

Review Article

Emerging roles of vitamin D in various spectra of diseases

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Abstract

Vitamin D has been found to be useful for a number of conditions. Various studies have found it useful in different disorders to varying degree. It is being prescribed very frequently in clinical practice. So, we decided to conduct review to clarify its role in prevention and treatment of different disorders. We found more than thousand articles and reviewed relevant literature from databases like Cochrane, Pubmed, Medline that tested role of this vitamin in various spectra of diseases. We found vitamin D to be efficacious in conditions like cardiovascular diseases, diabetes mellitus, osteoporosis; but its role in treatment of certain conditions like multiple sclerosis, cognition needs to be assessed further studies.

Keywords: Vitamin D3, diabetes mellitus, osteoporosis, cognition

1. Introduction

Vitamin D, also known as sunshine vitamin, until recently was known mainly for its effect on musculoskeletal system. However as more research has been carried out about the pivotal role it plays in functioning of several other organ systems, now there is abundant literature available regarding its vital role in prevention of various spectra of diseases. Here is brief evidence based review of the various diseases in which role of this vitamin has been tested and proven.

1.1 Vitamin D and Diabetes Mellitus: Vitamin D3 is the active form of Vitamin D. Receptors to this active form have now been found in beta cells of pancreas. Vitamin D plays a role in functioning of beta cells of pancreas by binding of active form of Vitamin D to its receptor on beta cells. Vitamin D deficiency has been proposed to predispose to development of both types 1 as well as type 2 diabetes mellitus. Lots of research studies have been carried out to identify its role in pathogenesis as well as in the treatment of diabetes.

Several studies point to a link between deficiency of this vitamin in early life & later onset of Type I diabetes.^{11, 12} Prospective observational study by Hypponen *et al.*⁷ in Finland conducted with Vitamin D supplementation during infancy, “regular” vs. “none”, followed the children up to 14 yrs. They found that relative risk 0.12 of later onset of type 1 diabetes in infants who were given regular Vitamin D compared to the one who were not given any supplementation. Vitamin D deficiency may predispose to glucose intolerance, altered insulin secretion & Type 2 diabetes mellitus. There are Vitamin D receptors & Vitamin D binding protein in pancreatic tissue and they are related to glucose intolerance and insulin secretion. Studies showed a consistent association between low Vitamin D status, calcium daily intake and prevalence of Type 2 diabetes or metabolic syndrome. Liu *et al.* conducted Women’s Health study (US) in 52 middle aged women and classified into low and high Vitamin D intake groups. Mean follow up in the study was 9yrs. This study reported relative risk 0.73 of developing type 2 diabetes in higher Vitamin D intake group as compared to lower intake. Similar study was done by Pittas *et al.*¹ in [Nurses’ Health Study] in 46 young women. This study reported the relative risk 0.87 of type 2 diabetes in higher

vitamin D intake group as compared to lower intake. Thus, the available literature clearly proves the important role of vitamin D in the prevention as well as treatment of Type 1, type 2 as well as gestational diabetes. The table below summarizes important studies.

Table 1 Vitamin D and Diabetes Mellitus

Main Author	Type of Study	Conclusion
Pittas ¹	Review & metaanalysis	Higher Calcium & Vit D associated with 33% lower risk of diabetes
Chakhtoura ²	Review	Vit D addition in pregnancy & in children reduces risk of autoimmune diabetes
Tahrani A A ³	cross sectional study	Vit D deficient females had higher HbA1c.
Balenchia AM ⁴	R.C.T.	Alfacalcidol preserves beta cell function in new onset type 1 diabetes
C Mathieu ⁵	Review	Vit D deficiency involved in pathogenesis of both forms of diabetes
Pitocco D ⁶	R.C.T.	Vit D preserves residual beta cell function, reduces HbA1c only insignificantly
Elina Hypponen ⁷	Birth cohort	Vit D supplementation associated with reduced risk of type 1 diabetes.
Britta M Svoren ⁸	cross sectional study	Significant Vit D deficiency observed in youth with type 1 diabetes.
Hidayat R ⁹	cross sectional study	No significant association between Vit D deficiency and type 2 diabetes.
Sabherwal S ¹⁰	Case control	Vit D replacement reduces HbA1c significantly in South Asians.

1.2 Tuberculosis and vitamin D deficiency : Vitamin D and its active form 1, 25 vitamin D induce antibacterial peptides in vitro that effectively inhibit tuberculosis (TB). Early studies in 1985 showed that vitamin D treatment of murine and human macrophages could potentiate the effects of IFN- γ to inhibit TB in vitro.¹³ Till recently Vitamin D deficiency was considered uncommon in India. Following an original observation of Vitamin D deficiency in patients with Tuberculosis a controlled study was done to verify that in Kerala.¹⁴ Vitamin D levels in patients with recently diagnosed active Tuberculosis and matched healthy controls were compared. Adequacy of dietary intake of Vitamin D and adequacy sun exposure was studied in the two groups. This study concluded that Vitamin D deficiency was present in all patients with tuberculosis. Deficiency was also noted in healthy controls even though the level was higher compared to patients. The incidence of TB is higher among subjects with relatively low serum vitamin D levels, such as the elderly, uremic patients, and Asian immigrants in the U.K.¹⁵ Several other studies from different parts of world support important role of vitamin D in immunity against tuberculosis as shown in table 2.

Table 2 Role of vitamin D in immunity against tuberculosis

Main Author	Type of Study	Conclusion
Salahuddin ¹⁶	R.C.T.	Vit D supplementation accelerates improvement in Tuberculosis patients
Dini C ¹⁷	Review	Vit D supplementation is protective in Tuberculosis patients
Rathored J ¹⁸	Cross sectional study	Hypovitaminosis D may predispose to MDR-TB.
Sato S ¹⁹	Prospective study	Low Vit D a good predictor of prolonged clinical course in Tuberculosis.
Conesa ²⁰	Prospective study	Vit D deficiency associated with elevated cytokines in HIV-TB co-infection.
Desai N S ²¹	Observational study	Vit D deficiency highly prevalent in patients with TB
Gray K ²²	Observational study	Refugee children with TB have reduced Vit D levels.
Ho-pham LT ²³	Case control study	Vit D insufficiency a risk factor for tuberculosis in men, but not women.
Nursyam ²⁴	R.C.T.	Radiologic improvement more in PTB patients with Vit D supplementation.
Talat N ²⁵	Cohort	Low Vit D associated with 5 fold increased risk of progression to tuberculosis.

Systemic review and meta analysis by Kelechi E Nnoaham *et al.*²⁶ concluded that Low serum vitamin D levels are associated with higher risk of active tuberculosis. Since Vitamin D has a role in cell mediated immunity. It's deficiency could be one of the causes for the infection. This has been supported by epidemiologic data which suggest that low vitamin D is associated with TB severity or susceptibility.²⁷ Genes also probably contribute to this as shown by a meta- analysis

showing a positive association between VDR polymorphisms and host susceptibility to tuberculosis.²⁷ Patients with untreated TB, particularly those from a temperate climate, have lower serum vitamin D levels than healthy subjects.¹⁵ Recently, a double blind, randomized and placebo controlled trial used three high- dose (1,00,000 I.U.) vitamin D supplements in Tuberculosis patients.²⁸ The study showed no beneficial effect in clinical outcome or mortality in Tuberculosis. Another recent report in patients on dialysis showed no correlation between vitamin D supplementation and decreased risk of Tuberculosis infection.²⁹ So, in spite of several studies supporting role of vitamin D in body defence against tuberculosis, evidence from large scale placebo controlled trials is lacking. And, there is not adequate information available to claim vitamin D as an anti-infective agent.³⁰ Hence, as of today, vitamin D cannot be recommended for prevention or as part of treatment of tuberculosis.

1.3 Vitamin D and Cardiovascular diseases: Vitamin D deficiency has been associated with cardiovascular diseases.^{31,32} Several mechanisms have been proposed to explain how vitamin D could affect CVD risk. Probable mechanisms are- due to effect of vitamin D on vascular smooth muscle cell proliferation, inflammation, vascular calcification, and blood pressure through the RAS. Third National Health and Nutrition Examination Survey data analysis showed an inverse association between vitamin D levels and blood pressure.³³ In this study, during 4 years of follow-up, men and women who had plasma vitamin D levels less than 15 ng/mL were 3 times as likely to have a new diagnosis of hypertension in the next 4 years compared with those with vitamin D levels greater than 30 ng/mL. Important studies regarding role of vitamin D in hypertension have been listed below in table 3.

Table 3 Role of vitamin D in hypertension

Main Author	Type of Study	Conclusion
Sabanayagam ³³	From 3rd NHNES	Lower Vit D levels associated with pre-hypertension.
Forman J P ³⁴	R.C.T.	3 months of Vit D lowered systolic BP significantly.
Kunutsor S K ³⁵	Meta analysis	pooled RR of HTN per 10ng/ml increase in Vit D levels is 0.88.
Weng S ³⁶	Mice model	Vit D deficiency contributes to development of HTN, accelerated atherosclerosis
Carrara D ³⁷	Interventional study	Vit D supplementaion blunts RAS activity in essential HTN with Vit D deficiency.
Wang L ³⁸	Prospective study	Plasma Vit D and risk of HTN inversely related.
Goel R K ³⁹	Interventional study	Vit D has a role in blood pressure reduction in hypertensive patients.
Kota S K ⁴⁰	Prospective study	Vit D supplementation can reduce RAS activity in Vit D deficiency.
Caro Y ⁴¹	Cross sectional study	Vit D status not found to be associated with blood pressure.
John P ⁴²	Prospective study	Plasma Vit D and risk of incident HTN inversely related.

Various study reports have linked vitamin D deficiency to such cardiovascular conditions as hypertension, diabetes mellitus, obesity and the metabolic syndrome, left ventricular hypertrophy, heart failure, coronary heart disease, renal disease, and mortality.^{43- 47} In small clinical trials, vitamin D supplementation has promoted reductions in blood pressure,^{48, 49} left ventricular hypertrophy,⁵⁰ and inflammatory cytokines.⁵¹ Park *et al*,⁵⁰ showed regression of LV hypertrophy in hemodialysis patients treated with vitamin D. Cohort study by Annamari Kilkkinen *et al*.⁵² provided evidence that a low circulating level of vitamin D may predict a higher risk of cardiovascular disease death. In this study, subjects in the highest quintile of serum vitamin D level had less than half the risk of cerebrovascular death as those in the lowest quintile.⁵⁴ Among participants in the Framingham Offspring Study cohort, vitamin D deficiency was associated with an increased risk of CVD. The association was observed only in hypertensive subjects, not in those without hypertension.⁵³ In the Health Professionals Follow-up Study, men with a high circulating level of vitamin D had half the risk of myocardial infarction as men with vitamin D insufficiency.⁵⁴ Vitamin D deficiency is associated with increased mortality rates in the setting of chronic kidney disease⁵⁵, and repleting vitamin D in such patients improves outcomes. Yadav and colleagues,⁵⁶ in their study on chronic kidney disease patients, found Vitamin D deficiency to be correlating with preclinical atherosclerotic changes. There is also emerging evidence that treatment with vitamin D analogues reduces mortality in hemodialysis patients. Lower vitamin D levels have been observed in individuals with acute myocardial infarction,⁵⁷ stroke,⁵⁸ heart failure,^{59,60} and cardiovascular disease,⁶¹ peripheral arterial disease⁶² in several small cross sectional studies.

Though many studies have highlighted the protective role of vitamin D in prevention of cardiovascular diseases, there is no unanimity. Hsia and colleagues⁶³ recently reported that use of calcium and vitamin D supplements was not associated with a reduction in cardiovascular events in the Women's Health Initiative. Recent cohort study based on data from the Third National Health and Nutrition Examination Survey, Melamed *et al.*⁶⁴ could not find a statistically significant association between vitamin D status and cardiovascular disease mortality in the general population. Systematic review by Anastassios G. Pittas *et al.* of 13 observational studies (14 cohorts) and 18 trials concluded that association between vitamin D status and cardiometabolic outcomes is uncertain.⁶⁵ Results of the studies assessing role of vitamin D in cardiovascular diseases has been listed in table 4.

Table 4 Studies assessing role of vitamin D in cardiovascular diseases

Main Author	Type of Study	Conclusion
Thomas J Wang ⁶⁶	Framingham Offspring	Reduced vit D associated with incident cardiovascular diseases.
Lu Wang ⁶⁷	Systematic review	Vit D reduces Cardiovascular disease risk. Calcium has minimal effect.
Jeffrey ⁶⁸	Review	Low Vit D associated with CHD, Myocardial infarction, stroke.
Mark Bolland ⁶⁹	Meta analysis of W.H.I.	Calcium& vit D supplementation increases CHD risk.
Annamari ⁵²	M.F.H.Survey	vit D deficiency not associated with coronary artery disease risk.
Anastassios ⁷⁰	meta analysis	Association of Vit D& cardiometabolic outcomes uncertain.
Yadav ⁵⁶	Cross sectional	Vit D deficiency correlates with subclinical atherosclerosis in CKD patients.
Lim ⁷¹	cohort study	Subjects with low Vit D had high risk of significant coronary artery stenosis.
Young ⁷²	Prospective study	Low Vit D predicts prevalence, development of coronary artery calcification.
Liu L C ⁷³	Prospective study	Low levels of Vit D is associated with a poor prognosis in HF patients.

It is too early to know if the beneficial effect of vitamin D treatment is mediated by effects on cardiac function; there is, however, sufficient literature to support the notion that vitamin D has a beneficial effect on cardiac tissue. Evidence from data available till now suggests that vitamin D supplements at moderate to high doses may reduce CVD risk, whereas calcium supplements seem to have minimal cardiovascular effects.⁷⁴ Vitamin D deficiency, thus, probably represents an important new cardiovascular risk factor and, may be an etiologic factor in the development of cardiovascular risk factors and cardiovascular diseases and adverse events, including death.⁷⁵

1.4 Vitamin D and Osteoporosis: Osteoporosis is the most common metabolic bone disease in the world. Vitamin D plays a key role in bone formation. A low vitamin D level is an established risk factor for osteoporosis. Vitamin D deficiency will decrease the active trans-cellular absorption of calcium. Vitamin D supplementation of more than 400 IU daily has been found to reduce incidence of non-vertebral fractures as shown by a meta analysis.⁷⁶ The effect was dose dependent and was not significant if doses were ≤ 400 IU daily.

Table 5 Role of Vitamin D in Osteoporosis

Main Author	Type of Study	Conclusion
Alibhai S M ⁷⁷	Prospective longitudinal	Vit D protective against loss of BMD due to androgen deprivation therapy.
Von Schacht ⁷⁸	Review	Alendronate, vit D meets demands of optimized therapy of osteoporosis.
Mata Granados ⁷⁹	cross sectional study	Vit D deficiency, high retinol are significant risk factors for osteoporosis.
Quesada ⁸⁰	cross sectional study	Vit D deficiency prevalent in both treated&untreated osteoporotic women
Hagino H ⁸¹	R.C.T.	Vit D reduces risk of severe vertebral fractures.
Jill Pothouse ⁸²	R.C.T.	No evidence that calcium, Vit D reduce risk of clinical fractures.
A Avenell ⁸³	R.C.T.	Vit D alone unlikely to prevent fracture. With calcium, reduces fracture.
P Lips ⁸⁴	cross sectional study	Low serum Vit D is common in females with osteoporosis.
Van Schoor M ⁸⁵	Longitudinal	Serum Vit D<12nmol/ml is associated with increased fracture risk.
Joane Homik ⁸⁶	Interventional review	Bone loss in patients on corticosteroid therapy reduced by Vitamin D

Results of several important studies favour vitamin D supplementation for prevention and treatment of osteoporosis (table 5). Thus prescribing vitamin D supplements in patients with osteoporosis seems to be adequately justified.

1.5 Vitamin D and Multiple Sclerosis^{87, 88}: Vitamin D is important for normal immune response of the body. It affects the growth and differentiation of immune-modulator cells like T and B lymphocytes, antigen presenting cells like macrophages, dendritic cells. This action has implications for a variety of autoimmune diseases including rheumatoid arthritis, systemic lupus erythematosus,⁸⁹ type 1 DM, inflammatory bowel disease, and Multiple Sclerosis.⁸⁷ Vitamin D supplementation may help prevent the development of MS and may be a useful addition to therapy.⁹⁰ Higher serum vitamin D levels are protective against MS as shown by a case-control study which showed that for every 10-nmol/L increase of serum vitamin D level the odds of MS was reduced by 19% in women.⁹¹ Several other studies have supported the finding that lower levels of vitamin D in MS patients are associated with more severe disability. Lower levels during relapses have also been reported in patients with relapse-remitting MS. A large observational study in the United States that followed the Nurses' Health Study involving 92,253 women and the Nurses' Health Study II⁹² involving 95,310 women—found that vitamin D supplementation in the form of a multivitamin seemed to lower their MS risk by 40%. However, several methodological weaknesses in study design made the results inconclusive.⁹³ Vitamin D supplementation at appropriate dosage has been shown to reduce gadolinium-enhancing lesions on magnetic resonance imaging without causing hypercalcemia, hypercalciuria, or other complication.⁹³ Support for vitamin D supplementation in MS patients is also given by A Finnish study which found that, compared with patients without MS, patients with MS had lower serum vitamin D levels during the summer.⁹⁴

Table 6 Role of Vitamin D in Multiple Sclerosis

Main Author	Type of Study	Conclusion
Soilu Hanninen ⁹⁴	longitudinal study	Vit D levels and MS clinical activity inversely related.
Simpson S Jr ⁹⁵	Cohort study	10nmol/l increase in vit D results in 12% reduction in risk of MS relapse
Runia T F ⁹⁶	Prospective study	Higher vit D associated with reduced exacerbation in RRMS
Pandit L ⁹⁷	Case control	Serum Vit D shows inverse relation with MS in Indian population.
Pozuelo ⁹⁸	R.C.T.	Evidence for Vit D as a treatment of MS is inconclusive.
Van Amerongen ⁹⁹	longitudinal case report	Vit D reduced pain and increased ambulation from 1 to 14km/day.
Mesliniene ¹⁰⁰	Review	Risk of MS might be reduced by normal Vit D in healthy population
Grau Lopez L ¹⁰¹	Cohort study	Vit D might regulate T cellproliferation to myelin peptides in RRMS patients
Fariba Mirzaei ¹⁰²	Nurses Health Initiative	Higher Vit D in pregnancy associated with lower MS risk.
Neau J P ¹⁰³	Prospective survey	Vit D levels are very low in MS, particularly RRMS& PPMS

From the table above, we can observe that vitamin D deficiency is associated with worse clinical course of multiple sclerosis, with more frequent relapses and disease exacerbations. A link between dietary intake of vitamin D and the incidence of MS has also been suggested. The Atlantic coastal areas of Norway have a lower incidence of MS than the rest of Scandinavia, which is thought to be due to the high amount of vitamin D from fish in the local diet.¹⁰⁴ So, the measures to increase blood levels of vitamin D either by diet or supplementation may be used to improve the course and prognosis of multiple sclerosis.

1.6 Vitamin D and Cognition: Vitamin D levels have been found to correlate with score on mental status examination in a study.¹⁰⁵ The biological plausibility of this relationship includes vitamin D's anti-oxidative effects and the presence of vitamin D receptors in the hippocampus, which has been seen in rats and humans. Vitamin D is needed for normal cognition and deficiency of this vitamin has been proposed to predispose to cognitive disorders like Alzheimers' disease (table 7).

Table 7 Role of Vitamin D in Cognition

Main Author	Type of Study	Conclusion
Peterson A ¹⁰⁶	Observational study	Vit D concentrations correlated with cognition
Wilkins C H ¹⁰⁷	Cross sectional study	Vit D deficiency was associated with impaired cognitive performance.
Annweiler C ¹⁰⁸	Cohort study	Vit D deficiency was associated with impaired cognition in older females.
Skalska A ¹⁰⁹	Cross sectional study	In elderly people, Vit D levels associated with cognitive function.
Rossom R C ¹¹⁰	R.C.T.	No association between Vit D treatment and cognitive impairment.
Annweiler C ¹¹¹	meta analysis	Alzheimer Disease cases had lower Vit D concentration than controls.
Balion C ¹¹²	meta analysis	Low Vit D levels are associated with poorer cognitive function.
Slinin Y ¹¹³	Cohort study	Low Vit D levels are associated with higher risk of cognitive decline.
Annweiler C ¹¹⁴	Longitudinal study	Higher Vit D associated with lower Alzheimer Disease risk in older women.
Annweiler C ¹¹⁵	Longitudinal study	Vit D deficiency predicted onset of non Alzheimer dementia in older women.

But this notion has not been supported by well designed randomized control trials till today. Hence, till evidence from such large and well designed studies is available, vitamin D supplementation cannot be recommended for either prevention or treatment of multiple sclerosis.

1.7 Vitamin D and Chronic Pain: Because of the important role vitamin D plays in bone homeostasis, it is only logical to think that vitamin D deficiency may correlate with chronic pain syndromes, including chronic low back pain. Most of the times Vitamin D deficiency occurs without any symptoms, if at all any symptoms present it indicates severe deficiency (<5ng/ml). Severe vitamin D deficiency leads to osteomalacic myopathy, as characterized in a case series demonstrating severe myalgia and muscle weakness in individuals with low serum concentration of vitamin D, with prompt resolution of symptoms following vitamin D replacement.¹¹⁶ 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. Patients often complain of aching nonspecific symptoms such as bones and myalgia. Such patients are often misdiagnosed with fibromyalgia, chronic fatigue syndrome, myositis, or other nonspecific collagen vascular diseases. It is estimated that 40-60% of patients with fibromyalgia may have some component of vitamin D deficiency and osteomalacia.¹¹⁷⁻¹²¹

Table 8 Role Vitamin D in Chronic Pain

Main Author	Type of Study	Conclusion
Al Faraj ¹²²	Cross sectional study	Vit D deficiency is a major contributor to chronic back pain.
Le Goaziou MF ¹²³	Prospective study	Vit D deficiency correction had positive impact on musculoskeletal pain.
Straube ¹²⁴	Retrospective study	No evidence of low Vit D in chronic pain than in control population.
Osunkwo ¹²⁵	Pilot study	Vit D reduces number of pain days in sickle cell disease.
Lotfi ¹²⁶	Prospective study	Low Vit D commoner in females with chronic low backache.
Huang W ¹²⁷	Case series	Vit D supplementation improves chronic pain levels.
Turner M K ¹²⁸	Case series	Low Vit D may represent under recognized source of nociception.
Knutsen K V ¹²⁹	Cross sectional study	Low Vit D highly prevalent in patients with non specific musculoskeletal pain.
De Rezende ¹³⁰	Cross sectional study	Low Vit D is not more prevalent in patients with fibromyalgia.
Prakash S ¹³¹	Case series	Headache improved first in Vit D deficiency on supplementation of Vit D.

Vitamin D deficiency often presents as musculoskeletal pain severity of which increases with lower vitamin D levels. Treatment of vitamin D deficiency produces an increase in muscle strength and a marked decrease in back and lower-limb pain within few months. However the verdict on this topic will remain undecided until this is evaluated by double-blind, randomized, controlled trials stratified by baseline vitamin D level with defined treatments and comparison placebo groups.

2. The Role of Vitamin D in Cancer Prevention: Role of vitamin D is being researched by studies around all over. More than 1000 laboratory and epidemiological studies have been published concerning the association between vitamin D and its metabolites and cancer. Emphasis is being paid on vitamin D in cancer prevention and treatment because of the easy availability and low cost of this molecule in addition to its positive results from lots of studies. The evidence suggests that efforts to improve vitamin D status could result in less cancer incidence and mortality at low cost, with few or no adverse effects. Raising serum vitamin D to appropriate level can prevent approximately 58,000 new cases of breast cancer and 49,000 new cases of colorectal cancer each year.¹³² In a cohort study by Edward Giovannucci *et al*, a vitamin D increment of 25 nmol/L was associated with a 17% reduction in total cancer incidence, a 29% reduction in total cancer mortality, and a 43% and 45% reduction in incidence and mortality, respectively, of digestive-system cancers.¹³³ Digestive system cancer incidence as well as mortality in men has been found to be associated with low levels of vitamin D.¹³⁵ Vitamin D synthesis³⁴ and serum vitamin D levels¹³⁵ are inversely correlated with latitude and directly with sunlight, consistent with higher incidence or mortality rates for colon¹³⁶ and breast cancer,¹³⁷ especially in areas 37° or more from the equator. There are also north–south gradients for ovarian¹³⁸ and prostate cancer.^{139,140}

2.1 Vitamin D and colon cancer: Relation between vitamin D deficiency and colon cancer has been subjected to various studies. Individuals with low circulating vitamin D levels have been shown to be at increased risk of colon cancer in various studies (table 9).

Table 9 Role of Vitamin D in Colon Cancer

Main Author	Type of Study	Conclusion
Garland C ¹⁴¹	prospective study	Risk of colorectal cancer inversely related with dietary Vit D, Calcium
Jean Wende ¹⁴²	R.C.T.(W.H.I.)	No effect on colorectal cancer
Stubbins R E ¹⁴³	Review	Vit D can be used to treat and prevent colon cancer.
Rawson J B ¹⁴⁴	Cohort study	Vit D may alter colorectal cancer risk.
Edward G ¹⁴⁵	Meta analysis	Vit D supplementation reduces colorectal cancer risk
Bai Y H ¹⁴⁶	Meta analysis	VDR gene polymorphism associated with increased colon cancer risk
Pereira F ¹⁴⁷	Review	Vit D is protective against colon cancer.
Schwartz ¹⁴⁸	Review	Vit D plays important role in cancer prevention.
Slattery ¹⁴⁹	case control study	Low Vit D may increase colon cancer risk
Martinez M E ¹⁵⁰	Review	Vit D is inversely associated with colorectal colon cancer risk.

Several epidemiological studies like Western Electric Cohort Study, the Nurses' Health Study, the Male Health Professionals' Follow-Up Study have reported higher risk of colon malignancy in individuals consuming lower amounts of vitamin D.¹⁴² Both human and animal studies-interventional as well as non-interventional support protective notion that vitamin D can reduce the risk of colon cancer related to high dietary fat intake.¹⁵¹⁻¹⁵⁴ Daily intake of 1000–2000 IU/day of vitamin D₃ could reduce the incidence of colorectal without any significant risk.¹⁴⁵ Population serum vitamin D level of 40 to 60 ng/mL has been found to be adequate to obtain various health benefits of this vitamin, which is obtained from intake of approximately 2000 IU per day of vitamin D₃.

2.2 Vitamin D and breast cancer: Western-style diet, which contains low calcium and vitamin D and increased fat content has been found to induce hyper-proliferation and hyperplasia in mammary gland and colonic epithelium in short-term studies; dietary calcium supplementation inhibited those changes.¹⁵⁵ Breast cancer death rates tend to be lower in areas with better sunshine. Women with lower serum Vitamin D levels (< 75nmol/l) have been found to have higher risk of breast cancer than those in whom vitamin D levels are in normal range. Lower vitamin D levels have also been associated with faster progression of metastatic breast cancer.¹⁵⁶ Several epidemiologic and experimental studies have now suggested that high dietary fat and decreased calcium and vitamin D intake have associations with mammary gland carcinogenesis.¹⁵⁷⁻¹⁵⁹

Table 10 Role of Vitamin D in breast cancer

Main Author	Type of Study	Conclusion
Villasenor A ¹⁶⁰	Retrospective	Higher Vit D associated with statistically insignificant improved survival.
Bilinski K ¹⁶¹	case-control	Vit D levels<75nmol/ml associated with higher breast cancer risk.
Karbasi A ¹⁶²	case-control	All patients with breast cancer were Vit D deficient
Hatse S ¹⁶³	Prospective study	High Vit D correlate with low tumor size and better outcome.
Fedirko V ¹⁶⁴	case-control	Inverse relation between Vit D levels& breast cancer risk.
Peppone L J ¹⁶⁵	case-control	aggressive, worse prognosis marker associated cancers had low serum Vit D
Trukova K P ¹⁶⁶	case-control	Vit D deficiency present in both controls&breast cancer survivors.
Kermani L A ¹⁶⁷	analytic-descriptive	Serum Vit D levels& prognosis of breast cancer associated.
Pazdiora P ¹⁶⁸	case-control	All cancers had low levels of Vit D
Mohr S B ¹⁶⁹	pooled analysis	Higher serum Vit D levels reduce breast cancer risk

2.3 Vitamin D and prostate cancer: Vitamin D has been proposed to have beneficial effect in prevention and treatment of prostatic cancer. Several studies have been carried to study this association. The results have been mixed as shown in table below. But, no large scale placebo controlled study has been carried out yet.

Table 11 Role of Vitamin D in prostate cancer

Main Author	Type of Study	Conclusion
Skowronski ¹⁷⁰	Experimental	Vit D can elicit anti-proliferative& differentiating action on prostate cancer cells.
Corder ¹⁷¹	Retrospective study	Low Vit D was important predictor for palpable& anaplastic prostatic tumors.
Wagner D ¹⁷²	R.C.T.	Ora l vit D lowered Prostate Specific Antigen
Mondul A M ¹⁷³	Pooled analysis	No protective association loci which influence vit D levels and prostate cancer risk.
Ma ¹⁷⁴	case control study	No significant association of VDR polymorphisms with prostate cancer risk.
Ansari M S ¹⁷⁵	Review	Vit D can be a part of chemopreventive strategies for prostatic cancer.
Tretli S ¹⁷⁶	Retrospective study	Medium or high vit D levels were related to better prognosis of prostate cancer.

Thus, though theoretically vitamin D is likely to have beneficial effects on prostatic cancer, in the absence of strong evidence to prove its therapeutic utility, no definite recommendations can be made for its use in prostatic cancer.

In addition to being associated with specific diseases and morbidity associated with those conditions, lower vitamin D levels also have been associated with increase in all cause mortality as noted from cardiovascular disease (CVD) mortality in 13331 nationally representative adults 20 years or older from the Third National Health and Nutrition Examination Survey (NHANES III) linked mortality files.¹⁷⁷ And Intake of usual doses of vitamin D supplements seems to be adequate to reduce these death rates.¹⁷⁸

3. Serum levels recommended:

Based on the serum levels, Vitamin D deficiency can be classified into different groups. This is shown in table below.

Table 12 Serum levels recommended

Classification	25 (OH) D level (nmol/L)
Deficient	< 20
Insufficient	20-50
Optimal	50-125
High	125-225
Toxic	> 225

4. Dosage recommendation

In patients with documented vitamin D deficiency, a cumulative dose of at least 6 lakh units administered over several weeks is essential to replenish stores.¹⁷⁹ According to mayoclinic, for type 2 diabetes patients, 400-5714 IU of vitamin D is recommended to be taken by mouth daily for 2 months to several years. According to KDOQI guidelines, in patients with chronic kidney disease, monthly intake of 50,000 IU orally is recommended. 10–15 min whole-body exposure to peak summer sun will generate and release up to 20,000 IU vitamin D-3 into the circulation. So, exposure to sunlight is very simple and effective measure to prevent vitamin D deficiency. Dark-skinned or veiled individuals not exposed much to the sun, elderly and institutionalized individuals may be supplemented (800 IU/day) without baseline testing.¹⁸⁰

4.1 Recommendation of vitamin D dosage in different age groups¹⁸¹

Table 13 Age group Vitamin D sufficient Vitamin D deficient

0-1 yr	400 IU/day	2000 IU/day or 50,000/week for 6weeks& 400-1000 IU/d maintenance
1-18 yrs	600 IU/day	2000 IU/day or 50,000/week for 6 weeks& 600-1000 IU/d maintenance
19-50 yrs	600 IU/day	6000 IU/day or 50,000/week for 8 weeks& 1500-2000 IU/d maintenance
51-70- yrs	600 IU/day	6000 IU/day or 50,000/week for 8 weeks& 1500-2000 IU/d maintenance
> 70 yrs	800 IU/day	6000 IU/day or 50,000/week for 8 weeks& 1500-2000 IU/d maintenance

5. Conclusion

Vitamin D has definite beneficial role in prevention and treatment of cardiovascular disease, osteoporosis, type 1 diabetes, type 2 diabetes, gestational diabetes. Intake of vitamin D is associated with reduced incidence and death rates of colon, breast, prostate, and ovarian cancers. It is probably also beneficial for chronic pain. But its role in cognitive disorders, multiple sclerosis and tuberculosis requires further research. Because of the overall health benefits of this vitamin for various diseases, measures to prevent deficiency of this vitamin like exposure to sunlight, dietary supplementation need to be encouraged in all the individuals.

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