Review Article

Miracle Vitamin: Role of Vitamin D in Human Health

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ABSTRACT

Vitamin D deficiency is an emerging problem in the world. It is an important vitamin for absorption, distribution and utilization of calcium. Factors responsible for vitamin D deficiency are malabsorption, liver diseases, use of sunscreen and medications such as antiepileptic and anticonvulsants. Sunlight is the main source which converts the inactive form [25(OH)D] to its active form [1,25-dihydroxyvitamin D] which is responsible for proliferation and differentiation of cells. Vitamin D had several functions such as anti inflammatory, immunomodulatory action in immune system and antioxidant property. A Vitamin D supplement has a clinical benefit in the improvement of diseases and maintenance of physical health of patients. This article is used to discuss the roles of vitamin D deficiency in pathogenesis of acute and chronic disorders.

Keywords: Vitamin D deficiency, Calcium, 1, 25-dihydroxyvitamin D, Vitamin D receptors.

INTRODUCTION

Vitamin D is a fat soluble vitamin that is essential for the absorption and metabolism of calcium and other several minerals in the body. It regulates more than 200 genes in the body which participate in cell differentiation and maturation. Vitamin D has several functions in the body: a) anti-inflammatory function and antioxidant property b) regulation of insulin production and its utilization c) regulate hormone synthesis d)maintenance of minerals in the body.[1] Sources of vitamin D was given in table 1.

Table 1: Sources of vitamin D

Sources	Food	Amount of vitamin D presents
Food	Milk Fish products	100 IU vitamin D3 200-300 IU vitamin D
Sunlight	Exposure to sunlight for at least 15 mins/week during summer season	3000 IU vitamin D3 per exposure
Vitamin D supplements	Cholcalciferol Ergocalciferol	1000 IU/day 50,000 IU every 2-4 weeks

Vitamin D is the only vitamin that is converted to its precursor form (cholcalciferol) by UV rays with wavelength of 290-320nm.[2]Liver plays an important role for the hydroxylation of cholecalciferol to its active form, 1, 25 dihydroxy vitamin D. Malabsorption of cholcalciferol from gastrointestinal tract or liver disease leads to vitamin D deficiency. The concentration of vitamin D below 30ng/ml is considered as deficient and below 10ng/ml as grossy deficient.[3] Vitamin D deficiency is linked to several cancers, respiratory tract infection, autoimmune disorders, hypertension, diabetes mellitus, psychological disorders, cardiovascular diseases (CV) and several infectious diseases.

The Food and Nutrition Board (FNB) at the Institute of Medicine of the National Academies established a Recommended Dietary Allowance (RDA) in 2010, recommended vitamin D level were based on age apart from race, gender, geographical areas.[4]

<6 months: 340 IU (8.5 mcg)

6-5 years:280IU (7 mcg)

1-70 years: 600 IU (15 mcg)
70 years and older: 800 IU (20 mcg)

Etiology of vitamin D deficiency[5]

- Dark pigmentation
- Use of sunscreen
- Less exposure to sunlight
- Chronic ill conditions : hepatic and renal disease
- Maternal vitamin D deficiency
- Reduced intake of vitamin D
- Peoples who stays away from equator
- Medicines: anticonvulsant and antiepileptics

Roles of Vitamin D

Respiratory tract infection

Vitamin D act as an immunomodulator helps in the prevention of recurrent upper and lower respiratory tract infection mainly occurred during winter season due to malabsorption of vitamin D.[6]The conversion of inactive to

active form [1, 25(0H)D3] is regulated by an enzyme, Ia hydroxylase and it enhances the release of a cathelicidial antimicrobial protein (hCAP18), which is involved in the immune function of the body. Cathelicidins belongs to an antimicrobial peptide group which involved in the disintegration of cell membranes of organisms, thus provide antibacterial and antiviral action. Always cathelicidin is stored in the body as inactive prepropeptide in the neutrophils and converted to its active form when need arises.[7,8] Epithelial cells present in the respiratory tract are involved in the production of 1,25(OH)D3 which regulate the expression of several genes involved in the maturation, differentiation and proliferation of cells.[9] Inadequate vitamin D concentration in pregnant women accompanied by several complications like premature birth, infection, hair loss in new born, cochlear deafness.[10] FDA recommended dose of vitamin D for pregnant and breastfeeding women is 1500-2000 IU.[11]Several studies reported that, administration of 600-700 IU vitamin D_3 with multivitamin supplements or 60000 IU/week reduces the incidence of upper respiratory tract infection(URTI).[12]Vitamin D regulates the absorption and metabolism of calcium, responsible for the maintenance of membrane permeability. Apart from calcium absorption, it causes an imbalance in magnesium and phosphate concentration and thus leads to osteoporosis, Meniere's disease, depression, rickettsia, osteomalacia, cochlear otosclerosis.[3]

Cancer chemotherapy

Several studies demonstrated that, low serum concentration of vitamin D leads to deficient production of protein which regulates genes involved in cancers such as prostate, lungs, breast and colon.[13] A 4-year ''gold standard'' study of cancer mortality in 1180 Nebraska women reported that vitamin D supplements reduces the risk of cancer among study population while risk of colon cancer was higher among men.[14]So, vitamin D had an anticancer effect through gene regulation.[2]Oral vitamin D supplements potentiates the effect of chemotherapy and radiation. Both breast and colorectal cancer has been reduced by 50% when 25-hydroxyvitamin D > 32ng/ml.[15]

Cardiovascular disease

Factors responsible for the development of CV are genetic, lifestyle changes, hypertension, diabetes mellitus, atherosclerosis, lack of exercise and smoking. When serum concentration of vitamin D below 32ng/ml increase the risk of high blood pressure among elder patients.[16] Vitamin D prevents the progression of CV diseases and its complication by several ways: inhibition of inflammatory mediators, reduce insulin resistance, regulates renin angiotensin-aldosterone production and suppresses vascular calcification.[17] Presence of vitamin Dreceptors (VDR) in myocardium regulates myocyte hypertrophy in CV patients.[18] Vitamin D plays a critical role in regulation of anti-inflammatory IL-10 in patients with left ventricular hypertrophy.[19]

Diabetes mellitus

Diabetes is a metabolic disorder characterized by hyperglycemia with sign and symptoms of dysuria, dyspepsia due to destruction of pancreatic islets. Animal and human studies concluded that, VDR present in the beta cells regulate the secretion of insulin in response to glucose and maintenance of glucose tolerance.[20]In diabetes mellitus, vitamin D deficiency decreases the efficacy of exogenous insulin and the pancreatic insulin production leads to insulin resistance. Thus, sufficient amount of vitamin D is not available for the inhibition of leptin hormone, produced by the fat cells in diabetic patients.[21]Datas from several studies predicts that diabetic patients had low serum concentration of 25(OH)D3 than healthy individuals.[22]Vitamin D deficiency in obesity patients altered the PTH level which contribute to secondary hyperparathyroidism.[23]Vitamin D supplements accelerates the production of insulin by the activation of non-selective voltage-dependent calcium channels. Calcium enhance the cleavage of proinsulin to insulin.[24] Other mechanisms of vitamin D in DM are biosynthesis of protein in islets of pancreas and direct modulation of beta cells.[25, 26]

Investigations reported that many inflammatory mediators destructs the pancreatic islets of Langerhans such tumour necrosis factor TNF-a and TNF-b, interleukin, 6 (IL-6) and its receptor, C-reactive protein and plasminogen activator inhibitor-1.[27] These mediators alter the insulin signaling pathway and accelerates insulin resistances. Vitamin D promotes its anti-inflammatory action by the inhibition of T lymphocyte mediated immunoglobulin synthesis in beta cells and blocks the progression of hypersensitivity reaction.[28]

Ocular diseases

Age related macular degeneration (AMD) is a chronic degeneration of macula results in vision loss in adults.[29]Multiple factors involved in the generation of AMD are inflammation, oxidative stress, genetic factors and disturbance in choroidal blood vessels. Apart from these factors, vitamin D deficiency also associated with AMD by its anti-inflammatory property by reducing C reactive protein, an inflammatory mediator. Sunlight exposure helps in the synthesis of dermal vitamin D which protects eye.[30] Vitamin D suppress the inflammation that occurred at retinal pigment epithelium–choroid interface in early stages of AMD.[31] Vitamin D modulates the immune response by acting on T-cell toward a T-helper 2 (anti-inflammatory) rather than a T-helper 1 (proinflammatory) response.[32] Evidences supported that low level of vitamin D are responsible for the progression of retinopathy among diabetic patients. Therefore, vitamin D supplements reduce the progression of several ocular disorders.[33] But there is no drug invented for the complete cure of AMD.

Uveitis is autoimmune inflammatory diseases which affect the retina and uvea. It is strongly supported that

uveitis patient had vitamin D hydroxylase gene polymorphism associated with high level human leukocyte antigen (HLA)-B27 gene.[34] Singman et al., reported a case study among corneal neuralgia patients with vitamin D deficient. Finding suggested that daily 1000IU of vitamin D supplement reduce the burning sensation in eye.[35]

Vitamin D deficiency increases the severity of multiple sclerosis (MS),as it reduces the production of C reactive protein, an inflammatory marker. Munger et al., concluded that people living away from equator are more prone to MS due to low concentration of 25-hydroxyvitamin D.[36]

Chronic kidney disease

A recent study implies that many tissues possess 1-hydroxylase apart from vitamin D receptors. Chronic renal failure contributes to vitamin D deficiency by 3 main pathways: a) reduced GFR limits the production of substrate for the activation of an enzyme,1-hydroxylase, b) elevated level of fibroblast growth factor-23 (FGF-23), c) hyperphosphatemia.[37]Kideneyincreases the absorption of calcium from several sources, reduce the excretion of calcium that maintain bone density. Studies suggests that, CKD patients are more prone to vitamin D deficiency due to several factors such as lack of exposure to sunlight, decreased the absorption and conversion of active vitamin D, decreased the amount of vitamin D receptors, increased the renal elimination of calcidiol.[38] Ali et al., reported that the prevalence of vitamin D deficiency (calcidiol < 30ng/ml) was higher among children with CKD.[39] So, vitamin D supplements are recommended to prevent renal osteodystrophy that impairs bone density. If calcidiol concentration is <5ng/ml, high dose of vitamin D2supplement (8000IU/day for 4 weeks) followed by 4000IU/day for 2 months. Calcidiol concentration should be assessed every 3 month of treatment up to the concentration is normalized.[40] Lagman et al., suggested that continues 2 year intake of vitamin D2supplement normalize the growth, velocity among pediatric with moderate CKD.[41]

A study by Agarwal et al., reported that oral paricalcitol therapy among CKD patients helps to reduce the proteinuria than who treated with ACEI or ARB.[42]Other mechanisms of vitamin D in renal system are: regulation of renin angiotensin system (RAS) and reduce glomercular growth, prevent the progression of podocyte hypertrophy, inhibits the generation of glucose induced fibronectin in mesangial cells, reduced the expression of inflammatory mediators such as TGF-beta and monocyte chemoattractant protein-1.[43]

Asthma

Vitamin D is an important factor for the growth and maturation of fetal lungs. Animal studies concluded that airway resistance was occurred during vitamin D deficiency. Koutkia et al., reported that asthma patients had elevated immunoglobulin E level due to vitamin D deficiency.[44] Vitamin D exerts its anti-inflammatory action by inhibiting IgE expression in B cells and promotes IL-expression.[45] Foods rich in vitamin D reduces the early symptoms of asthma such as wheezing and blocks the tracheal contractibility.[46]Some studies postulated that there is no significant relation between asthma and vitamin D deficiency.[47]Vitamin D supplements increases the anti-inflammatory action of corticosteriods used among asthmatic patients by enhancing the glucocorticoid-induced mitogen-activated protein kinase phosphatase-1 expression.[48]

Pregnancy and reproductive disorders

Reports highlighted that about 80% women had low concentration of vitamin D. Vitamin D and its metabolite is essential for calcium absorption and bone strength. Calcium regulates several functions such as muscle contraction, hormone and neurotransmitter generation and bone mineralization.[49] Third National Health and Nutrition and Examination Survey reported that 69% of pregnant women and 78% of non-pregnant women had insufficient vitamin D.[50] Studies concluded that pregnant women were less exposed to sunlight. Around 2 to 5% of pregnant and lactating women were suffered from osteoporosis and menstrual disorders.[51] Vitamin D enhance pancreatic insulin secretion, normalizes menstrual cycle and increased the number of dominant follicle in poly cystic ovarian syndrome (PCOS) patients.[52]Hofmeyr et al., suggested that calcium supplement of 1 gm throughout pregnancy period significantly reduces the risk of both gestational hypertension and pre-eclampsia.[53] Merewood et al., demonstrated that VDR present in the skeletal muscles will contribute for contraction of smooth muscles in uterus during delivery.[54]

PTH regulates the calcium hemostatis, as PTH increases calcium concentration decreases. Other function of PTH is to activate the enzyme,1-α-hydroxylase responsible for the conversion of 25(OH)D to 1,25(OH)2D. So PTH level act as an marker for vitamin D deficiency during pregnancy.[55] Mannion et al., strongly supported that maternal intake of 40 IU (1 µg) of vitamin D will increased 11 gm of newborn body weight.[56]

Psychiatry disorders

Insufficient vitamin D has been associated with psychiatric disorders such as schizophrenia, depression and alcoholism. Gloth et al., conducted a randomized study among eight affective disorder receiving 100,000 IU of vitamin D3supplement and seven members undergo phototherapy. Finding concluded that vitamin D improves the condition of patients.[57] Jorde et al observed that one year treatment with either 20,000 IU or 40,000 IU of vitamin D improves the depressive scores of patients.[58] Brown et al., assessed that insufficient vitamin D level has been found in all psychotic patients.[59] So vitamin D therapy in early stage of life had reduced the risk of schizophrenia.[60] Low serum concentration of calcidiol was

observed in both depressive and anxiety patients when compared with control group and are having normal range of vitamin D (30-40ng/ml).[61] A cross sectional study conducted among 112 people with several psychiatric disorders found that prevalence of vitamin D deficiency was higher among sominoform disorder (17.85%).[62] Patients with chronic schizophrenia had high serum concentration of inflammatory mediators like C reactive protein, TNF-α and IL-6.[63] Celecoxib as an adjunctive therapy with risperdone shows the improvement in Positive and Negative Syndrome Scale (PANSS) score.[64]Long term use of celecoxib or other COX inhibitors are associated with cardiovascular events and gastrointestinal bleeding.[65]

Autism

Autism Spectrum Disorder (ASD) is a neurological disorder characterized by difficulty in talking and understanding emotions, abnormal behaviour, impairment in daily physical activity and make an irrespective relationship with others.[66] ASD starts at early stage of life, especially within three year of age.[67] Evidences shows that ASD may occur due to the presence of abnormal autoantibodies, inflammation and oxidative stress in the brain.[68] One of the reason for ASD is low maternal concentration of 1,25(OH)2D. Genetic studies explained that, autism is an abnormal growth of brain may be due to over and under connectivity of neurons, loss of signal production and maintenance of neurotransmitters, disruption in synaptic cleft.[69] Studies conducted by Whitehouse et al., showed that maternal vitamin D deficiency had offspring with physical inability and mental disorders.[70] A case report by Jia et al., in 2015 successfully shown the improvement in 32 year old autism patient with vitamin D supplements.[71]

VDR present in several parts of brain including neurons and glial cells. It promotes cell differentiation and proliferations, thus protects several genomes from oxidative stress. Vitamin supplements prevent the production of 8-hydroxy-2-deoxyguanosin, which damage brain cells by oxidative stress, protein synthesis and maintain double strand of chromosomes.[72]Evidences illustrated that mitochondrial dysfunction, low level of glutathione peroxidase, imbalance in redox /antioxidant property are responsible for the development of chronic inflammation in cerebellum and temporal cortex of brain.[73] Vitamin D exert its neuroprotective action by increasing cellular production of glutathione, reducing the iron and zinc induced oxidative stress.[74]

Gastrointestinal diseases

Data from a retrospective cohort study among 504 inflammatory bowel disease patients reveals that vitamin D deficiency worsen the quality of life of Crohn's disease patients.[75] The immunomodulatory effect of vitamin D is effective in the treatment of Crohn's disease.[76]Oral vitamin D supplement (1200IU/day) significantly increased the serum concentration of vitamin D and reduce the relapse of Crohn's disease.[77] Vitamin D bind to its receptor (VDR) in intestinal epithelial layer to modulates the functions such as cell proliferation, differentiation and induction of apoptosis.[78]

It is clearly evident that 25(OH)D concentrations of > 100 nmol/L will increase the pancreatic cancer 2 fold than healthy individuals.[79]Villar et al., carried out a meta-analysis with a result of low serum concentration of vitamin D in hepatitis C patients (71%).[80] VDR polymorphism may be the predisposing factors for several autoimmune liver diseases such as cirrhosis, non-alcoholic fatty liver diseases, biliary tract infections, inflammatory bowel disorders and hepatitis infections.[81-84]Patients who undergo biliopancreatic bypass surgery had vitamin D deficiency.[85] Bone biopsies reported that cirrhosis patients had insufficient amount of vitamin D binding proteins and albumin.[86] Malabsorption of calcium, vitamins and several nutrients from enterohepatic circulation during cirrhosis and inflammatory disorders, worsens the cystic fibrosis.[87] The European Association for the Study of the Liver has designed new management of cholestatic diseases with 400-800 IU/day of vitamin D.[88] Calcium supplements (4g/day) is prescribed for duodenal malabsorption.[89]

Autoimmune disorders

Epidemiological studies stated that insufficient vitamin D was observed in autoimmune disorders such as rheumatoid arthiritis, systemic lupus erythromatosus and multiple sclerosis.[90] Vitamin D plays a numerous function in immune system such as: a) blocks B cell differentiation and proliferation b) promotes the anti-inflammatory effect by suppressing inflammatory cytokines c) increased the expression of type 2 Th (Th2) transcription factors d) maintenance of T cell dependent immunity.[91] Vitamin D supplements in lupus patients diminishes the expression of cytokine inducible genes than control groups.[92] Frequency of MS was subsequently decreased in patients with high 25(OH)D3.[93] Kamen et al., conducted a study to identifies the role of vitamin D in SLE patients. It seems that SLE patient's shows low serum level of vitamin D than healthy individuals.[94]

CONCLUSION

Vitamin D is an important vitamin/steroid used for calcium absorption and to make body strength. Low concentration of vitamin D was seen in several disease such as psychiatrial disorders, renal disease, gastrointestinal disease and pulmonary diseases. So, proper monitoring in every three month helps to maintain normal hemostatis and to modify treatments if deficiency presents. Several vitamin D3 supplements are now available in market with or without the combination with multivitamins or calcium as a source.

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