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-dehydrosterol) [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

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

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

<table>
<thead>
<tr>
<th>Source</th>
<th>Serving in Ounce</th>
<th>Contains Vit D3 in IU's</th>
<th>Vit D3 IU/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmon</td>
<td>100</td>
<td>3.5</td>
<td>360</td>
</tr>
<tr>
<td>Mackerel</td>
<td>100</td>
<td>3.5</td>
<td>345</td>
</tr>
<tr>
<td>Sardines</td>
<td>50</td>
<td>1.75</td>
<td>250</td>
</tr>
<tr>
<td>Tuna</td>
<td>100</td>
<td>3.5</td>
<td>235</td>
</tr>
<tr>
<td>Cat Fish</td>
<td>85</td>
<td>3.0</td>
<td>425</td>
</tr>
<tr>
<td>Eel</td>
<td>100</td>
<td>3.5</td>
<td>200</td>
</tr>
<tr>
<td>Egg</td>
<td>60</td>
<td>2.0</td>
<td>20</td>
</tr>
<tr>
<td>Liver (beef)</td>
<td>100</td>
<td>3.5</td>
<td>15</td>
</tr>
<tr>
<td>Milk</td>
<td>115-124</td>
<td>1 cup</td>
<td>12</td>
</tr>
<tr>
<td>Cheese Swiss</td>
<td>30</td>
<td>1.0</td>
<td>12</td>
</tr>
<tr>
<td>Cod liver Oil</td>
<td>13.7</td>
<td>1 tsp</td>
<td>1360</td>
</tr>
</tbody>
</table>
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 and also cause poor outcomes in Vitamin D.

Comparisons of Potency between Vitamin D2 and Vitamin D3.

In the early years of 1990s, fortifications of milk with Vitamin D2 were used as a major tool for eradication of rickets in infants. Specker, B et al. in an article illustrated that fortification of milk with either Vitamin D2 or Vitamin D3 with a minimal intake of 2.5g (100 IU) per day along with little sun exposure produces itself as an effective remedy for the elimination of infantile rickets[25]. Studies conducted between cod liver oil (Vitamin D2) and Viosterol (Vitamin D3), by Hess et al.[26] showed that one unit of Vitamin D2, found in cod liver oil is as effective as 4 units of Vitamin D1, of Viosterol in treatment of rickets. This study had been confirmed in 1950s in Germany, illustrating that Vitamin D1, in samples of Vigantol oil were found to be 4 times as potent per unit mass as compared to formulations of Vitamin D2. Based on the facts of potencies between Ergocalciferol and Cholecalciferol, many famous organizations worldwide which used to supply in their product of Vigantol in most part of Europe reformulated their product by replacing Vitamin D2 content with Vitamin D3[27]. Vitamin D3 is no longer considered as a nutrient suitable or equivalent to Vitamin D, in terms of efficacy, supplementation or fortification. Norman A et al.[28], in a review illustrated that the efficiency of efficacy between these two vitamins has led to the practice that 1 IU of Vitamin D2 or Vitamin D3, is to be defined in moles rather than in 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 D2 and Vitamin D3, and found that 70% elevations in 25(OH)D levels in serum with Vitamin D3, as compared to Vitamin D2. 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 D3, is required[30]. Armas et al.[31], evaluated potencies of vitamins D2 and D3, by administering simple 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 D2, was found to be increasing in the 14th day, whereas in case of Vitamin D3, the 25(OH)D dropped in the 14th day and the levles were maintained in the 25(OH)D in the subjects treated with Vitamin D2. The relative potencies of both the vitamins D2, D3, after a span of 28 days were obtained to be 9:5:1, showing that Vitamin D2 potency is less than one third that of Vitamin D3. Thus indicating that Vitamin D3 has markedly lower potency and shorter duration of action relative to Vitamin D2.

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 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 occur by due to excess intakes of Vitamin D. Vitamin D 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 hyperparathyroidism[36]. The conditions of hypercalcaemia results in elevated levels of calcium in the blood, which further leads to large deposition of phosphatude in bones and also in soft tissues affecting normal functioning of neuromuscular, gastrointestinal, renal, skeletal, and cardiovascular systems[37]. Ekeram 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 6 days to 8 months. Theses infants were fed with...
HIV disease progression in infected persons. Reduction of autophagy by HIV-1 between Vitamin D deficiency and thickening of the carotid artery in HIV subjects including HIV-Infected and HIV-Uninfected women’s in United States, hydroxyVitamin D concentrations in cord blood plasma of HIV-1-infected preg-

Al, presented scientific studies conducted on high prevalence of Vitamin D defi-

responses in human body. In an article Published in “Med Page Today” written improvements in physical performance of Vitamin D deficient humans.

made in the studies conducted on Vitamin D in recent decades, detailed research type II muscle fibers after treating an elderly stroke survivor subject, with 1000 IU of Vitamin D  daily for a period of 2 years. Despite of the enormous advances type II muscle fibers morphology. Studies conducted by Sato et al [53] showed significant increase in diameter and percentage of mean supplementation and type II muscle fibers morphology. Studies conducted by Yoshikawa et al in their studies, revealed enlargement of interstitial spaces and infiltration of fat, fibrosis and glycogen granules in Vitamin D deficient individuals[47]. Studies conducted in 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 con-

ducted on Vitamin D levels lesser than 20 and 10ng/ml in human subjects were found in association with reduced muscle function. 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 tissue[46]. Yoshikawa et al in their studies, elucidated role of 1,25-dihydroxyvitamin in contrast to the cellular microenvironment of the muscle, which influence's functioning and matura-

levels were less likely to develop type 2 diabetes as compared to people with Vita-

Diabetes in the Australia’s “The Age”, states that people with higher Vitamin D levels [77]. In a report published on Vitamin D Deficiency Linked to breaks in the bone 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 in lines with the antivirus activity. Whereas, elderly women with Vitamin D concentrations more than 20ng/ml were found to produce better muscle function-100 IU of Vitamin D, 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 in muscle fibers. Following this type of research 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 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 medicine. Key advances are highlighted by Holick 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 exacerbations especially in those with a history of mild-to-moderate per-

fections of the several medications taken by the subjects on serum Vitamin D lev-

trial studies conducted on 100 HIV infected postmenopausal women's deter-

infections, kills stander lymphocytes rapidly than infected cells [60, 61]. Clinical

autophagy by gp120. HIV-infected

infection provides a substantial biological explanation for the rapid rate of increased risk of respiratory infections. Infants born to infected mothers 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 through route of HIV-1 [39]. Thus, HIV-infected persons are more likely to have release of toxic viral products by gp120. HIV-infected CD4+ lymphocytes causes apoptosis, which further results in programme d cell death of uninfected lymphocytes [59]. Reduced autophagy conditions in acute

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 matura-

fection. In a review by Bouillon R. in a review on Vitamin D and extra skeletal health[45] illustrated interrelationship between Vitamin D and normal muscle functioning. Evidence 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 tissue[46]. Yoshikawa et al in their studies, elucidated role of 1,25-dihydroxyvitamin in contrast to the cellular microenvironment of the muscle, which influence's functioning and matura-

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 diabetes issue 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 to normal levels [72]. In an article published by J. 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 Bramciner in an article correlated several 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 bene-

fits from high blood sugar levels were given [74]. Jasmine Williams and Ivanhoe [75-76] illustrated more than 20% children's were reported to be suffering from obesity due to lower Vitamin D levels also had higher degrees of insulin resistance. In Support of these statements, studies conducted by Michal 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 levels among 41 0-12 year old children. Among the children who 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 Vita-
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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 Yalcın, effect of Vitamin D on CD34 progenitor cells and its deficiency causing rickets were highlighted. This study showed the interrelationship between treatment given with Vitamin D, 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. MacLaughlin et al. in another study illustrated about the role played by Vitamin D on immune diseases and sarcoidosis. According to her findings Vitamin D is mainly responsible for differentiation and proliferation of immune response, which further converts the hematopoietic-stem-cells growth into monocyes and then to leukocyte (basic White Blood Cell), these cells further grows into the macrophages and dendritic cells. Characteristic of an article published in “science daily” the ability of Vitamin D to fight placentation invarity of from pathogenic organisms, including staphylococcus, streptococcus and E. coli by producing antibacterial response in the trobophlast and production of cathelicidin were illustrated [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 off platelet rich plasma on the process of differentiation, which may be a critical factor for wound healing and templating 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 hypothalamic-pituitary-gonadal axis. In another study by Jorde et al. it was found that Vitamin D deficiency is associated with increased risk of Alzheimer’s disease [86]. In an epidemiological study based on age, race, and winter [94], Studies conducted by John P. Forman et. al. among 613 men and 201 samples collected from females subjects in the season of summer and winter [94]. Adetunji T Toriola studied role of Vitamin D in the aetiology of ovarian cancer among 501 female 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 by sandwich enzyme linked immunosorbent assay (ELISA). The study had shown that children born in Vitamin D deficient areas were at a higher risk of developing ovarian cancer compared with their counterparts born in areas with higher Vitamin D levels [93]. In an epidemiological studies were conducted by M. Rossi et. al. among 2569 female subjects in Italy [99]. As sever health issues are emerging day by day among world populations, it has been found that deficiency of Vitamin D is associated with breast cancer [93]. Studies were conducted by BahHAL et al. 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. from 34 human subjects containing both male and female mixed subjects in the ratio of 24:10 between the age group of 39.2 - 9.9 years, established a correlation between the severe outcome 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 socio-economic community of northern India, established existence of deficiency of Vitamin D in rural 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].

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 conducted by M. Rossi et. al. among 2569 female subjects between the age group of 23 to 74 and used 5886 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 613 men and 205 rural subjects and also determined Vitamin D status among Andhra Pradesh population [104].

Despite of availability of plenty of sunshine in India, Vitamin D deficiency still remains 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 study among 1484 women subjects aged between 32 to 52 years and found to be 2.2 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].

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