Review Article Vitamin D Deficiency, Role in Chronic Diseases

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Abstract— Vitamin D is a sunshine vitamin and is key player in Bone diseases (like Osteoporosis,Osteoarthritis,Rheumatoid Arthritis),Autoimmune diseases,Chronic diseases like Diabetes Mellitus,Hypertension,CardiovascularDiseases,Metabolic Syndromes and Cystic fibrosis Calcium,Magnesium and Phosphorus are the key ions whose interplay is closely linked to each other in positive bone metabolism and Vitamin D is the regulator of this process.Northern Hemisphere due to its geographic location and westernized lifestyle has a high prevalence of Vitamin D population,which has further been linked to growing numbers of cancers and autoimmune diseases in this region.

This Review article throws light on Vitamin D and its role in chronic diseases .Based on the aspects discussed in this review the article recommends"PCP's should not overlook the levels of this vital vitamin .In all chronic disease sufferers and old age people,Vitamin D levels should be ascertained and Vitamin D supplementation should be a part of treatment regimen .Vitamin D is a preventive Vitamin in itself".

Index Terms— Vitamin D, Chronic Diseases, T2DM, CF, HTN, RA, Autoimmune disease, Rheumatoid Arthritis, Osteoporosis, Osteoarthritis, Bone disease, ,Metabolic Syndrome, Cystic fibrosis Calcium

1. INTRODUCTION

Vitamin D deficiency is common in Northern hemisphere due to latitude exposure of sun is limited and more of indoor lifestyles.Vitamin D is a silent disease and linked to T2DM,CF,HTN,RA and a risk factor for Autoimmune diseases and CVD outcomes. AlsoSymptoms crop up when the levels lower down significantly.Limited evidences exist on specific guidelines of treatment.
Targetting Vitamin D deficient populationand treating them with regular vitamin D status assessment will help in designing treatment strategyfor such model population.Vitamin Din its active form, vitamin D3 is the most superior treatment modalityin such population.

Vitamin D3 to be superior at raising 25-hydroxy vitamin D (25(OH)D),thebestmarkerforvitaminDstatus. Calcitrioltherapysignificantlycorrects the levels.VitaminDdeficiencyiscommonandcanbecorrectedwithadequatevitaminDsupplementation.CorrectformanddoseofvitaminDtoandthemechanismforvitaminD's.is the main arena of exploration indiseases where Vitamin D levels are the key player in pathogenesis of the disease.VitaminDdeficiency (definedas25 (OH) D<20ng/mL) is of epidemiological importance in United States.

Vitamin D deficiency has found its role as a risk factor in a host of conditions osteoporosisandrheumatoidarthritis,immunefunction, and autoimmunediseasesandcancer.Infact, resolutionofdeficiencymayprovideinexpensiveprophylaxisformanyconditions.However, treatmentofvitaminDdeficiencyislargelyoverlookedinclinicalpractice.
Lackofawarenessamongst PCP's is attherootoftheproblem(1).Inpart,thisisbecause vitaminDrequirementsmayvarybydiseaseand evenbypersonwhichcomplicates thedevelopmentofatreatmentprotocol.Factors that could judge Vitamin D requirement are still to be explored to get the General recommendation of treatment.
RootcausesofvitaminDdeficiencyattributedtofat malaabsorptionanddecreasedsunexposurerelatedtodecreasedoutdooractivity (2, 3).InRA, vitaminDdeficiencyisassociatedwithlowbone density, and immunefunction(4).Therefore,theRA Foundationhasrecommendedactivelytreating vitamin-Ddeficiency.

Conversely RA isacommonchronicconditionaffectingnearly onethirdoftheUSpopulation(5).Thecauseofth

e vitaminDdeficiencyislargelyunknownbutmaybeduetodecreaseddietaryintake,decreasedsunexposure,andexcessiveexcretionofthevitaminDcarrierprotein,vitaminDbindingprotein(DBP)(6).Currentlythereisnoconsensusmedicalopinionregardingtreatment ofvitamin-DdeficiencyinRA eventhoughlowvitaminDlevelsareassociatedwithincreasedbloodpressure,diabetes,andcardiovasculardisease(7-10).

VitaminD: History, Structure, andFunctionVitaminDbecameanutrientofnotewhen,attheturnofthetwentiethcentury,SirEdwardMellanbyestablishedthatcodliveroilhadanti-rachiticactivity(11).However, it was McCollum who later determined thatanutrientpresentincodliveroilwasresponsibleforitsanti-rachiticactivityandnamedthisnutrientvitaminD (12).

MellanbyoriginallysuggestedvitaminAincodliveroilpreventedrickets;however,McCollumconcludedthiswasnotthecase.Hedestroyedthevitamin Ainthecodliveroilbyheatingitandtheoilstillhadanti-rachiticactivity.Thus,hedeclaredthenew

Substanceremainingincodliveroiltobevitamin D (13).However, evenbeforthediscoverythatcodliveroilcouldcurerickets, TrousseauofFranceandPalmofGreatBritainnotedthatsunlightcouldbeusedtocurerickets,thoughitwasnotknownthatthistoowasthroughthevitaminDendocrinesystem (14).It isnowknownthatvitaminDispresentinlimited foodsuchascodliveroilandproducedendogenouslyintheskin.

2. Vitamin D Structure & Function

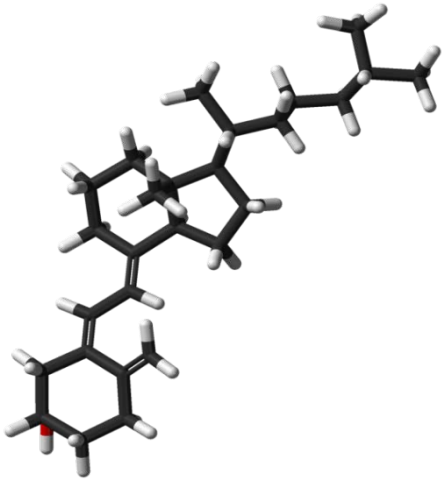
Figure 1.

Metabolic pathways by which vitamin D exerts its many effects in the body. (A) The prevailing scheme before recognition of the role of peripheral 1-α-hydroxylation. In this scheme, essentially all conversion of 25-hydroxyvitamin D [25(OH) D] to calcitriol occurs in the kidney, and the synthesized calcitriol appears in the serum, where it can be measured. Calcium-binding protein (CaBP) is a stand-in for the complex calcium absorptive apparatus induced in the enterocyte by calcitriol. (B) The current scheme, explicitly incorporating extrarenal 1-α-hydroxylation, with the resulting calcitriol appearing mainly intracellularly, where it is clinically unmeasured able. (Copyright Robert P. Heaney, 2008. Used with permission.)

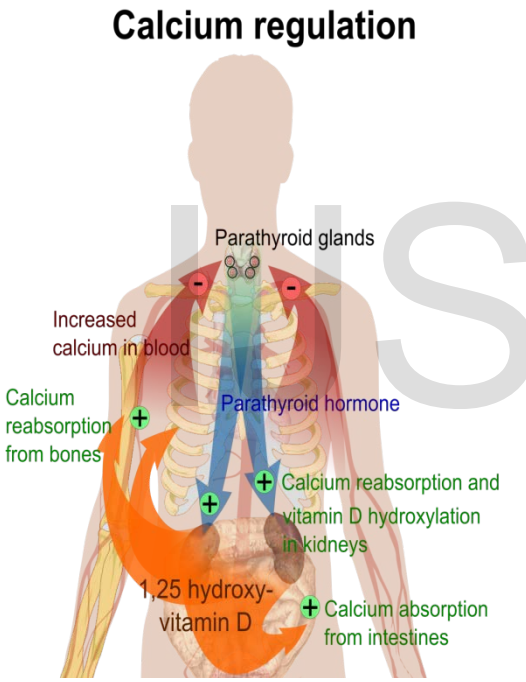
3. Vitamin – D

Vitamin D is a group of fat-soluble secosteroids, the two major physiologically relevant forms of which are vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol). Vitamin D without a subscript refers to either D_2 or D_3 or both. Vitamin D_3 is produced in the skin of vertebrates after exposure to ultraviolet B light from the sun or artificial sources, and occurs naturally in a small range of foods. In some countries, staple foods such as milk, flour and margarine are artificially fortified with vitamin D, and it is also available as a supplement in pill form [15]. Food sources such as fatty fish, mushrooms, eggs, and meat are rich in vitamin D and are often recommended for consumption to those suffering vitamin D deficiency[16].

Vitamin D is carried in the bloodstream to the liver, where it is converted into the prohormonecalcidiol. Circulating calcidiol may then be converted into calcitriol, the biologically active form of vitamin D, either in the kidneys or by monocyte-macrophages in the immune system. When synthesized by monocyte-macrophages, calcitriol acts locally as a cytokine, defending the body against microbial invaders [17]



Cholecalciferol(D_3)



Calcium Regulation In Body[1]

When synthesized in the kidneys, calcitriol circulates as a hormone, regulating, among other things, the concentration of calcium and phosphate in the bloodstream, promoting the healthy mineralization, growth and remodeling of bone, and the prevention of hypocalcemictetany. Vitamin D insufficiency can result in thin, brittle, or misshapen bones, while sufficiency prevents rickets in children and osteomalacia in adults, and together with calcium, helps to protect older adults from osteoporosis Vitamin D also modulates neuromuscular function, reduces inflammation, and influences the action of many genes that regulate the proliferation, differentiation and apoptosis of cells [18]

Forms –

Several forms (vitamers) of vitamin D have been discovered. The two major forms are vitamin D_2 or ergocalciferol& vitamin D_3 or cholecalciferol;those are known collectively as calciferol [19]. Vitamin D_2 was chemically characterized in 1932. In 1936 the chemical structure of vitamin D3 was established and resulted from the ultraviolet irradiation of 7-dehydrocholesterol [20].

Name	Chemical Composition
Vitamin D_1	Molecular compound of ergocalciferol with lumisterol, 1:1
Vitamin D_2	Ergocalciferol (made from ergosterol)
Vitamin D_3	Cholecalciferol (made from 7-dehydrocholesterol in the skin)
Vitamin D_4	22-dihydroergocalciferol
Vitamin D_5	Sitocalciferol (made from 7-dehydrositosterol)

Chemically, the various forms of vitamin D are secosteroids; i.e., steroids in which one of the bonds in the steroid rings is broken[21]. The structural difference between vitamin D_2 and vitamin D_3 is in their side chains. The side chain of D_2 contains a double bond between carbons 22 and 23, and a methyl group on carbon 24.

Vitamin D_2 (made from ergosterol) is produced by invertebrates, fungus and plants in response to UV irradiation; it is not produced by vertebrates [22]. Little is known about the biologic function of vitamin D_2 in non vertebrate species. Because ergosterolcan more efficiently absorb the ultraviolet radiation that can damage DNA, RNA and protein, it has been suggested that ergosterol serves as a sun screening system that protects organisms from damaging high energy ultraviolet radiation[23].

In 1923, it was established that when 7-dehydrocholesterol is irradiated with light, a

form of a fat soluble vitamin is produced. Alfred Fabian Hess showed that "light equals vitamin D" [24]. Adolf Windaus, at the University of Gottingen in Germany, received the Nobel Prize in Chemistry in 1928, for his work on the constitution of sterols and their connection with vitamins [25]. In the 1930s he clarified further the chemical structure of vitamin D.

In 1923, Harry Steenbock at the University of Wiscosnsin demonstrated that irradiation by ultraviolet light increased the vitamin D content of foods and other organic materials[26]. After irradiating rodent food, Steenbock discovered that the rodents were cured of rickets. It is now known that vitamin D deficiency is a cause of rickets. Using $300 of his own money, Steenbock patented his invention. Steenbock's irradiation technique was used for foodstuffs, most memorably for milk. By the expiration of his patent in 1945, rickets had all but been eliminated in the US [27].

The vitamin D receptor belongs to the nuclear receptor superfamily of steroid/thyroid hormone receptors, and VDRs are expressed by cells in most organs, including the brain, heart, skin, gonads, prostate, and breast. VDR activation in the intestine, bone, kidney, and parathyroid gland cells leads to the maintenance of calcium and phosphorus levels in the blood (with the assistance of parathyroid hormone and calcitonin) and to the maintenance of bone content[28].

Vitamin D increases expression of the tyrosine hydroxylase gene in adrenal medullary cells. Vitamin D is involved in the biosynthesis of neurotrophic factors, synthesis of nitric oxide synthase, and increased glutathione levels [29]. The VDR is known to be involved in cell proliferation and differentiation. Vitamin D also affects the immune system, and VDRs are expressed in several white blood cells, including monocytes and activated T and B cells [30]. Apart from VDR activation, various alternative mechanisms of action are known. An important one of these is its role as a natural inhibitor of signal transduction by hedgehog (a hormone involved in morphogenesis) [31-32].

TheactiveformofvitaminD,1α,25(OH)$_2$D, hasmanyfunctionsincludingsignaltransductio nand genetranscription.1α,25(OH)$_2$Dbindstoitsrece ptor,thevitaminDreceptor(VDR), andentersthenucleuswhereitenablestranscripti onofthosegeneswithavitaminDresponseeleme nt(VDRE).TheVDRhasahighaffinityfor1α,25(O H)$_2$Dasopposedtootherformsofvitamin-D.IthasbeenestimatedthattheVDRregulatesthe expressionof2.5%ofthegenesinthehumangeno me.Thegenesrangeinfunctionfrombonemetab olism,tocelldifferentiationandproliferation,Ina dditiontocellularregulationatthenucleartransc riptionlevel,1α,25(OH)$_2$Dalsohasrapidactions. HuhtakangasetalHaveshownthattheVDRpres entoncellmembranesisassociatedwithcaveolae involvedinsignaltransduction.Activationofthe VDRonthecellmembranecanresultinavarietyof signaltransductionresponsesincludingsecond messengersystemssuchasproteinkinase-Cand phosphate idylinositol-3-kinase(PI3K).Anynumberofcellularfunctionsc ouldberegulatedinthisway.Thefactthat1α,25(O H)$_2$Dcouldhavebothrapidandgenomicrespons eshelpstoexplainsomeofthedifferencesbetwee ntheacuteresponsesto1α,25(OH)$_2$Dandlongert ermresponsesoutlinedlaterinthechapter.

4. DEFICIENCY

Low blood calcidiol (25-hydroxy-vitamin D) can result from avoiding the sun[33]. Deficiency results in impaired bone mineralization, and leads to bone softening diseases [34] including:

- Rickets, a childhood disease characterized by impeded growth, and deformity, of the long bones which can be caused by calcium or phosphorus deficiency as well as a lack of vitamin D; today it is largely found in low incme countries in Africa, Asia or the Middle East [35] and in those with genetic disorders such as pseudovitamin D deficiency rickets [36]. Rickets was first described in 1650 by Francis Glisson who said it had first appeared about 30 years previously in the countries of Dorset and Somerset [37]. In 1857 John Snow suggested the rickets then widespread in Britain was being caused by the adulteration of bakers bread with alum [38]. The role of diet in the

development of rickets [39-40]. Was determined by Edward Mellanbybetween 1918-1920[41]. Nutritional rickets exists in countries with intense year round sunlight such as Nigeria and can occur without vitamin D deficiency [42-43]. Although rickets and osteomalacia are now rare in Britain there have been outbreaks in some immigrant communities in which osteomalacia sufferers included women with seemingly adequate daylight outdoor exposure wearing Western clothing [44]. Having darker skin and reduced exposure to sunshine did not produce rickets unless the diet deviated from a Western omnivore pattern characterized by high intakes of meat, fish and eggs, and low intakes of high extraction cereals [45-47]. The dietary risk factors for rickets include Abstaining from animal foods [48-49]. Vitamin D deficiency remains the main cause of rickets among young infants in most countries, because breast milk is low in vitamin D and social customs and climatic conditions can prevent adequate UVD exposure. In sunny countries such as Nigeria, South Africa, and Bangladesh where the disease occurs among older toddlers and children it has been attributed to low dietary calcium intakes, which are characteristic of cereal-based diets with limited access to dairy products[47]. Rickets was formerly a major public health problem among the US population; in Denver, where ultraviolet rays are approximately 20% stronger than at sea level on the same latitude[50] almost two thirds of 500 children had mild rickets in the late 1920s[51]. An increase in the proportion of animal protein[52] in the 20th century American diet coupled with increased consumption of milk[53-54] fortified with relatively small quantities of vitamin D coincided with a dramatic decline in the number of rickets cases.

- Osteomaiacia, a bone-thinning disorder that occurs exclusively in adults and is characterized by proximal muscle weakness and bone fragility. The effects of osteomalacia are thought to contribute to chronic musculoskeletal pain [55-56] there is no persuasive evidence of lower vitamin D results in chronic pain sufferers [57].

Adequate vitamin D may also be associated with healthy hair follicle growth cycles [58]. There are also associations between low 25 OH vitamin D levels and peripheral vascular disease,[59] certain cancers, multiple sclerosis, rheumatoid arthritis, juvenile diabetes[15 Parkinson's and Alzheimer's disease[60]. However these associations were found in observational studies and vitamin D supplements have not been demonstrated to reduce the risks of these diseases [61].

Research shows that dark-skinned people living in temperate climates have lower vitamin D levels[62-63]. It has been suggested that dark-skinned people are less efficient at making vitamin D because melanin in the skin hinders vitamin D synthesis, however a recent study has found novel evidence that low vitamin D levels among Africans may be due to other reasons [64]. Recent evidence implicates parathyroid hormone in adverse cardiovascular outcomes, black women have an increase in serum PTH at a lower 25 OH vitamin D level than white women [65]. A large scale association study of the genetic determinants of vitamin D insufficiency in Caucasians found no links to pigmentation [66-67].

5. MEASURING VITAMIN D STATUS

The serum concentration of 25-hydroxy-vitamin D is typically used to determine vitamin D status. It reflects vitamin D produced in the skin as well as that acquired from the diet, and has a fairly long circulating half-life of 15 days. It does not, however, reveal the amount of vitamin D stored in other body tissues. The level of serum 1,25-dihydroxy-vitamin D is not usually used to determine vitamin D status because it has a short half-life of 15 hours and is tightly regulated by parathyroid hormone, calcium, and phosphate, such that it does not decrease significantly until vitamin D deficiency is already well advanced.

There has been variability in results of laboratory analyses of the level of 25-hydroxy-vitamin D. Falsely low or high values have been obtained depending on the particular test

or laboratory used. Beginning in July 2009 a standard reference material became available which should allow laboratories to standardize their procedures.

There is some disagreement concerning the exact levels of 25-hydroxy-vitamin D needed for good health. A level lower than 10ng/mL (25nmol/L) is associated with the most severe deficiency diseases: rickets in infants and children, and osteomalacia in adults. A concentration above 15bg.nk (37.5nmol/L) is generally considered adequate for those in food health. Levels above 30 ng/ml (750 nmol/L) are proposed by some as desirable for achieving optimum health, but there is not yet enough evidence to support this

Levels of 25-jydroxy-vitamin D that are consistently above 200 ng/mL (500 nmol/L) are thought to be potentially toxic, although data from humans is sparse. In animal studies levels up to 400 ng/mL (1000 nmol/L) were not associated with toxicity. Vitamin D toxicity usually results from taking supplements in excess. Hypercalcemia is typically the cause of symptoms, and levels of 25-hydroxy-vitamin D above 150 ng/mL (375 nmol/L) are usually found, although in some cases 25-hydroxy-vitamin D levels may appear to be normal. It is recommended to periodically measure serum calcium in individuals receiving large doses of vitamin D.

In overweight persons increased fat mass is inversely associated with 25 OH vitamin D levels [57][58]. This association may confound the reported relationships between low vitamin D status and conditions which occur more commonly in obesity as the circulating 25 OH vitamin D underestimates their total body stores.

A study of highly sun exposed (tanned) healthy young skateboarders and suffers in Hawaii found levels below the proposed higher minimum of 30 ng/ml in 51% of the subjects. The highest 25 OH vitamin D concentration was around 60 ng/ml (150nmol/L). A similar (using the same data) study in Hawaii found a range of (11-71 ng/mL) in a population with prolonged extensive skin exposure while as part of the same study Wisconsin breastfeeding mothers were given supplements.

The range of circulating 25 Oh vitamin D levels in women in the supplemented group was from 12-77 ng/mL. It is noteworthy that the levels in the supplemented population in Wisconsin were higher than the sun exposed group in Hawaii (which again included surfers because it was the same data set).

6. ASSESSING AND TREATING VITAMIN D DEFICIENCY

Theconcentrationof25(OH)Dismeasuredineither ng/mLoraccordingtoSIunits,nmol/L(thereare2 .5nmol/Lfore- ach1ng/mL)Historically, apersonwasconsideredtobedeficientinvitamin Dif25(OH)Dlevelswerelessthan20ng/mLor50 nmol/L(56).Theselevelsweredefinedbasedon circulating 25(OH)DlevelsintheU.S.populationthatappear edtobeadequateinpreventingbonedisease.

Therefore,mostexpertsbelievethatvitaminDins ufficiencyshouldbedefinedasserumlevelslessth an30ng/mLor75nmol/mL.

The US Endocrine Society guideline defines vitamin D deficiency as 25(OH)D less than 20 ng/ml (50nmol/l), vitamin D insufficiency as 25(OH)D between 21 and 29 ng/ml, and the safety margin to minimize the risk of hypercalcemia as 25(OH)D equal to 100 ng/ml (250 nmol/l)

In fact, theprimarywaytoobtainvitaminDisfrom exposuretosunlight.Inparticular, olderindividualsandthosewithdarkerskinareag reaterriskfordefficiencyduetodecreasedproduc tionofvitaminDintheskin,themajorityoftheUnit edStatesconsumptionofvitaminDcomesfromfo rtifiedfoods(Table2.2).

Table2.2AmountofVitamin Din Food

(AdaptedfromtheOfficeofDietarySuppleme ntsDietaryFactSheet)

Food	IUs perserving*
Codliveroil,1tablespoon	1,360
Salmon,cooked,3.5ounces	360
Mackerel,cooked,3.5ounces	345
Tunafish,cannedinoil,3ounces	200
Sardines,cannedinoil,drained,1.75ounc	250
Milk,vitaminD-fortified,1cup	98
FortifiedCereal	40*
Egg,1whole(vitaminDisfoundin yolk)	20
Liver,beef,cooked,3.5ounces	15
Cheese,Swiss,1ounce	12

*Amountmayvary

Severaltreatmentstrategicsexistforrestoringvita minDlevelstosufficientstatus

- Sun exposure
- LargerquantitiesofvitaminD

a) 100 IUofadditionalvitaminDeachday
b) Multivitaminscontainbetween400 IU ofvitaminD
c) Anotherstrategyfortheindividualwithvita minDdeficiencyistreatment withvitaminD50,000IUperweekforeightwe eks
d) CorrectionofvitaminDdeficiencydependso ntheseverityofdiseaseandcouldbeachieved bybothsunlightandoraltherapy

7. CO-MORBIDITIES ASSOCIATED WITH VITAMIN D DEFICIENCY

- Hypertension
- Cysticfibrosis(CF)
- Diseaseoftheheart,bones,endocrine,and immunesystems
- Osteoporosis-Osteoporosisisaskeletalondictionresultingfr omdecreasedbonestrengthandincreasedrisk offracture.Preventingfractures.Fallsintheeld erlyfromosteoporosisandinmaintainingmus clehealthorneurologicalbalance.Metabolicbo nedisease
- TypeIandTypeIIdiabetes(hyperglycemiaand hypovitaminosisD)
- Riskofcomplicationsassociatedwithdiabetes suchasallcausemortality, myocardialinfarctionandcardiovasculardise ase.
- Vitamin D plays a vital role in reducing inflammation by reducing inflammatory profile of T cells

Mortality

Using information from the National Health and Nutrition Examination Survey a large scale study conducted that having low levels of vitamin D (<17.8ng/ml) was independently associated with an increase in all-cause mortality in the general population However it has been pointed out that increased mortality was also found in those with higher concentrations, (above 50 ng/ml). A sophisticated August 2010 study of plasma vitamin D and mortality in older men concluded that both high (>39 ng/ml) and low

(<18 ng/ml) concentrations of plasma 25(OH)D are associated with elevated risks of overall and cancer mortality compared with intermediate concentrations. These boundaries were less than suggested by the Melamed et al study of National Health and Nutrition Examination Survey data but the immunoassay used by National Health and Nutrition Examination Survey tended to overestimate vitamin D values.

Overall, excess or deficiency in the calcipherol system appear to cause abnormal functioning and premature aging

Complex regulatory mechanisms control metabolism and recent epidemiological evidence suggests that there is a narrow range of vitamin D blood levels in which metabolic functions are optimized. Levels above or below this natural homeostasis of vitamin D are associated with increased mortality

8. RECOMMENDATIONS

PCP 's should not overlook the levels of this vital vitamin .In all chronic disease sufferers and old age people ,Vitamin D levels should be ascertained and Vitamin D supplementation should be a part of treatment regimen .Vitamin D is a preventive Vitamin in itself.

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9. CONCLUSIONS

Vitamin D is more than a vitamin .Pleiotropic substrate for repair and serves multiple gene-regulatory functions in your body.3000 genes are influenced by Vitamin D .Vitamin D receptors are present in every cell of the body.Vitamin D plays a vital role in human health

Optimum Vitamin D levels can fight at least 16 different types of cancer, including pancreatic, lung, ovarian, prostate, and skin cancers.,coloncancers.Vitamin D levels plays role in prevention and treatment of type 1 and type 2 diabetes, hypertension, glucose intolerance, multiple sclerosis, and other medical conditions.