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CLINICO PATHOLOGICAL SPECTRUM OF VITAMIN-D DEFICIENCY: CURRENT PERSPECTIVES

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ABSTRACT

Vitamin–D is a fat soluble vitamin whose function is to help the absorption of Calcium. Latest literature points to a greater role of this Vitamin in the Human body. This study aims to highlight the complete functions of Vitamin –D and identify the various groups at risk of insufficiency of this Vitamin and the conditions associated with it. Clinico –pathological aspects of the lack of this Vitamin will be depicted .The Study hopes to rein force the Knowledge of Medical Fraternity with regards to this Vitamin, with overall benefit to Patients.

Key-words: Vitamin D, Clinical, Pathological, Deficiency, Condition, Study.

INTRODUCTION

Physiology of vitamin D

Vitamin D is a fat soluble chemical substance which bears significant physiological influence. There are different sources of Vitamin D ,Endogenous or Dietary .Diet related can be either of plant origin [Ergocalciferol or Vitamin D2] or of Animal origin[cholecalciferol or vitamin D3],both of which are not readily available, so humans mostly depend on Endogenous synthesis [Vitamin D3] for which daily exposure to U.V sun light is important. Vitamin D3 induces its physiological effects mostly through its Metabolic product 1α,25-dihydroxyvitaminD3 (1,25(OH)2D3),which behaves as a nuclear hormone, because it is the substance with highest affinity for the transcription factor vitamin D receptor (VDR). VDR is distributed in variety of human tissues and cell types, i.e., at sites far from the location of calcium homeostasis and proper bone formation. Evidence for the wide physiological sites of Vitamin D action is derived by the fact that Genome Wide associated studies of VDR showed their extensive distribution thereby concluding the various sites of action of Vitamin D in human body.[1]

Table 1: Physiological functions of Vitamin D on Different Organ Systems

Organ system	Functions
Cardio vascular system[c.v.s][2]	1.Crucial effect on structure, growth and survival of cardiac cells 2.Controls the Synthesis and release of Atrial Natriuretic Peptide[ANP] 3. Vitamin D inhibits the calcification of blood vessels by regulating the activities of interleukins
Respiratory system[3]	Augmentation of Natural Defences of Respiratory system
Immune blood and lymphatic system[4]	1.Improves the antibacterial actions of Monocytes /Macrophages by increased transcription of Defensin beta2 and Cathelicidin antimicrobial peptide (hCAP18) 2.Enhance the natural function of innate immune cells
Gastrointestinal system[5]	1.Involve in proliferation and differentiation of cells, maintenance of normal function by facilitation of exocrine/endocrine secretion, digestion and absorption 2.Maintenance of innate mucosal immunity,

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Reproductive system[6]	1.Facilitates Ovarian steroidogenesis by endocrine/paracrine action 2.Stimulates maturation of ova 3.Enable the reception of endometrial tissue 4.Increases intracellular calcium thereby Improves Acrosine activity which helps in Acrosome reaction that facilitates fertilization
Skin and integumentary system[7]	1.In low amounts helps in proliferation of keratinocytes ,but high amounts lead to inhibition of proliferation 2. immune modulation, by suppression of local T cell activation and promotion of immunotolerance and facilitates formation of regulatory T cells 3. Inhibition of keratinocyte Apoptosis by induction of Mg2+ dependent sphingomyelinase ,which forms ceramides that have proliferative effect on keratinocytes.
Musculoskeletal System[8]	Effect of Vitamin D on Skeletal Muscle/Bone is classified into 1. Genomic Effects 2.Non Genomic Effects 1.**Genomic Effects**- Binding of 1,25D to VDR leads to conformational changes within the receptor that allows it to interact with its heterodimeric partner, retinoidXreceptor(RXR).VDR also forms homodimers that bind DNA and regulate gene expression which controls Muscle differentiation, Contractile Protein expression/activity and Phospholipid composition ,while the effects in Bone include Transcriptional control of Bone Proteins(osteocalcin, osteopontin, and receptor activator of nuclear factor *K*B ligand) 2.**Non Genomic Effects**- Control of protein kinaseA(PKA)/cAMP, proteinkinaseB, proteinkinaseC(PKC), CAMK which leads to glucose uptake by Muscle ,and activation of multiple MAPK pathways leads to expression of genes involved in cellular proliferation and Differentiation.
Kidney[9]	1.Active form of Vitamin D has protective effect on Kidney due to its Antiinflammatory and Antifibrotic effect[by inhibition of Renal Interstitial Myofibroblasts] 2. Negative control of Renin Angiotensin Aldosterone System[RAAS] Thereby implying its role in homeostasis of electrolytes ,blood volume and blood pressure
Endocrine system[10,11,12,13,14]	**Pituitary gland**-Presence of VDR in pituitary as demonstrated by VDR mRNA expression using the reverse transcription-polymerase chain reaction (RT-PCR), as well as the cellular expression of VDR by immunohistochemistry, both in the human pituitary gland thereby suggesting the possible role of vitamin D in control of Pituitary gene expression and hormone secretion **Thyroid gland-** Vitamin D regulates cell proliferation, differentiation, Apoptosis, **Parathyroid**-1.Vitamin D inhibits the proliferation and helps in Differentiation of the Parathyroid Tissue. 2. Parathyroid tissue has VDR and 1-α-hydroxylase enzyme which helps in Vitamin D formation within Parathyroid. **Adrenal gland-**1.Evidence of Paracrine effect of Vitamin D by formation of Active Vitamin D from inactive form by ability of 1-α-hydroxylase encoded by CYP27B1 in Adrenal gland.

	2.Significant association of Vitamin D with Adrenal Steroidogenesis as evidenced by presence of Vitamin D response Element in the promoter region of CYP21A2, the gene encoding the 21-hydroxylase. 3.Active form of Vitamin D can down regulate the 21-Hydroxylase expression ,which is needed for synthesis of glucocorticoids/mineralocorticoids as demonstrated in a human adrenocortical cell line model (NCI- H295R] **Endocrine Pancreas-**Expression of VDR/CYP27B1 in pancreatic β cells along with presence of vitamin D response element in Insulin gene promotor region suggests its role in Insulin secretion and improvement of Insulin sensitivity could be due to increase receptors in target tissues.
Central Nervous System[15,]	1.Presence of VDR/ enzyme 25(OH)D3-1α-hydroxylase,needed for Vitamin D activation in regions of Brain especially hypothalamus and dopaminergic neurons of the substantia nigra, and Microglia suggests the association of Vitamin D role in Nervous System 2. Vitamin D has Impact on Nervous System through regulation of production of Neural factors like nerve growth factor (NGF], Glial cell line-derived neurotrophic factor (GDNF],Acetyl Choline, GABA, Catecholamines 3.Vitamin D has protective effect on Nervous System by production of Calcium binding proteins[Parvoalbumin] which maintains Calcium homeostasis thereby preventing Intracellular Calcium buildup and Neuronal excitation.

Discussion

Vitamin D deficiency is implicated in the development of different Clinico-pathological conditions, Which is proved by various experimental and clinical studies .The **Cardiovascular effects** can range from **Hypertension**[as shown by increased prevalence of Hypertension in Knocked out VDR Animal Model, along with reduced Plasma Renin Activity, Angiotensin -2 levels, Blood pressure and Myocardial Hypertrophy in response to Calcitriol supplementation in several clinical trials] **Coronory Artery Disease**[Lack of Vitamin D is related to development of predisposing conditions for Coronary Artery Disease and also in Patients with End Stage Renal disease, Vitamin D substitution leads to improved survival from CardioVascular disease] and **Congestive Heart Failure** [due to formation of Proinflammatory Cytokines IL-6,8,12 &IFN-gamma ,TNF-alpha and oxidative stress along with Stimulation of RAAS ,with defective remodeling of Cardiac cells. Clinical proof is obtained by improvements in Ejection Fraction and decreased levels of Atrial Natriuretic peptide in patients with Cardiac failure who were given Vit D supplements][.2]

Studies have been conducted with an attempt to associate Pulmonary diseases like Asthma ,COPD and Lung Cancer with Vitamin D deficiency. Lack of Vitamin D leads to impaired Steroid responsiveness in Patients with Asthma, due to low IL-10[potent Anti Inflammatory Cytokine] whereas on substitution of Vitamin D Improved Steroid response is noted along with increase in IL-1O.In addition Vitamin D is shown to reduce the receptors for Rhinovirus in Human Umbilical cord cell cultures/peripheral blood cells thereby having an effective control of Rhinovirus Infection as seen in clinical trials of Patients with COPD and Asthma who showed reduced disease exacerbations. With regards to Lung Cancer, Vitamin D has Anti Cancer effect in Vitro due to inhibition of cell cycle at G0/G1 stage along with impaired formation of VEGF/MMP-2,9 / PTHrP. These findings were substantiated by Large Cohort studies of lung cancer patients who had low Vitamin D levels along with evidence of reduced activation/increased destruction of Vitamin D in tissues of Lung Cancer.[3]

Association of Autoimmune diseases due to lack of Vitamin D is noted in various studies which could be due to increased Inflammation/Infection in Patients with Type 1 D.M /Inflammatory Bowel Disease, whereas in Multiple Sclerosis there is decreased TH17 cells in Brain ,in response to Vitamin D supplementation.[4]

Deficient Vitamin D is attributed to development of Colorectal Cancer and Inflammatory Bowel disease. Studies have documented that abundant Vitamin D levels has less predisposition for Colorectal Cancer ,which was also supported by other studies by 30% decline in formation of Colonic Adenomas supporting the natural protective role of Vitamin D in Colonic Cancer. Higher Incidence of Inflammatory Bowel Disease is noted in areas where there is insufficient sun exposure compared to those which had adequate sun exposure suggesting beneficial effect of Vitamin D, further lack of Vitamin D leads to Mucosal Epithelial Barrier defects and also down regulation of IL-10[regulatory anti inflammatory cytokine], which is observed in experimental studies of VDR/IL-10 Knocked out Mice by development of Severe Colitis.[5]

The effect of deficient Vitamin D on Reproductive Tract is evidenced by manifestations like Polycystic Ovarian Syndrome[PCOS], Myomas of Uterus, Endometriosis ,Premature Ovarian Failure, Male Infertility PCOS is postulated due to Increased Anti Mullerian Hormone[AMH] and decreased pro-inflammatory advanced glycation end products receptor (sRAGE), a particle binding those glycation end products (AGEs) noted in Vitamin D deficiency and proven clinically by decreased AMH and increased(sRAGE) upon treatment with Vitamin D. Uterine Myomas have greater predilection for African Americans than European Americans ,which correlated with relatively low Vitamin D levels in African Americans. The role of Vitamin D deficiency in Myomas of Uterus is proved in Animal model studies by beneficial effect of Vitamin D analogue. Endometriosis could be due to Increased spill over of Endometriotic tissue into peritoneum through ovarian regurgitation in Vitamin D deficient situations .Patients with Premature Ovarian failure have low levels of AMH[Anti Mullerian Hormone] ,which is a marker for this condition and this level can be increased by Vitamin D , as noted by positive link of AMH with Vitamin D in clinical studies. Male infertility is attributed to Vitamin D deficiency induced defects in Sperm motility, abnormal Acrosome reaction, in Human studies which was confirmed by in Vitro Animal studies.[6]

Published studies relating Vitamin D deficiency and Skin diseases reveal the association with Psoriasis, Atopic Dermatitis, Vitiligo, Ichthyosis, Skin Cancer, Skin Fibrosis, Skin infections, Cutaneous Tuberculosis and Autoimmune diseases of Skin. Patients with Psoriasis show altered proliferation of epidermal cells /Nuclei ,changes in Ki-67[proliferation marker] and differentiation along with reduced inflammation/immunoglobin in insitu skin lesions in response to Vitamin D.Clinical improvement of Psoriatic lesions on exposure to sun has prompted Vitamin D as treatment agent for Psoriasis which showed good response in clinical studies. The protective role of Vitamin D in Atopic Dermatitis is derived by the fact that it has immunoregulatory properties along with reduced skin infections due to formation of Antibacterial substances in skin, which was showed by declined concentration in Cathelicidins in lesional tissue and also diminished in vitro immunoglobulin E (IgE) production and IgE-mediated cutaneous reactions in response to Vitamin D. The role of Vitamin D in Pathogenesis of Vitiligo is exemplified by the observations that there is increased Melanocyte proliferation/Melanogenesis in human cultured Melonocytes along with analytically important decreased Vitamin D levels relative to Controlled subsets.In addition Vitamin D has immunoregulatory actions which can protect Melanocytes from damage induced by sunlight.

Studies from India showed an association of lack of Vitamin D in children with Ichthyosis ,evidenced by low Vitamin D levels along with clinical improvement on Vitamin D substitution. The mechanism of Ichthyosis is due to Vitamin D deficiency induced defective Keratinization. The presence of VDR on Normal and Cancer Skin cells has prompted the role of Vitamin D in genesis of Cutaneous Cancer,which is substantiated by formation of Tumors in Animal models that are deficient in Vitamin D along with clinical studies showing link between Vitamin D levels and Melanoma stage. Anti Neoplastic effect of Vitamin D is due to its role in differentiation ,Apoptosis of Skin cells. The role of Vitamin D in Inhibition of Fibrosis of skin is related to suppression of fibroblast proliferation, and Collagen synthesis along with immunomodulation, as proved by its beneficial effect in clinical conditions like Morphea and Lichen Sclerosus et atrophicus. Association of Low Vitamin D and risk of Cutaneous Tuberculosis is shown by reduction of tubercle bacilli in response to Vitamin D application of Infected Macrophages

.These findings are in line with clinical improvement of Cutaneous Tuberculosis on exposure to sunlight.[7]

Relationship of Vitamin D deficiency with Musculo skeletal Pathology [Rickets, Osteomalacia, Osteoporosis, Sarcopenia] is an established fact. Rickets which is a sign of Vitamin D deficiency in children has symptoms like Leg deformities ,Wrist swelling with widening of growth gap along with retarded Fontanelle closure, deformed craniofacial structure ,Pain in Musculoskeletal system .These symptoms are noted with increased frequency in winter months in England and other Northern European countries , suggesting the causal role of Vitamin D. Osteomalacia ,which is a manifestation of Vitamin D deficiency in Adults is characterized by reduced Calcification in Bones and clinically Non specific Pain in Shoulder/Pelvis/proximal Muscles, the diagnosis of which is usually made by finding of low Serum Calcium/ Phosphate and Increased Alkaline Phosphatase along with Radiological demonstration of diminished Mineralization. Osteoporosis ,which is another Presenting feature of Vitamin D deficiency shows reduced Bone Mass along with Structural changes in Microenvironment of Bone can present clinically with Fractures of Bones of pelvis, vertebral column , Upper femur/hip, upper humerus and the forearm. The symptoms are related to low Vitamin D levels and Calcium in Women but not in Men as shown by clinical improvement upon Calcium substitution. The Prevalence of Osteoporosis is 14% in women younger than 45 years but is 30% in women who are 60-70 years of age.

Clinical studies showed a improvement in symptoms of Osteoporosis due to Vitamin D Substitution of 792 IU/Day. The diagnostic confirmation of osteoporosis is done by estimation of bone mineral density in the lumbar spine or femoral neck by dual-energy X-ray absorptiometry (DXA).Sarcopenia which is reduction in Skeletal Mass due to degenerative changes induced by Vitamin D deficiency is being increasingly reported .There exists a clinical correlation between Vitamin D levels and Muscle Mass /strength with increasing age. Upon substitution of Vitamin D [700 I.U/day] in Elderly, there is noted improvement in Muscle function. The range of Pathological findings In Type 2 Fibres in cases of Muscle Atrophy include wide interfibrillar gaps, adjacent fibrosis, Fat/glycogen infiltration, which are overcome upon treatment with Vitamin D by clinically Improved Muscle performance as shown in Biopsy by Increased Type 2a fibres.[16]

Vitamin D deficiency related Endocrine diseases are Primary Hyperparathyroidism, Diabetes Mellitus [type1/2], Autoimmune Thyroid disease [Hashimotos Thyroiditis, Graves disease] and Addison,s disease. Primary Hyperparathyroidism is attributed to defects in normal inhibition of proliferation of Parathyroid tissue/PTH ,which is induced by lack of Vitamin D. Likely association of Vitamin D deficiency with Type 1 Diabetes Mellitus is suggested due to changes in Innate immune system like weakened Macrophage function ,abnormality of beta cells. Evidence for Vitamin D role is derived from Population based studies from various countries showing low Vitamin D levels in Newly diagnosed cases of Type 1 Diabetes Mellitus relative to Control group, also notable presence of Vitamin D deficiency was observed in the Population group with Type 1 Diabetes compared to Non Diabetics. Many Observational researches have documented the reduced risk of Type 1 Diabetes in those who were substituted by Vitamin D early in life by decreased formation of Auto antibodies to GAD or IA-2A.

There is a link of Vitamin D deficiency with development of Type 2 Diabetes ,which could be attributed to defective Insulin secretion/sensitivity along with role of Inflammation ,as shown by decreased Insulin secretion in VDR knocked out Mice and Increased fat infiltration of skeletal muscle in Humans that contribute to reduced Insulin sensitivity. Addisons disease is hypothesized to occur in Vitamin D deficient state due to the role of Susceptibility genes [VDR/CYP27B1] in the pathogenesis along with invitro evidence of destruction of Adrenal Tissue in Adrenal Cell Model[NCI-H295R line].Development of Thyroid disease [Hashimotos Thyroiditis &Graves Disease] is reported due to insufficient Vitamin D. Hashimotos Thyroiditis may be due to loss of normal regulation of T cell stimulation /MHC -2 expression /HLA –DR antigens in Thyrocytes, in Vitamin D deficient condition. The Pathogenesis of Graves disease is related to VDR gene/Vitamin binding Protein gene polymorphisms and clinically proven by low Vitamin D levels in Women with newly onset Graves disease. [17]

Relationship between low Vitamin D levels and its effect on kidney is observed.

Low Vitamin D levels were noted in patients who were admitted to Hospital with clinical evidence of Acute Kidney Injury, who also showed progressive decline in Vitamin D levels as the Severity of Acute Kidney Injury increased[18]. Animal model studies involving Wistar Rats ,were subjected to Vitamin D deficit along with induction of Ischemia/ Reperfusion Injury and then studied for their effects, which showed reduced Renal capillary density[by Cablin staining] increase in urinary volume /Kidney weight along with evidence of Inflammation and Fibrosis by notable presence of CD4/CD8 [which showed staining for IFN-gamma &IL-17] expression of Fibroblast specific protein-1 and increased TH-17 cell to Regulatory T cell ratio. These findings substantiated the Anti inflammatory/Antifibrotic role of Vitamin D in Kidney. [19]

Various Central Nervous System disorders could be due to insufficient Vitamin D, such as Neurodegenerative conditions[Alzheimers disease, Parkinson disease, Huntington disease], Schizophrenia, Major Depression, Multiple Sclerosis. Neurodegenerative diseases might be related to excess oxidative stress due to lack of suppression of I-NOS enzyme caused by deficient Vitamin D. Pathologic Conditions like Major Depression and Multiple Sclerosis are thought to be because of excess synthesis of Pro-Inflammatory compounds [IFN-gamma/IL-2]and reduced Anti-inflammatory Substances [IL-10] in Brain. Various studies have found the association of Schizophrenia in people who are deficient in Vitamin D such as Children born in winter months and those born to African American Mothers who were deficient in Vitamin D , dark skinned people with inadequate Vitamin D exposure along with observation of More Risk of Schizophrenia in Finnish children who had Vitamin D deficiency in early life.[15]

Laboratory Assessment of Vitamin D

Latest literature suggests that 25[OH]D is the complete biological hallmark of the status of Vitamin D in body. It is estimated by adding the 25[OH]D2 and 25[OH]D3 ,since both of them have equal significance biologically . 25[OH]D has more half life in circulation relative to 1,25[OH]2D,in addition it is free from the action of PTH. Automated Immunoassay method is the most commonly used technique, because of its high sensitivity even though it shows cross reactions among different fractions of Vitamin D. Other method is Mass Spectrometry/Liquid Chromatography which is free from cross reactions and is consistent /accurate but is difficult to maintain due to high cost. Various Pre Investigative factors [Genetics of Vitamin D, gender, season of year, age, ethnic background and Body mass index] and Investigative factors [Type of laboratory test] can influence the Laboratory value of Vitamin D.[20]

Screening for Vitamin D deficiency- According to American Endocrine Society Screening is advocated for some high risk groups having clinical evidence of Vitamin D deficit [such as Rickets, Osteomalacia, Osteoporosis], long term Renal disease, Liver failure, Malabsorptive Conditions, Some Drugs, Children/Adults of African American &Latin descent ,Gravid Lactating females, Elderly People who had history of falls /Non traumatic Fractures, children and Adults who are obese, diseases which show Granulomas, certain types of Lymphomas. Screening can help to identify above risk groups who could be beneficially treated[21].

Reference Values[21] –According to American Endocrine Society

1.Less than 20ng/ml- Vitamin D Deficiency (25-OH-D)

2. 20–30 ng/ml -- Vitamin D Insufficiency (25-OH-D)

3. Greater than 30 ng/mL-Adequate Vitamin D (25-OH-D)

4. Greater than 150ng/ml-Toxicity (25-OH-D)

Sources of Vitamin D[22]-1.Fish rich in oils 2.Eggs 3.Fortified Foods[Milk/Dairy products, Margarine, Breakfast Cereals]

Recommended Daily Allowance[23]-According to European Food Safety Authority [EFSA]

1. Infants [7-11months] ---- 10 µg/day

2. Children 1-17 years------ 15 µg/day

3. Pregnant/Lactating women--- 15 µg/day

4. Adults ---------- 15 µg/day

Nearly half of the Population throughout the World is affected by Vitamin D deficiency. Deficiency has

reached mammoth proportions to the extent that one Billion people are affected in World through various ethnicities/age groups. The wide spread deficiency of the Vitamin could be related to changes in style of life[decreased outside movements],climatic changes[eg-air pollution] that prevent contact with sunlight which is needed for ultraviolet –B [UVB]related Vitamin D synthesis in Skin[24].Humans can obtain adequate Vitamin D from plentiful sunshine by 18% exposure of the surface of body[without sun screen application] to mid afternoon sun for nearly 30-45 minutes which can generate 600 to 1000 IU of vitamin D[25]This amount equals the daily requirements. In areas of World people having inadequate sunlight contact, conservative dressing that limit sun exposure and those who use sun screen with sun protection factor[spf] of more than 8,Vitamin D substitution is required.[25.]

Conclusion

With the background knowledge of Vitamin D , it is now definitely associated with many diseases other than Skeleton .Knowledge about the insufficiency of this Vitamin is essential to identify the various Clinical and Pathological conditions associated with this crucial Vitamin. Identification of People who are at risk of deficiency of this Vitamin helps in prevention of various diseases and associated Morbidity. Enlightenment of wellbeing and encouragement of campaign is mandatory for understanding of the Problem in Society as a whole.

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