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ROLE AND ASSOCIATION OF VITAMIN D DEFICIENCY IN VARIOUS DISEASES

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ABSTRACT

To study the role and association of vitamin D deficiency in various diseases.,the sample of 51 reviewed articles was randomly choosen. All the reviewed articles were of different diseases caused by vitamin D deficiency.Among 51 reviewed articles, the effect of vitamin D deficiency was observed in pregnancy (15.9%) followed by bone health, cardio vascular diseases and liver diseases (13.63%), brain health and inflammatory bowel disorders(9.09%), diabetes(6.81%), cancer and obesity(4.54%), anemia, kidney diseases, respiratory health and hormones(2.27%). From the result, it is very clear that the reviewed article studied, was majorly observed among pregnant woman and also the people with bone health problems and cardio-vascular diseases.

KEYWORDS: Vitamin D, cardiovascular diseases, pregnancy, bone health, obesity, liver diseases.

INTRODUCTION

Micronutrient deficiency is global health burden, especially among developing countries (vitamins and minerals constitute micronutrients in the food) vitamin D is one of the most essential fat soluble vitamin responsible for increasing intestinal absorption of calcium, magnesium, phosphate and multiple other biological effects.In humans, the most important compounds among these groups are vitamin D3 also known as cholecalciferol and vitamin D2 known as ergocalciferol.

Vitamin D is an extremely important vitamin that has powerful effects on several systems in the body. Unlike other vitamins, vitamin D functions like a hormone and every single cell in the body has a receptor for it. Body makes cholesterol when the skin is exposed to sunlight.

The serum 25 hydroxy vitamin D levels <30nmol/L (12ng/ml) is considered as vitamin D deficiency. Vitamin D deficiency is very common. It is estimated that one billion people worldwide have low levels of vitamin in their blood.

Common risk factors for vitamin D deficiency are having dark skin, being elderly, being overweightor obese, not eating much fish or dairy, living far from the equator where there is little sun year round, always using sunscreen when going out, staying indoors.

The common symptoms of vitamin D deficiency include getting sick or infected often, fatigue and tiredness, bone and back pain, depression, impaired wound healing, bone loss, hair loss, muscle pain.

OBJECTIVES:

1. The main objective of current study is to associate the deficiency of vitamin D and diseases.
2. To assess the prevalence of vitamin D deficiency in India.

3. To raise priority and to integrate prevention and control of vitamin D deficiency and its relateddiseases.
4.To discuss the risk factors of vitamin D deficiency and describe impact on overall health.

A thorough literature survey is done bysearching for original articles on vitamin D deficiency associated diseases among general population by considering the articles published from January 2014 to 2020. The most commonly carried methods in the following selected articles are cross-sectional study, prospective, observational study, cohort study, randomized control trials (RCTs).

PREVALANCE

A community-based cross-sectional study was conducted Suryanarayana P and his co-workers among 298 urban elderly (≥60 years)population in the south Indian city of Hyderabad by adapting a random sampling procedure. The mean ± SE plasma vitamin D and the prevalence of Vitamin D Deficiency (VDD)among the urban elderly population were found to be 19.3 ± 0.54 (ng/ml) and 56.3%, respectively. The significant associated factors of VDD are High BMI(Body Mass Index), metabolic syndrome, hypertension and education. [1]

A study in 2018 was conducted by Garg R et. al. among 1052 women attending the clinic and it was found that the prevalence of vitamin D level <20 ng/ml was 64.06% and the level of vitamin D <30 ng/ml was 98.75% and it was higher in younger (65.51%), illiterate (89.92%), housewife women (70%) and its prevalence was higher in women residing in rural areas (69.94%) and also having an income <10,000 (61.96%).The reasons may be because of skin pigmentation, not adequate direct sunlight exposure and winter-related reduced sunlight exposure. Additionally, most Indians are unaware of their requirement of vitamin D and availability of vitamin D supplements.[2]

Serum 25(OH)D concentrations were influenced by the duration of sunlight exposure and the body fat percentage , as in spite of a majority reporting sunlight exposure of >2 hour , the prevalence of vitamin D deficiency was high among school going children of age 6-12 from semi-rural areas in India. Sunlight exposure had a positive impact on Serum 25(OH)D levels while the body fat percentage (adiposity) had a negative impact. [3]

Severe vitamin D deficiency increases the risk of infections, mortality, and many other diseases. As it has rare side effects and relatively wide safety margin, it may be an important, inexpensive, and safe adjuvant therapy(vitaminD supplements)for many diseases, but future studies should be done for further evaluation. [4]

A retrospective study evaluating the prevalence of VDD in psychiatric patients was done revealing 94% of the subjects with mental illness showed vitamin D deficiency.Vitamin D receptors are located in different parts of the brain, including the amygdala, which is associated with the regulation of emotions and behaviour.The genes that regulate immune system and release neurotransmitters (e.g., dopamine and serotonin) are also activated by vitamin D. [5]

A study among 12,346 participants >18years of which 36.9% were male and 63.1% female from Abu Dhabi Emirati population revealed majority of them were vitamin D deficient. Vitamin D deficiency was similar in both sexes (male 83.1% and female 83.8%).[6]

Ventilatory threshold is an index used to estimate exercise capacity.As the intensity of the exercise begins to increase, Ventilatory threshold-1 (VT1) can be identified at the point where the breathing rate begins to increase, at this point lactate begins to accumulate in the blood. In this state a person can no longer talk comfortably, but can still string together a few words. Upon treating healthy young adults with the serum levels of 25 Hydroxyvitamin D3 <20 ng/ml with 50,000 IU/week of oral administration of vitamin D3 for 8 weeks, an improved VT1 was observed. [7]

BONE

Inadequate amount of $1,25(OH)_2D$ in the bloodstream, may cause less or no absorption of dietary calcium which may eventually lead to low bone density and brittle bones . Serum 25(OH)D levels (usually <5 ng/mL), elevated alkaline phophatase levels and hypophosphatemia are biochemical abnormalities leading to rickets which is inadequate mineralization of growing bone in children.[8]

In adults, chronic vitamin D deficiency may decrease bone quality leading to osteomalacia, whereas vitamin D insufficiency increases the risk of osteoporosis and bone fractures.[9]

Along with role of vitamin D in bone and mineral homeostasis, it has a wide range of effects in skeletal muscles. It modulates muscles and bone derived hormones. Vitamin D acts as a potential therapeutic target for musculoskeletal diseases.[10]

In a study it was found that Patients with atypical osteomalacia due to aluminum or focal osteomalaciadidn'trespond to vitamin D therapy. The serum levels ofpatients with vitamin D deficiency osteomalacia were found to be <10 ng/ml.[11]

In patients with arthritis, muscle pain and chronic widespread pain ,lower 25(OH)D concentration was observed suggesting that itmay be associated with pain conditions.[12]

According to a study it was observed that factors such as female gender, increasing age, abnormal BMI, low serum 25-hydroxyvitamin D, and pioglitazone use further increase the risk of osteoporosis. [12]

BRAIN

The deficiency of vitamin D was confirmed to increase the risk of Alzheimer's disease.[14]

It was found that Increasing age and elevated body fat mass contribute to an increased risk of Vitamin D deficiency. The deficiency is also associated with depression and impaired cognitive function.[14]

A study conducted on male rats demonstrated that vitamin D deficiency influences multiple pathways necessary for optimal neural development and adult brain function.[16]

In a study conducted in adolescents the behavioural problems were assessed. The externalising problems i.e. misbehaviour directed towards external environment such as physical aggression and disobeying rules, was 1.8 times higher in children with VDD than that in children without VDD.Thus concluding that VDD and low Vitamin D binding protein in middle childhood are related to behavior problems in adolescence.[17]

INFLAMMATORY BOWEL DISEASE

There is an association between low vitamin D levels and increased disease activity, particularly in Crohn's disease.Low vitamin D levelsincreased the risk of Crohn's disease.[18]

A stratified analysis showed that IBD patients have twice the odds of vitamin D deficiency when compared with healthy adult controls.[19]

Low vitamin D levels were found to be related with increased morbidity and severity of IBD.[20]

Vitamin D deficiency is found in inflammatory bowel disease (IBD), especially in Crohn's disease (CD), associated with increased disease activity, a return to disease course and higher inflammatory activity. [**Error! Reference source not found.**]

PREGNANCY

Low vitamin D during pregnancy is a risk factor for the development of postpartum depression symptoms, women in the lowest quartile for 25(OH)-vitamin D status were more likely to report a higher level of postnatal depression symptoms than women who were in the highest quartile for vitamin D, even after accounting for a range of confounding variables including season of birth, body mass index and socio-demographic factors.[**Error! Reference source not found.**]

During pregnancy, maternal vitamin D status may be of concern because of the essential role in fetal skeletal development and due to the alliance between hypovitaminosis D and adverse maternal–fetal outcomes.[**Error! Reference source not found.**]

The women with vitamin D deficiency (25[OH]D levels <12.02 ng/mL) during early pregnancy was associated with a nearly 2-fold increased risk of Multiple Sclerosis in the offspring (relative risk, 1.90; 95% CI, 1.20-3.01; P = .006) . There was no statistically significant association between the risk of Multiple Sclerosis and serum 25(OH)D levels (P = .12).[**Error! Reference source not found.**]

Pregnant women who has serum vitamin D levels less than 20 ng/mL, experienced an increasing risk of preterm birth. [**Error! Reference source not found.**]

A systematic review, from 1959 to 2014, worldwide of vitamin D status of pregnant women and newborns suggested Vitamin D deficiency, as defined by a serum 25(OH)D concentration <50 nmol L−1, was present in 54% of pregnant women and 75% of newborns, and in severe vitamin D deficiency, serum 25(OH)D concentration <25 nmol L−1 in 18% of pregnant women and 29% of newborns.[**Error! Reference source not found.**]

vitamin D deficiency is of considerable importance in many societies, particular concern in pregnant women. Vitamin D deficiency during pregnancy is associated with a wide range of adverse maternal and offspring health outcomes, the information indicate a large unfulfilled need in this population.[**Error! Reference source not found.**]

The risk of infants being small for gestational age,growth retardation in infants,increased risk of fetal or neonatal mortality or congenital abnormality is reduced by Vitamin D supplementation during pregnancy [**Error! Reference source not found.**]

ANEMIA

Vitamin D deficiency is associated with increased risk of anemia, especially iron deficiency anemiain healthy female children and adolescents. [**Error! Reference source not found.**]

OBESITY

The prevalence of vitamin D deficiency was more raised in obese subjects. The vitamin D deficiency was related with obesity irrespective of age, latitude, cut-offs to define vitamin D deficiency and the Human Development Index.[**Error! Reference source not found.**]

A Cross-section study of 75 subjects were grouped into 3 groups; obese, overweight and normal subjects. Sclerostin, fasting insulin, fasting plasma glucose and 25(OH)D levels were measured and compared among these 3 groups. 25(OH)D levels werelower in obese subjects than overweight and control groups.Sclerostin was significantly lower in obese subjects when compared with the control group. These results lead to hypothesize the relationship between sclerostin and Vitamin D levels hasa major role in link between obesity and bone metabolism.[**Error! Reference source not found.**]

CANCER

Higher 25(OH)D concentrations were related with a decrease in breast cancer risk among women with concentrations ≥60 ng/ml. There was an 82% lower occurrence of breast cancer among women with 25(OH)D concentrations ≥60 ng/mlwhen compared with women having lower levels25(OH)D. [**Error! Reference source not found.**]

High serum levels of 25(OH)vitamin D were related with reduced risk of breast cancer in both case-control and cohort studies; these results were consistent on premenopausal women for case-control studies but itcould not be examined for cohort studies.[**Error! Reference source not found.**]

CARDIO VASCULAR DISEASE

Evidence from observational studies exhibits inverse associations of circulating 25-hydroxyvitamin D with risks of deathcauseddue to cancer,cardiovascular disease, and other causes. Supplementation with vitamin D3 has remarkably reduced overall mortality among older adults; but before any widespread supplementation, further research will be needed to establish recommended dose and timeperiodwhether vitamin D3 and D2 have different effects on mortality risk.[**Error! Reference source not found.**]

Hypovitaminosis D was observed in prevailing majority of patients undergoing coronary angiography. Vitamin D deficiency is significantly related with the prevalence and extent of Coronary artery disease(CAD), especially for patients with values < 10 ng/mL.As a result, future large studies are required toassess whether vitamin D supplementation may reduce the progression of disease and prevent CAD[**Error! Reference source not found.**]

Low vitamin D levels may increase the risk of atherosclerosis enabling vascular inflammation, endothelial dysfunction, formation of foam cells, and can cause multiplication of smooth muscle cells.

- Vitamin D deficiency wasrelated with the number of affected coronary arteries, cardiac remodeling in patients with myocardial infarction, direct electromechanical

effects and inflammation in atrial fibrillation, and neuroprotective effects in stroke,postinfarction complications and inflammatory cytokines

- In peripheral arterial disease, vitamin D status was associated with decrease in functional performance, arterial stiffness, vascular calcifications, and arterial aging,severity, atherosclerosis and inflammatory markers,.[**Error! Reference source not found.**]

Vitamin D deficiency is a predisposing factor for incident stroke and the strength ofassociationdoesn't differ by race.[**Error! Reference source not found.**]

A study conducted on 43 women having HIV who had low vitamin d levels had high number of segments with any coronary plaque and segments with non calcified coronary plaque compared to women with HIV in high vitamin D group. Conclusions reveal a significant independent relationship between vitamin D status and coronary atherosclerosis in women having HIV.[**Error! Reference source not found.**]

Vitamin D binding protein levels showed a statisticalrelation with in-hospital death rates, supporting the utility of VDBP as a good prognostic marker in septic shock patients.[**Error! Reference source not found.**]

DIABETES

There is a relationof a higher rate of vitamin D deficiency and lower concentrations of 25(OH)D with diabetic retinopathy in patients with type 2 diabetes,further these parameters of poor vitamin D status are also linked with severity of diabetic retinopathy.[**Error! Reference source not found.**]

Vitamin D deficiency is found to be prevalent among patients with diabetic nephropathy and increasesthe severityof diabetic nephropathy progression. Age, obesity, glucose level and renal function are the factors that largely affect 25(OH)D deficiency in diabetic nephropathy.[**Error! Reference source not found.**]
Type 1 diabetes mellitus (T1DM) is highly prevalent in Kuwait with incidence of around 40.1/100,000 individuals. A significant correlation was detected between vitamin D deficiency and high prevalence of of Type 1 diabetes mellitus due to the crucial importance of Vitamin D in modulating the immune system and thus has a great impact on Kuwaiti T1DM patients.[**Error! Reference source not found.**]

LIVER

The study demonstrates that vitamin D is an essential mediator of intestinal epithelial defenses against the infectious agents. Vitamin D deficiency can predisposethe peopleto more-severe intestinal injury leading to colitis.[**Error! Reference source not found.**]

Vitamin D has remarkable immune modulatory properties and hence exerts an anti-hepatitis C virus (HCV) effect in vitro and enhances the response to interferon-based therapy in patients suffering with chronic hepatitis C (CHC).[**Error! Reference source not found.**]

Treatment of DHA along with vitamin D was found to significantly improve the insulin-resistance, lipid profile, amino transferases levels and NAFLD Activity Score (NAS) .[**Error! Reference source not found.**]

Vitamin D plays a crucial role in regulation of the immune system and affects the outcome of allografts.

- The incidence of ACR, and bacterial and fungal infection was found to be reduced in patients with vitamin D supplementation, hence suggesting the possibility that, it may promote immune tolerance towards the liver allografts
- A study conducted on Two hundred and nine patients whose liver tissue examination was done and their serum vitamin D levels were determined and found to be considered severely deficient. [**Error! Reference source not found.**]

Concludingthat severe vitamin D deficiency is potentially associated with treatment non-response, progression to cirrhosis, and liver-related death or need for liver transplantation[**Error! Reference source not found.**]

A study conducted that group of patients with significant fibrosis (stage≥ 2) was higher in those severe Vitamin D deficiency when compared to those who have normal vitamin D levels.[**Error! Reference source not found.**]

KIDNEY

Severe vitamin D deficiency is found to be significantly associated with increase in prevalence of Renal Hyperfilterationin a relatively healthy adults.[**Error! Reference source not found.**]

RESPIRATORY

Vitamin D deficiency (plasma 25(OH)D levels <50 nmol/L) was found to be common among patients with ARDS and present significantly in majority of the patients at risk of developing ARDS following oesophagectomy.

- Dietary-induced vitamin D deficiency was found to result in increased alveolar inflammation, epithelial damage and hypoxia

According to in vitro studies, vitamin D has remarkable trophic effects on the primary human alveolar epithelial cells affecting more than 600 genes[**Error! Reference source not found.**]

HORMONES

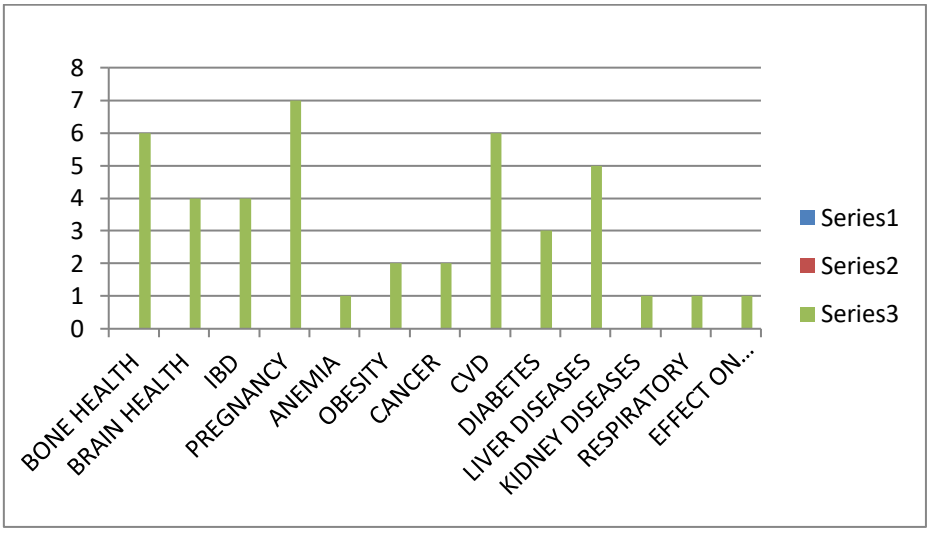
A cross-sectional data highlights the regulatory role of vitamin D in PCOS-related aspects such as ovulatory dysfunction, insulin resistance as well as hyperandrogenism. And the results of randomized controlled trials (RCTs) suggests that vitamin D supplementation may be greatly beneficial for maintaining normal metabolic, endocrine and fertility aspects in PCOS.

- In men, vitamin D status has been related to androgen levels and hypogonadism.
- Vitamin D supplementation have remarkable effects on testosterone concentrations, although others failed to show a significant effect on testosterone levels.[**Error! Reference source not found.**]

CRITICAL REVIEW AND DISCUSSION

Table1

S.no	Effect of vitamin D deficiency on different diseases	No. of articles	Percentage %
1	Bone health	6	13.63
2	Brain health	4	9.09
3	IBD	4	9.09
4	Pregnancy	7	15.9
5	Anaemia	1	2.27
6	Obesity	2	4.54
7	Cancer	2	4.54
8	CVD	6	13.63
9	Diabetes	3	6.81
10	Liver diseases	6	13.63
11	Kidney diseases	1	2.27
12	Respiratory diseases	1	2.27
13	Effect on hormones	1	2.27



GRAPHICAL REPRESENTATION OF VITAMIN D DEFECIENCY AND ASSOCIATED DISEASES

The effect of vitamin D deficiency disorders was majorly observed in pregnancy (15.9%) followed by bone health, cardio vascular diseases and liver diseases (13.63%), brain health and inflammatory bowel disorders(9.09%), diabetes(6.81%), cancer and obesity(4.54%), anemia, kidney diseases, respiratory health and hormones(2.27%).

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