Multiple sclerosis correlates most strongly with rising latitude in both the northern and southern hemispheres. Migration studies show that risk can be modified at an early age from both low to high and high to low prevalence rates. Exposure to sun in early childhood is associated with reduced risk of developing Multiple sclerosis and population-based studies about MS in Canada have also shown that birth timing is a risk factor for Multiple sclerosis because there are statistically significantly fewer patients with Multiple sclerosis born in November and more born in May compared with controls. A birth-timing association suggests that seasonality and sunlight exposure may also have an effect on the developing fetus in utero.

VITAMIN-D AND COGNITION:
Observational studies have shown that people with Alzheimer dementia have lower vitamin-D levels than do matched controls without dementia. The biological plausibility of this relationship includes vitamin D's antioxidative effects and the presence of vitamin-D receptors in the hippocampus, which has been seen in rats and humans. A cross-sectional study of 225 outpatients diagnosed with Alzheimer disease found a correlation between vitamin-D levels and their score on a Mini Mental Status Examination

VITAMIN-D AND CHRONIC PAIN:
Because of the important role vitamin-D plays in bone homeostasis, some have questioned whether vitamin-D deficiency may also correlate with chronic pain syndromes, including chronic low back pain. Several case series and observational studies have suggested that vitamin-D inadequacy may represent a source of nociception and impaired neuromuscular functioning among patients with chronic pain.

VITAMIN-D SUPPLEMENTATION FOR INFANTS AND BREASTFEEDING MOTHERS:
Breast milk is an ideal form of nourishment for a newborn. Because of most nursing mother's own vitamin-D deficiency, however, and despite the mother taking a prenatal vitamin, breast milk alone is not sufficient to maintain newborn vitamin-D levels within a normal range. Many nursing mothers or their infants require vitamin- D supplementation for optimal health.

SUPPLEMENTING THE NEWBORN:

The American Academy of Paediatrics recommends supplementing all children who are exclusively breastfed with 400 international units of vitamin-D from the first few days of life. Children who are fed by breast and formula or who are exclusively formula fed should also be supplemented until they are consistently ingesting 1 L of formula a day. The supplementation should continue until 1 year of age, when children begin ingesting vitamin-D fortified milk. All formulas sold in the United States contain at least 400 international units/L of vitamin D_3; therefore, 1 L per day would meet the vitamin-D recommendations set by the American Academy of Paediatrics.

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