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VITAMIN D; THE NECESSITY OF TODAY'S WORLD

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ABSTRACT

Vitamin D the sunshine Vitamin, Discovered hundreds of years ago, is regarded as a protection provider of human health from many diseases. Vitamin D now a day's is recognized not only for its importance for good health, but also for the deficiency diseases caused in children and adults. In today's life changing scenario due to fast pace of life, most of the Vitamin D requirements in humans are met either from prescribed supplements and fortified foods. Regular exposures to sunlight which is one of the most cheapest and best methods to acquire Vitamin D becomes impossible due to faster pace of life and lesser availability of free time among people residing in urban areas. Vitamin D Deficiency in human body leads to sever health problems among peoples of all age groups including pregnant and lactating women's. In woman's, sufficient Vitamin D levels are very much essential for fighting placental infections during and after pregnancy. Maintenance of good neonatal health and upper respiratory infections in infants also depends upon maternal Vitamin D levels. Vitamin D plays a vital role in improvement or worsening of human immune virus infections in patients. Whereas, deficiency of Vitamin D is also responsible for introduction of type I, type II and gestational diabetes in humans. Epidemic studies conducted worldwide shows, deficiencies of Vitamin D cause's mental illnesses such as; multiple sclerosis, schizophrenia and impaired synaptic network both in adult's and infant's.

KEYWORDS: Vitamin D; Diabetes; Human Immune Virus; Upper Respiratory Infections; Stem Cell.

Introduction

In human body Vitamin D is stored in the body's fatty tissues. into five different categories of fat-soluble prohormones[1] such as, Vitamin D1 (molecular compound of ergocalciferol with lumisterol), D2(ergocalciferol), D3(cholecalciferol), D4(22-dihydroergocalciferol), D5(sitocalciferol made from 7-dehydrositosterol)[2,3].

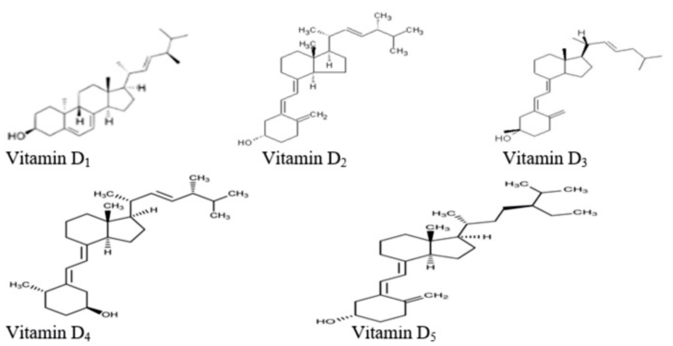

Figure 1: Structural orientation of various forms of Vitamin D from D1 to D5.

Adequate exposure to natural sun light through skin encourages absorption and metabolism of calcium and phosphorous, essential for normal muscle functioning and bone formation in human body. As per vital uncovered mysteries by researchers, two forms of Vitamin D, Ergocalciferol (D2) and Cholecalciferol (D3) are of great relevance from human health point of view. Both the forms are hydrophobic forms in nature and chemically differ in their molecular composition due to their side chains. Although sufficient levels of Vitamin D can be easily achieved by direct exposure of skin to the natural sunlight but most of the people meet their Vitamin D requirements from prescribed supplements or fortified foods containing either of two forms of vitamin D (Ergocalciferol or Cholecalciferol).

As per the published data the Recommended Dietary Allowance (RDA) values for Vitamin D intake on a daily basis of various factors related to age, gender, pregnancy and lactating are illustrated in the table below [4].

Table 2: Recommended Dietary Allowance Levels for Vitamin D

Age	Vitamin D Levels Recommended for Intake	Upper Limit for Vitamin D Intake
Infants 0 - 6 months	400 IU (10 mcg/day)	1,000 to 1,500 IU/day (25-38 mcg/day)
Infants 7 - 12 months	400 IU (5 mcg/day)	
Children 1 - 3 years:	600 IU (15 mcg/day)	2,500 to 3,000 IU/day (63-75 mcg/day)
Children 4 - 8 years	600 IU (15 mcg/day)	
Older children and adults 9 - 70 years	600 IU (15 mcg/day)	4,000 IU/day (100 mcg/day)
Adults over 70 years	800 IU (20 mcg/day)	
Pregnancy and breast feeding women	600 IU (15 mcg/day)	

Naturally there are very few food sources that contains considerable amount of Vitamin D, so Vitamin D supplementations are often considered as an alternative of exposure of sunlight on skin on regular basis. The suggested naturally occurring dietary sources of Vitamin D are listed in below [5].

Table 3: Animal Sources of Vitamin D3

Source	Serving in gms	Serving in Ounce	Contains Vit D3 in IU's	Vit D3 IU/g
Salmon	100	3.5	360	3.6
Mackerel	100	3.5	345	3.45
Sardines	50	1.75	250	5.0
Tuna	100	3.5	235	2.35
Cat Fish	85	3.0	425	5.0
Eel	100	3.5	200	2.0
Egg	60	2.0	20	0.33
Liver (beef)	100	3.5	15	0.15
Milk	115-124	1 cup	12	9.6/10.5
Cheese Swiss	30	1.0	12	2.5
Cod liver Oil	13.7	1 tsp	1360	90.6 IU/ml

Metabolism of Vitamin D in Human Body

The natural process of Vitamin D production in human body takes place through the skin by robust photolytic process induced by sun's ultraviolet "B" light which operates in the wavelength range of 290–315 nm. The 7-dehydrocholesterol present in the plasma membranes of both epidermal keratinocytes and dermal fibroblasts [6-7] undergoes slow isomerization and leads to breaking of the "B ring" to produce PreVitamin D_3 [8-9]. This PreVitamin D3 further undergoes thermally induced transformation known as sigmatropic shift to form Vitamin D3. During this process many biologically inert photoproducts such as tachysterol and lumisterol are also generated [10-11]. Vitamin D acquired either naturally or through supplements enters the circulation and undergoes transformation within the body to remain in biologically active form. This transformation takes place in liver and kidney of human body where these vitamins are metabolized in hormonally-active forms. In liver 25-hydroxylase enzyme hydroxylates cholecalciferal into 25-hydroxycholecalciferol, whereas in kidney this 25-hydroxycholecalciferol acts as a substrate for 1-alpha-hydroxylase enzyme to produce 1,25-dihydroxycholecalciferol also known as calcitriol[12]. 1,25-dihydroxycholecalciferol production in kidney is tightly controlled by inhibitory process by fibroblast growth factor-23 and parathyroid hormone levels, along with presence of calcium and phosphate metabolites. Both Ergocalciferol or Cholecalciferol alters in their binding sites on the carrier protein and albumin and enters in the blood stream producing similar activities. In this process very little amount of Vitamin D exist in the free state[13].

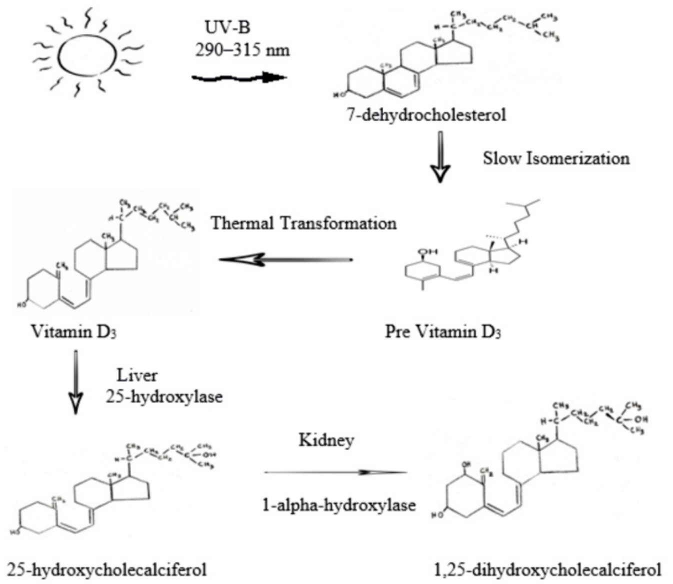

Figure 2: Schematic diagram of Vitamin D Metabolism in Human Body

Factors Influencing Vitamin D_3 Production

M. Holick [14] in an article illustrated numerous factors related to age, skin type, sunscreen utilization, time of day, and season influencing cutaneous production of Vitamin D_3. These factors either attenuate the solar UV-B penetration through skin or cause alteration in the amount of 7-dehydrocholesterol present in the skin. Age plays an important role in cutaneous absorption of UV-B radiation. Sever decline in the amount of 7-dehydrocholesterol, which is essential for Vitamin D_3 production was observed in the epidermis of the people with increasing age. Comparisons among many studies showed that a 20-year-old person generates 4 times more of Vitamin D as compared to a 70-year-old person through cutaneous absorption [15-16]. Vitamin D_3 inadequacy is also caused due to certain biological factors, one of the biological factors is skin pigmentation generally known as melanin. People with dark skin pigmentation require longer exposures to sunlight, as compared to light-skinned people to make the same amount of Vitamin D_3[17-18]. As per the published literature, Vitamin D levels may be lowered by the use of many pharmaceutical drugs belonging to certain families of drugs such as[19],

1. **Anticonvulsants :** Phenobarbital, Phenytoin (Dilantin), Primidone (Mysoline), Valproic acid (Depakote).

2. **Corticosteroids :** Beclomethasone, Budesonide, Dexamethasone, Tobramycin, Flunisolide, Fluticasone, Hydrocortisone, Methylprednisolone, Mometasone, Prednisone, Prednisolone, Triamcinolone, Questran, Prevalite.

3. **Anti-Tuberculosis Drugs :** Rifampin or Rifampacin lowers the Vitamin D levels, whereas isoniazide is known to raise blood-Vitamin D levels.

4. **Bile Acid Sequestrates :** Cholestyramine (Questran, Prevalite), Cholestipol (Colestid) are medications used to control high cholesterol levels.

5. **Medication for Weight Loss** : Orlistat (Alli)

6. **Antacids :** Antacids consumed for longer periods of time may alter the levels, metabolism, and availability of Vitamin D.

All pharmaceutical drugs belonging to the above mentioned families, leads to unrecognized interactions with Vitamin D_3 and also cause poor outcomes in cutaneous Vitamin D_3 production. Some of these interactions may be acute in onset, whereas, other interactions may develop over years and become evident (eg osteoporosis) [20-21]. Environmental factor such as, winter season plays an important role in alteration of cutaneous Vitamin D_3 productions because a big part of UV-B rays emitted by sun during in winter season enters the earth's atmosphere at zenith angle and gets absorbed by the ozone layer, thus leaving less amount of UV-B rays available for skin penetration for cutaneous Vitamin D_3 production. Time of day is also an important parameter for sun light exposure for cutaneous Vitamin D_3 production. The recommended time of day for exposure of sun light to the skin is between 10.00am to 3.00pm, because this is the only time when enough of UV-B rays reaches the earth's surface and helps in the cutaneous production of Vitamin D_3 [22-23]. When atmospheric conditions are ideal and skies are clear 30 minutes of whole-body exposure of pale skin to sunlight without clothing or sunscreen results in the synthesis of large quantities of Vitamin D_3 between 10,000 to 20,000 IU thus thereof capable of supplying body's full needs for Vitamin D_3[24].

Comparisons of Potency between Vitamin D_2 and Vitamin D_3

In the early years of 1930s, fortifications of milk with Vitamin D_2 were used as a major tool for eradication of rickets in infants. Specker .B et. al. in an review illustrated that fortification of milk with either Vitamin D_2 or Vitamin D_3 with a minimal intake of 2.5g (100 IU) per day along with little sun exposure has proven itself as an effective remedy for the elimination of infantile rickets[25]. Studies conducted between cod liver oil (Vitamin D_3) and Viosterol (Vitamin D_2) by Hess et al [26] showed that one unit of Vitamin D_3 found in cod liver oil is as effective as 4 units of Vitamin D_2 of Viosterol in treatment of rickets. This study had been reconfirmed in 1950s in Germany, illustrating that Vitamin D_3 in samples of Vigantol oil were found to be 4 times as potent per unit mass as compared to formulations of Vitamin D_2. Based on the facts of potencies between Ergocalciferol and Cholecalciferol, many famous organizations worldwide which used to supply in their product of Vigantol oil in most part of Europe reformulated their product by replacing Vitamin D_2 content with Vitamin D_3[27]. Vitamin D_2 is no longer considered as a nutrient suitable or equivalent to Vitamin D_3 in terms of efficacy, supplementation or fortification. Norman A et al [28], in a review illustrated that the inequality of efficacy between these two vitamins has led to the practice that 1 IU of Vitamin D_2 or Vitamin D_3 is to be defined in moles rather than in terms of weight. Subsequently 1 IU of Vitamin D3 with a molecular weight 384 and Vitamin D2 with molecular weight 396 are considered to be equivalent to 25 ng and 25.78 ng, respectively. Trang et al [29] conducted a comprehensive 2 week study during the time of year when solar exposure was minimal and compared the efficacy of equimolar doses of 4000IU of both Vitamin D_2 and Vitamin D_3 and found 70% elevations in 25(OH)D levels in serum with Vitamin D_3 as compared to Vitamin D_2. A continuation study conducted by Mastaglia et. al. found that to achieve similar serum 25(OH)D levels concentrations, a dosage of 10000IU of Vitamin D_2 is required[30]. Armas L et al[31], evaluated potencies of vitamins D_2 and D_3 by administering single doses of 50,000 IU in 20 healthy male volunteers over a period of 28 days and found similar initial rises in serum 25(OH)D over the first 3 days, but the 25(OH)D levels in subjects treated with D_3 was found to be increasing till the 14^{th} day, whereas, significant drop was observed in the levels of 25(OH)D in the subjects treated with Vitamin D_2. The relative potencies of both the vitamins D_3:D_2 after a span of 28 days were obtained to be 9.5:1, showing that Vitamin D_2 potency is less than one third that of Vitamin D_3. Thus indicating that Vitamin D_2 has markedly lower potency and shorter duration of action relative to Vitamin D_3.

Vitamin D Induced Toxicities

Although Vitamin D is considered as an essential vitamin for maintenance of good health and its deficiency is recognized as a problem in children, adults, pregnant and lactating women's worldwide [32-33] there is always a risk of excess intake of Vitamin D which may cause serious health problems and leads to presence of high toxic levels of Vitamin D in the body which is generally termed as Hypervitaminosis D[34]. Natural production process of Vitamin D by sunlight is safe and under no circumstances results in an overdose, because once the body's requirements have been met, further production of this Vitamin D is shutdown. As human body does not have a mechanism to shutdown the absorption of large amounts of Vitamin D consumed from supplemental vitamin preparations, Vitamin D toxicity is most likely to be caused by due to its excessive intake [35]. Toxicity induced by overdosage of Vitamin D includes number of serious health risks, the first indication of toxicity is a rise in the calcium to creatinine ratio in the urine, which further precedes to life-threatening emergency known as hypercalcemia[36]. The conditions of hypercalcemia results in elevated levels of calcium in the blood, which further leads to large deposition of phosphate and calcium in soft tissues affecting normal functioning of neuromuscular, gastrointestinal, renal, skeletal, and cardiovascular systems[37]. Ekrem U et al [38] in a review shared his experiences about the adversity of iatrogenic Vitamin D intoxication in infants. Three case reports were illustrated for three different infants between the age group of 60 days to 8 months. Theses infants were fed with

1,200,000 IU to 1,500,000 IU of Vitamin D over a very short span of time by their parents to induce growth in their infants without consultation of a medical doctor. This over feeding of Vitamin D has led to tremendous elevation in serum calcium level, urinary calcium/creatinine ratio and parathyroid hormone level as compared to normal levels. Further sever complaints of failure to thrive, loss of weight, irritability, diarrhea, decreased appetite, seizures, vomiting and fever in all the three infants were also reported. Chambellan. T et al [39], in an article reported Vitamin D intoxication in a four month old infant, leading to severe hypercalcemia with initial symptoms of anorexia, axial hypotonia, constipation, lethargy and weakness, along with sings of moderate intracellular dehydration, polyuria and leucocyturia.

Vitamin D Deficiency and Skeletal Muscles Tissues and Its Functioning

Vitamin D and its metabolites are classically recognized for their role in calcium homeostasis and skeletal metabolism, which influence's functioning and maturation of muscle cell. Vitamin D deficiency predominantly affects functional ability and mobility of the proximal muscle groups in people of all age groups. Janssen. H et al [40], illustrated various risk factors associated with inadequate serum Vitamin D levels in elderly people that are associated with muscle weakness. Endo I. et. al. investigated the physiological role of 1,25-dihydroxyVitamin D and its receptors in skeletal muscle development [41]. Ceglia L in a review summarized the role of Vitamin D in development of skeletal muscle tissue and its participation in various physio-chemical functions of body[42]. Vitamin D_3 in molecular level imparts great level of impact via its receptors that are present in both genomic and non-genomic muscle tissues. In genomic muscles, binding of 1,25-dihydroxyvitamin to its nuclear receptor results in changes in gene transcription of mRNA and subsequent protein synthesis. Whereas, Non-genomic performance of Vitamin D are rapid and mediated through cell surface receptors [43]. Studies conducted on muscle biopsies obtained from Vitamin D deficient adults, showed predominantly type II muscle fiber atrophy, thus giving us a complete explanation on the falling tendency of Vitamin D deficient elderly individuals[44]. Bouillon. R in a review on Vitamin D and extra skeletal health[45] illustrated interrelationship between Vitamin D and normal muscle functioning. Evidences of abnormalities were observed in immature muscle genes and smaller striated muscle fibers in Vitamin D receptor in tissues of both human and null mice muscle tissues[46]. Yoshikawa et al in their studies, revealed enlargement of interfibrillar spaces and infiltration of fat, fibrosis and glycogen granules, in Vitamin D deficient individuals[47]. Studies conducted on Vitamin D deficiency showed similarity between morphological features of the myopathy associated with chronic renal failure and Vitamin D deficient osteomalacia, with type II muscle fiber atrophy [48-49]. Most of the studies conducted on Vitamin D levels lesser than 20 and 10ng/ml in human subjects were found to be associated with weaker muscle functioning. Whereas, elevated Vitamin D concentrations more than 20ng/ml ware found to produce better muscle functions[50-51]. Studies performed by Sorensen et. al. [52] on muscle biopsies obtained from an elderly woman, who had been treated extensively for 3–6 months with 1-a-hydroxyVitamin D and calcium supplementation showed considerable increase in relative fiber composition of type IIa muscle fibers and thus attempts were also been made to explain the correlation between Vitamin D supplementation and type II muscle fibers morphology. Studies conducted by Sato et al [53] showed significant increase in diameter and percentage of mean type II muscle fibers after treating an elderly stroke survivor subject, with 1000 IU of Vitamin D_2 daily for a period of 2 years. Despite of the enormous advances made in the studies conducted on Vitamin D in recent decades, detailed research is still needed to fully characterize the exact mechanisms of Vitamin D and its action on muscle tissue along with cellular changes. This type of study could be easily utilized for its transformation into clinical research improvements and also improvements in physical performance of Vitamin D deficient humans.

Vitamin D Deficiency in HIV Infection

Vitamin D is also considered essential for cell metabolism and immunity responses in human body. In an article Published in "Med Page Today" written by Smith M, studies were conducted at Georgia facility with HIV-positive subject's which revealed that most of the subjects were deficient in their serum Vitamin D levels. Data collected in this cross-sectional studies among 900 HIV treated veterans showed that around 52.3% of the subjects were found to be deficient in Vitamin D levels [54].

In 6^{th} International Aids Society Conference conducted in Rome Italy Ross A et. Al, presented scientific studies conducted on high prevalence of Vitamin D deficiency in HIV-infected pregnant women. This study showed comparisons of 25-hydroxyVitamin D concentrations in cord blood plasma of HIV-1-infected pregnant women and HIV-uninfected healthy pregnant women's [55]. Studies conducted by Oluwatoyin A et. Al, for Vitamin D levels in more than 1700 women subjects including HIV-Infected and HIV-Uninfected women's in United States, showed sever levels of Vitamin D deficiency in most of the women's encompassing majority of women's belonging to Afro-American race [56]. Studies were also conducted to show the association between Vitamin D deficiency and atherosclerotic vascular disease among HIV-infected patients. Significant amount of thickness of carotid intima-media showed an extensive relationship between Vitamin D deficiency and thickening of the carotid artery in HIV patients [57]. As Vitamin D is known to play a vital role in intracellular process known as autophagy, deficiency of Vitamin D leads to increased risk of rapid HIV disease progression in infected persons. Reduction of autophagy by HIV-1 infection provides a substantial biological explanation for the rapid rate of increased disease progression [58]. Infants born to HIV-infected women have showed decreased levels of survival due to Vitamin D deficiency which leads to further development of pathogenesis conditions. In many reported cases, HIV infected persons with Vitamin D receptor variants, showed association with reduced Vitamin D bindings, which leads to increased risk of HIV progression towards AIDS. HIV-Infected subjects with CD4+ cell count less than 200/µL are more likely to have release of toxic viral products by gp120. HIV-infected CD4+ lymphocytes causes apoptosis, which further results in programmed cell death of uninfected lymphocytes [59]. Reduced autophagy conditions in acute infections, kills stander lymphocytes rapidly than infected cells [60, 61]. Clinical trial studies conducted on 100 HIV infected postmenopausal women's determined the effects of Vitamin D repletion on rates of bone loss and indices of immune function. HIV infected subjects consuming stable amounts of antiretroviral therapy (ART) regimen were randomize and made to receive 1000 or 3000 IU of Vitamin D daily for a span of one year, so as to understand the interferences of the several medications taken by the subjects on serum Vitamin D levels [62]. Studies developed by Szep Z et. al. showed association of lower levels of Vitamin D i.e.>20ng/ml with type 2 diabetes mellitus and metabolic syndrome among HIV-infected patients [63].

Vitamin D Deficiency and Respiratory Tract Infections

Studies conducted on association of lower Vitamin D levels, leading to decreased lung functioning and several chronic lung diseases are also one of the major focuses in modern world. Key advances are highlighted by Holick M, in a review [64] illustrating many common medical problems associated with increased risk of upper respiratory tract infections that are encountered due Vitamin D deficiency. On the other hand Vitamin D supplementation was found to reduce asthma attack by 93% among children's with a history of mild-to-moderate persistent asthma between 6–15 years of age group. Vitamin D supplementation also lead to reduction in relative risk of seasonal influenza infection by 42% among the children's of same age group. Risk of acute viral respiratory tract infections were also found to be reduced in adults with Vitamin D_3 concentrations ≥95nmol/l[65,66]. Belderbos M. et. al. in a study showed interrelationship between plasma Vitamin D concentrations and pathogenic activities which causes severe subsequent risk of lower respiratory tract infection that are caused by respiratory syncytial virus in infants [67]. In a Respiratory Medicine Reviews by Professor Martineau A, Vitamin D is considered as one of the key determinant for acquiring good respiratory health. Evidences from both the laboratory and the clinical researches studies suggested that the deficiency of this micronutrient could be responsible for the diverse condition of pathogenesis which further leads to sever conditions of asthma, allergy, respiratory infection and even lung cancer in some of the cases [68]. Finklea J et. al. in a review on Vitamin D and chronic lung disease gave a detailed illustration on molecular mechanisms of Vitamin D in various pulmonary diseases. His studies elaborated that, deficiency of Vitamin D leads to increased risk of respiratory infections such as, influenza A, Mycobacterium tuberculosis and other chronic respiratory diseases including cystic fibrosis, interstitial lung disease and chronic obstructive pulmonary disease [69]. Hansdottir S and Monick M in a review explained immunomodulatory effects of Vitamin D. Vitamin D produced within the lungs by the airway epithelium, alveolar macrophages, dendritic cells, and lymphocytes leads to increased secretion of the antimicrobial peptide cathelicidin, which is responsible for reduction in chemokine production and inhibits dendritic cell activation along with decreased alteration of T-cell activation thus imparting a great deal of impact against allergic lung diseases, respiratory tract infections and mycobacterial infections[70].

Vitamin D Deficiency and Diabetes

Patrina Shuck, in an article on issues associated with type II diabetes and Vitamin D deficiency, emphasized that Vitamin D supplementation is very necessary for women's suffering from gestational diabetic issues caused due to type II diabetes. Use of Vitamin D supplementation as a remedy for type II diabetes is known to stimulate the parathyroid glands which further leads to calcium circulation into the insulin, thus creating beta cells of the pancreas and leads to reduction of blood sugar levels to normal [71]. In an article published in "the telegraph" by Stephen Adams [72] children's with Vitamin D deficiency were likely to be at greater risk of developing Type II diabetes and obesity along with higher degrees of insulin resistance. Deborah Braconnier in an article correlated sever conditions of type I and type II diabetes and condition of hypoglycemia, in which blood sugar drops to a level below 70mg/dL due to faster consumption of blood sugar caused due to deficiency of Vitamin D [73]. In an article by Tanya Louise Coad on "Vitamin D deficiency and hypoglycemia" emphasis on Vitamin D intake for protective benefits from high blood sugar levels were given [74]. Jasmine Williams and Ivanhoe Newswire in their published articles [75-76] illustrated, that the children's suffering from obesity due to lower Vitamin D levels also had higher degrees of insulin resistance. In Support of this statements, studies conducted by Micah Olson at University of Texas Southwestern Medical Center Dallas, where researchers measured the Vitamin D levels, blood sugar levels, serum insulin, BMI and blood pressure, among 411 obese subjects and 87 control non-overweight subjects and came to a conclusion that children's with poor dietary habits such as skipping of breakfast and increased intake of soda and juice are associated with the lower Vitamin D levels [77]. In a report published on Vitamin D Deficiency Linked to Diabetes in the Australia's "The Age", states that people with higher Vitamin D levels were less likely to develop type 2 diabetes as compared to people with Vitamin D deficiency. This type of research study could play an important role in slowing down the increasing rates of diabetes cases in the region [78].

Vitamin D Deficiency and Stem Cell Research

Vitamin D is also known to play an important role on hematopoiesis. In an article by Sevgi Yetgin and S. Songül Yalçyn, effect of Vitamin D_3 on CD34 progenitor cells and its deficiency causing rickets were highlighted. This study showed the interrelationship between treatment given with Vitamin D_3 and bone marrow stem cells with 2% decline in CD34+ cell levels in an infant suffering from severe conditions of rickets, myelofibrosis and myeloid metaplasia[79]. Trevor G Marshall in an article [80] illustrated about active role played by Vitamin D_3 on immuno diseases and sarcoidosis. According to her findings Vitamin D_3 is mainly responsible for differentiation and proliferation of immune response, which further converts the hematopoetic-stem-cells growth into monocytes and then to leukocyte (basic White Blood Cell), these cells further grows into the macrophages and giant cells characteristic of sarcoid granuloma [81,82]. In an article published in "science daily" the ability of Vitamin D to fight placental infection from variety of pathogenic organisms, including staphylococcus, streptococcus and E. coli by producing antibacterial response in the trophoblast cells and production of cathelicidin were highlighted [83]. Richard W. Joseph et. al. in an study on deficiency of Vitamin D in the pre and post allogeneic transplant (stem cell transplants), found most of the patients with high incidence of Vitamin D deficiency during allogeneic stem cell transplantation [84]. In a review, scientist demonstrated that Vitamin D is capable of increasing effects of platelet rich plasma on the process of differentiation, which may be a critical factor for contemplating manipulation of stem cells into therapeutically active cells playing an important role in terms of growth [85]. Yuriko Kawamori et al. in a review illustrated the importance of Vitamin D receptor in the neuronal control of the hematopoietic cell, as Vitamin D_3 receptor is known for durable β2-AR signaling, along with critical modulation of hematopoietic stem/ progenitor cells and sympathetic nervous system mediation with bone remodeling mechanism [86]. Another article by Hans Van Luween showed that Vitamin D_3 affects mineralization of osteoblast causing differentiation by alteration of gene regulation [87].

Vitamin D Deficiency and Brain Disease

Studies conducted by Lionel Almeras et. al. on rats, showed Vitamin D deficiencies are interrelated to brain disorders such as multiple sclerosis, schizophrenia and impaired synaptic network as a consequence of mitochondrial dysfunction[88]. In study conducted at Queensland Brain Institute on interrelationship between development of schizophrenia in infants with lower Vitamin D levels, showed confirmed risk of increase of developing schizophrenia by two-fold among these infants[89]. Eyles DW et. al. studied the impact of environmental factors on brain development and neuropsychiatric diseases. Various disorders were encountered when Vitamin D deficiency test were conducted on infant rats subjects, these deficiency related disorders were found to cause a mild distortion in the shape of brain, along with increased lateral ventricle volumes and reduced differentiation and diminished expression of neurotrophic factors. Continuation of these deficiency disorders to adulthood showed persistence of alterations in ventricular volumes and alterations in brain gene and protein expressions that leads to behavioral sensitivity to agents that causes psychosis[90]. In an review by Joel Fuhrman, Vitamin D is considered to be a main transporting agent of glucose and calcium within brain tissues, and protects the brain from cognition and increases availability of neurotransmitters. Vitamin D also plays an important role in memory formation, thus reducing the risk of cognitive impairment and dementia in older people[91]. David Clark in a review, illustrated that deficiency of Vitamin D is a major causes of abnormal brain development and brain functions, which further leads to psychotic disorder in children's[92].

Worldwide Epidemiological Studies on Vitamin D Deficiency and Indian Perspective

As sever health issues are emerging day by day among world populations, it has become very necessary to conduct population based studies including large number of individuals in order to generate a reliable prevalence estimate of serum Vitamin D levels that exists among urban and rural population of world. Epidemiological studies were conducted by M. Rossi et. al. among 2569 female subjects between the age groups of 23 to 74 and used 2588 control subjects between the age group of 20 to 29. Studies were performed to understand the risk associated with deficiency of Vitamin D and breast cancer[93]. In an Epidemiological study, Adetunji T Toriola studied role of Vitamin D in the aetiology of ovarian cancer among 201 samples collected from females subjects in the season of summer and winter[94]. Studies conducted by John P. Forman et. al. among 613men and 1198 women subjects on interrelationship of Vitamin D deficiency and Risk of Hypertension. During this study it was found that there was 2.31 fold increase in the incident of hypertension[95]. In an epidemiological study based on age, race, and month of blood collection, body mass index, physical activity, family history of hypertension, oral contraceptive use, and plasma levels of parathyroid hormone, calcium, phosphorous, creatinine, and uric acid levels, John P. Forman et. al. conducted this study among 1484 women subjects aged between 32 to 52 years and found to develop 2.21 fold increase in hypertension cases due to hypovitaminosis[96]. In a cross sectional study conducted by Rolf Jorde among 4125 subjects who did not use any blood pressure medication, showed significant association between hypovitaminosis and hypertension increase[97].

Despite of availability of plenty of sunshine in India, Vitamin D deficiency still remains as an epidemic. In today's life changing scenario due to fast pace of life, exposure to sunlight in urban parts of the country is seldom possible which leads to Vitamin D deficiency. Deficiency of Vitamin D leads to significant morbidity and mortality among humans and imparts greater burden over economic development of India. Numerous problems are encountered due to Vitamin D deficiency. Epidemiological studies were conducted among 541 pregnant female subjects by Marwah R K et al. This study was utilized for the determination of Vitamin D status, among Indian women across all the three trimesters and different seasonal impact and its co-relation on neonatal serum levels[98]. Borkar V V et. al. conducted studies among 100 child subjects out of which 50 child subjects were diagnosed type 1 diabetes and another 50 control subjects were in healthy state. This study was conducted between the age group of 6 to 12years to find out whether Vitamin D levels are lower in children with newly diagnosed type 1 diabetes. The technique used for determination of Vitamin D levels in child subjects was High Performance Liquid Chromatography[99]. Studies were conducted by U Bhalala et. al. for determination of subclinical hypovitaminosis D among exclusively breastfed young infants of female subjects between the age group of 25 to 35 years. These infant subjects were extensively followed for their Vitamin D levels for the duration of three months and the results it described that subnormal Vitamin D status in female subjects were associated with Vitamin D deficiency in new born[100]. Studies conducted by Joseph A.J et. al. among 34 human subjects containing both male and female mixed subjects in the ratio of 24:10 between the age group of 39.2 ± 12.9 years, established a correlation between Crohn's disease and low serum 25-hydroxy Vitamin D concentrations[101]. Studies conducted by Sahu M et. al. among 121 adolescent girls and 139 pregnant women subjects from low socioeconomic community of northern india, established existence of deficiency of Vitamin D in rural girls and pregnant women despite of availability of abundant sunshine in northern parts of India[102]. Marwah R K et. al. developed study among 1345 healthy elderly subjects in two different groups: Group-1 (50 - <65 years) and Group-2 (≥65 years) and determined Vitamin D Status among elderly Indians [103]. Harinarayan C.et. al. determined Vitamin D levels in both males and female groups of 943 healthy urban and 205 rural subjects and also determined Vitamin D status among 76 urban and 70 rural healthy children so as to establish Vitamin D status among Andhra Pradesh population[104].

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