# Review :

# Role of Vitamin D in Health and Diseases in Children

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**History:**

Vitamin D and its role in bone related diseases had a long history before various researches comes into scene. Rickets, the bone disease caused by vitamin D deficiency was known in antiquity and was described first in detail by Glisson et al in 1650[1].In 1923, American biochemist Harry Steenbock[2] at the University of Wisconsin demonstrated that irradiation by ultraviolet light increased the vitamin D content of foods and other organic material. After irradiating rodent food, Steenbock discovered the rodents were cured of rickets. A vitamin D deficiency is a known cause of rickets. 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[3]. In 1971–72, the further metabolism of vitamin D to active forms was discovered. In the liver, vitamin D was found to be converted to calcidiol. Part of the calcidiol is then converted by the kidneys to calcitriol, the biologically active form of vitamin D[4] Calcitriol circulates as a hormone in the blood, regulating the concentration of calcium and phosphate in the bloodstream and promoting the healthy growth and remodelling of bone. Both calcidiol and calcitriol were identified by a team led by Michael F. Holick in the laboratory of Hector DeLuca[5,6]

**What is Vitamin D?**

Vitamin D is a fat-soluble vitamin that is converted to a hormone within the body. By definition, hormones are considered to be chemical messengers that relay messages to cells. Hormones cause cells to express specific sequences of deoxyribonucleic acid (DNA), which is contained within the cell nucleus. When this specific sequence of DNA is expressed within a cell, the cell then responds through the process of transcription and translation and produces specific proteins, which then perform direct functions in the Body[7]. The active form of vitamin D, calcitriol, acts as a hormone by binding to vitamin D receptors (VDRs) both on the cell membrane as well as in the nucleus. This binding then leads to specific gene expression[8].

**Vitamin D Metabolism:**

The two main sources of vitamin D are sunlight and diet. The skin synthesizes a steroid, 7-dehydrocholesterol, which is capable of absorbing specific wavelengths of light. When the skin is exposed to certain wavelengths of ultraviolet B (UVB) rays from the sun, the stored 7-dehydrocholesterol is converted to previtamin D3 or precalciferol[8,9] . In two to three days, the previtamin D3 is thermally isomerized to produce vitaminD3, cholecalciferol. Vitamin D3 then diffuses into the blood stream via a vitamin D binding protein (DBP), which then transports the vitamin to the liver. Once in the liver, it is hydroxylated and becomes 25-hydroxyvitamin D3 after which it is transported to the kidney for a second hydroxylation in which it is converted to 1,25-(OH)2 D3, which is the active form of vitamin D. Vitamin D3 is then transported throughout the body to cells where it binds to VDRs and leads to specific gene expression8 When dietary vitamin D is consumed, it is absorbed in a micelle along with lipids via passive diffusion. The vitamin D is incorporated into chylomicrons and is then transported to the liver. Once in the liver, vitamin D

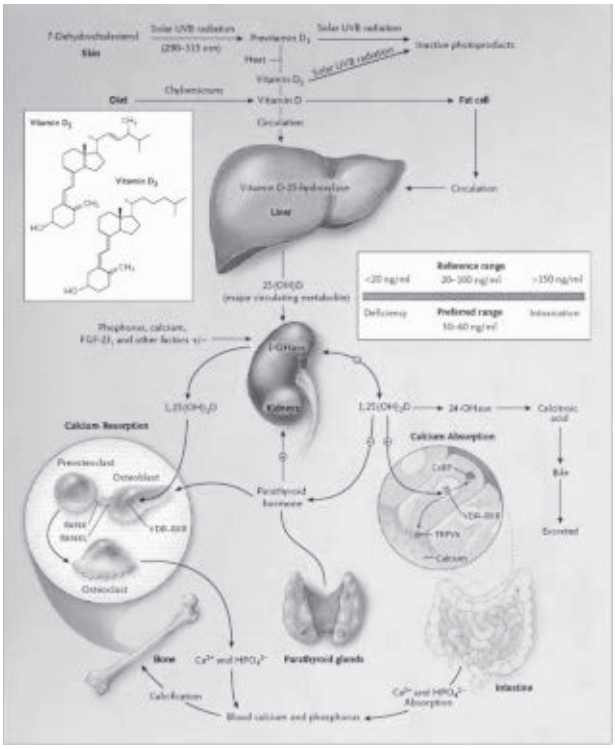


**Fig.1.:** The following diagram is a visual representation of vitamin D metabolism[10]

is metabolized and completes its first hydroxylation after which it is released into the blood. The serum vitamin D (25-OH D3) level reflects vitamin D status and concentration within the body. If serum 25-OH-D3 becomes depleted, cholecalciferol will be released from its storage sites within the blood, muscle, and adipose tissue[8].

After the hydroxylized vitamin D enters the blood, it is primarily taken up by the kidney in order to undergo a second hydroxylation upon which it is considered to be in the active form of the vitamin. Calcitriol, or 1,25-(OH)2 D3, is then released from the kidney and travels via vit D BP into the blood where it will be delivered to target tissues[9].

**Physiology of Vitamin D :**

The classic effect of 1,25(OH)2 D on active calcium transport occurs in the intestinal cell. Calcium enters the cell through membrane proteins. In the intestinal cell, 1,25(OH)2D binds to the vitamin D receptor and the calcium binding protein is synthesized and this regulates the active transport through the cell . The calcium is transported to the extracellular fluid by an ATP dependent mechanism. There also is passive transport through paracellular diffusion of calcium. The vitamin D-dependent calcium absorption has a maximum. The vitamin D-independent calcium absorption through passive diffusion does not have a maximum, but depends on the calcium gradient, this means on the calcium intake[9].

The 1,25(OH)2D has its effect on the classic target organs bone, intestine and kidney and stimulates calcium transport from these organs to the blood. The production of 1,25(OH)2D is stimulated by parathyroid hormone (PTH). There is a negative feedback through calcium which decreases PTH and a direct negative feedback from 1,25(OH)2D to PTH. The active metabolite 1,25(OH)2D also shows rapid actions through a membrane receptor9.

**Sources of Vitamin D:** The primary sources of dietary vitamin D include dairy products, fatty fish, and fortified foods and sunlight exposure wavelength 290-315. The following table highlights the amount of vitamin D in these foods.

**Food Serving Vitamin D (IU) Vitamin D (mcg)[11]**

| | | |
|---|---|---|
| Pink Salmon, 3 ounces | 530 | 13.3 |
| Cow milk, fortified with Vit D 8 ounces | 98 | 2.5 |
| Soya Milk, fortified with Vit D | 100 | 2.5 |
| Egg Yolk 1 large | 21 | o.53 |

Role of Vitamin D:Vitamin D has several roles in the body; many of these arise from its action on gene transcription and expression. Vitamin D receptors (VDRs) are located on many cells and respond to the presence of vitamin D by initiating a cascade of events that leads to transcription of specific genes[11] Vitamin D has both genomic and non-genomic functions. For the genomic functions, 1,25(OH)2D interacts with nuclear vitamin D receptors to influence gene transcription. Nuclear receptors for 1,25(OH)2D have been identified in over 30 cell types, including bone, intestine, kidney, lung, muscle and skin. For the non-genomic functions, 1,25(OH)2D acts like a steroid hormone, working through activation of signal transduction pathways linked to vitamin D receptors on cell membranes. Major sites of action include bone, intestine, parathyroid, liver and pancreatic beta cells[11].

One of the major biological functions of vitamin D is to maintain calcium homeostasis which impacts on cellular metabolic processes and neuromuscular functions. Vitamin D affects intestinal calcium absorption by increasing the expression of the epithelial calcium channel protein, which in turn enhances the transport of calcium through the cytosol and across the basolateral membrane of the enterocyte. Vitamin D also facilitates the absorption of intestinal phosphate. 1,25(OH)2D indirectly affects bone mineralization by maintaining plasma calcium and phosphorus concentrations, and subsequently extracellular calcium and phosphorus concentrations at the supersaturating range necessary for mineralization. 1, 25(OH)2D, in concert with parathyroid hormone, also causes demineralization of bone when calcium concentrations fall to maintain plasma concentrations within a narrow range[9].

In addition to intestine and bone, a wide range of other tissues and cells that are influenced by vitamin D. Five biological systems have vitamin D receptors and are responsive to 1,25(OH)2D. These systems include immune system, pancreas, cardiovascular, muscle and brain.1,25(OH)2D3 has been shown to inhibit cancer cell growth, induce cancer cell maturation, induce apoptosis, and decrease angiogenesis. 1,25(OH)2D inhibits renin production in the kidney and has a immunomodulatory activity on monocytes and activated T and B lymphocytes. Currently, there are at least 200 genes known that respond to 1,25-dihydroxyvitamin D[8].

**Bone Health and Calcium Absorption:**

The roles of vitamin D in the body are increasingly more understood as additional research is conducted in this area. One of its most widely known functions is its involvement in bone health. Vitamin D facilitates calcium absorption in the intestine by influencing the expression of epithelial calcium channels and thus calcium-binding proteins. This process allows calcium to be better absorbed from the foods eaten1.Due to the increase in absorption on calcium, parathyroid hormone (PTH) levels are better regulated. When serum calcium levels are low, the parathyroid gland secretes PTH, which leads to increased production of vitamin D3. This further increases absorption of calcium from the intestine as well as increases reabsorption of calcium by the kidneys. The third effect that increased PTH levels have on the body is that it leads to resorption of calcium from the bone in order to maintain adequate serum levels. Leaching calcium out of the matrix of bone leads to decreased bone strength. If adequate vitamin D3 is present before this occurs, PTH levels are likely to be kept low as calcium absorption is increased[11]. Another way in which vitamin D works to increase bone strength is by mediating the incorporation of calcium into the matrix of bone. This strengthens the network of fibers within the bone itself thus leading to stronger bones[12].

**Cellular Differentiation:**

Vitamin D also plays a role in cellular differentiation. It has been shown to decrease proliferation of cells and plays a role in their maturation. This is a very important function in

terms of cancer prevention. Cells that proliferate at faster rates are at increased risk for developing mutations. The active form of vitamin D, calcitriol, helps to regulate cellular proliferation by promoting cellular differentiation[11,13]

**Immunomodulator:**

VDRs are located on activated T and B lymphocytes, monocytes, and macrophages thus showing vitamin D is also an immunomodulator. It helps to regulate the function of lymphocytes, the production of cytokines, maturation of monocytes, and macrophage activity. Its role in the immune system may lead to the prevention of autoimmune diseases when adequate serum levels of vitamin D are maintained [8].

**Insulin Secretion:**

Vitamin D and the prevention of diabetes is another recent area of study. VDRs are located on the beta cells of the pancreas. It appears that in situations in which the body requires increased amounts of insulin, vitamin D plays a role in the secretion of insulin. Recent studies have concluded that when an insufficient amount vitamin D3 is present, glucose intolerance and impaired insulin secretion are observed in population with type 2 diabetes[11].

**Blood Pressure:**

Adequate vitamin D3 levels are also associated with a decreased risk for cardiovascular disease. VDRs are located on vascular smooth muscle, endothelium, and cardiomyocytes [14]. One of the main mechanisms where by vitamin D appears to decrease cardiovascular disease risk is its effect on hypertension through the rennin-angiotensin system. The expression of renin leads to the stimulation and production of angiotensin which then causes a series of reactions that increase blood pressure. These reactions include constriction of small arteries as well as an increase in the amount of sodium and water reabsorbed by the kidneys. Vitamin D has been shown to depress the gene expression of renin thus leading to decreased blood pressure[13].

**What is Vitamin D Defficiency?**

Vitamin D deficiency can be easily diagnosed in presence of clinical features of rickets. But rickets is an extreme form of vitamin D deficiency. Serum 25 (OH) D levels is the best available biomarker for the diagnosis of vitamin D deficiency. Serum level of 1,25(OH)2D is not a good indicator of vitamin D deficiency because

(i) subtle hypocalcaemia causes PTH elevations leading to increased 1-?-hydroxylase activity resulting into normal or elevated 1,25(OH)2D in face of vitamin D deficiency,

(ii) circulating concentrations of 1,25(OH)2D are 100 to 1000 fold less abundant than 25 (OH) D,

(iii) half-life of 1,25(OH)2D is only 4 hours as against 3 to 4 weeks in case of 25 (OH) D and

(iv) 25 (OH) D is the storage form of vitamin D.

Holick defined vitamin D deficiency as 25-OH D < 20 ng/mL (50 nmol/L) and vitamin D insufficiency as 25-OHD at 21 to 29 ng/mL (52-72 nmol/L)15.

**Vitamin D deficiency:**

Vitamin D deficiency is defined by most experts as a serum 25(OH)D level of less than 20 ng/mL (50 nmol/L).

**Vitamin D insufficiency:**

Vitamin D insufficiency has been defined as a serum 25(OH)D level of 21-29 ng/mL (52-72 nmol/L). This is based on the observed physiological changes in calcium absorption and parathyroid hormone levels that occur with changes in vitamin D levels. But in this study it is included in deficient category.

**Vitamin D sufficiency:**

Vitamin D sufficiency has been defined as

serum 25(OH) D levels of 30 ng/ mL (75 nmol/L) and above based on analysis of observational studies of vitamin D and various health outcomes.

**Vitamin D toxicity:**

Vitamin D toxicity is observed when serum 25(OH)D levels are greater than 150 ng/mL (374 nmol/L).

**Vitamin D deficiency causes:**

The Vit D is present in very few food items and in a very low quantity required to fulfill the adequate need. It is present in food such as egg, milk some fishes (salmon, Indian name Rawas and tuna) in a very less quantity. The major source of Vit d is sunlight exposure between 10 am to 3 pm ( 290-315 nm) so Inadequate exposure to sunlight causes a deficiency in cutaneously synthesized vitamin D, as most of children are home bound, playing indoor games, inadequate place to get sunshine specially in metro cities like Mumbai. Adults in nursing homes or health care institutions are at a particularly high risk.[16] This is further increased by use of sunscreens, skin pigmentation, low dietary intake and shadow seeking behavior seen in the country.

Vitamin D malabsorption problems - People who have undergone resection of the small intestine are at risk for this condition; diseases associated with vitamin D malabsorption include celiac sprue, short bowel syndrome[44] and cystic fibrosis[17].

**Vitamin D Defficiency Effects:**

Vitamin D deficiency causes poor mineralization of the collagen matrix in young children's bones leading to growth retardation and bone deformities known as rickets. In adults, vitamin D deficiency induces secondary hyperparathyroidism, which causes a loss of matrix and minerals, thus increasing the risk of osteoporosis and fractures. In addition, the poor mineralization of newly laid down bone matrix in adult bone results in the painful bone disease of osteomalacia. Vitamin D deficiency causes muscle weakness, increasing the risk of falling and fractures. Vitamin D deficiency also has other serious consequences on overall health and well-being. There is mounting scientific evidence that implicates vitamin D deficiency with an increased risk of type I diabetes, multiple sclerosis, rheumatoid arthritis, hypertension, cardiovascular heart disease, and many common deadly cancers.[18]

More than 80 yrs ago, it was reported that living at higher latitudes in the United States correlated with an increased risk of dying of common cancers.[19] In the 1980s and 1990s, several observations suggested that living at higher latitudes increased the risk of developing and dying of colon, prostate, breast, and several other cancers. Because living at higher latitudes diminishes vitamin D3 production, it was suggested that an association may exist between vitamin D deficiency and cancer mortality. Both men and women exposed to the most sunlight throughout their lives were less likely to die of cancer. [20-24]

Several retrospective and prospective studies that evaluated circulating concentrations of 25(OH)D support the concept that vitamin D deficiency increases the risk of developing and dying from cancer.[24-26] It has been suggested that adults with 25(OH)D of <50 nmol/L who were then followed for up to 19 y had a 30-50% increased risk of developing colorectal, breast, prostate, and many other cancer[27]. Person who ingested >400 IU vitamin D/d had a markedly reduced risk of developing several cancers, including those of the pancreas and esophagus and non-Hodgkin lymphoma.

Living at higher latitudes is associated with an increased risk of type 1 diabetes[28] multiple sclerosis[29,30] and hypertension. Children who received 2000 IU vitamin D/d during the first year of life and who were followed for 31 year were found to have a reduced risk of developing type 1 diabetes by 78% compared with children who were not supplemented with vitamin D [31]. Women who

received >400 IU vitamin D/d were found to have a >40% reduced risk of developing multiple sclerosis[32] and rheumatoid arthritis[33]. Hypertensive patients who were exposed to a tanning bed raised their blood concentrations Of 25(OH)D by >180% in 3 months and became normotensive [34]. Patients who live at higher latitudes and are at risk of vitamin D deficiency are also more prone to developing schizophrenia[35] and vitamin D deficiency has been associated with depression [36]. Vitamin D deficiency in pregnancy has also been associated with an increased risk of preeclampsia [37].

African Americans are at higher risk of developing and having more severe cases of tuberculosis. It has been known for >100 y that exposure to sunlight helped in the treatment of tuberculosis.

Likely mechanism is that when a macrophage is infected with tuberculosis, it stimulates the cell to increase the production of 1,25-dihydroxyvitamin D3 [1,25(OH)2D3] and increase the expression of the vitamin D receptor. In combination, they enhanced the gene expression of the bactericidal protein cathelicidin, which is known to kill tuberculosis and other infective agents.[38]

Contributory Factors for VitaminD Defficiency: Worldwide, naturally occurring dietary sources of vitamin D are limited, and food fortification is optional, inconsistent, inadequate, or nonexistent. Therefore, for most people, vitamin D is primarily obtained by cutaneous production from sun exposure[39]. However, many variables influence the amount of UVB from sunlight that reaches the skin and its effectiveness. These include time of day, season, latitude, altitude, clothing, sunscreen use, pigmentation, and age. In Minnesota in 2008, less than half of days provided enough solar UVB radiation at noon to effect cutaneous vitamin D production. Even those who normally reside in sunny climates are commonly found to be deficient in vitamin D, probably due to cultural habits and/or dress. Even if regularly exposed to sunlight, elderly people produce 75% less cutaneous D3 than young adults. Further barriers to Cutaneous vitamin D production are ongoing public health campaigns promoting sunscreen use, as advocated by the American Academy of Dermatology.[40]

**Vitamin D deficiency:**

An Indian scenario :It is surprising as to why vitamin D deficiency is such a common problem among Indians in spite of abundant sunshine. For example, study by Dr. AV Khadilkar vitamin D status of adolescent girls in Pune (latitude18.34º N) was similar to that of adolescent girls in Manchester, UK (latitude 53.4º N), assessed during an equivalent season[41]. This was probably because Pune girls had very low calcium intake and a high fibre diet which may have led to a depletion of body stores of vitamin D. Other reasons may be genetic factors. For example, South Asians have increased 25(OH)D-24-hydroxylase, which degrades 25(OH)D to inactive metabolites[42,43]. More recently, it has been shown that the increment in serum 25OHD in response to treatment depends on the heritability of vitamin D binding protein[71]. Marwah, et al[44] have also found that post supplementation, serum parathyroid hormone (PTH) values have increased above the baseline levels particularly in the lower socio economic stratum, in spite of increment in serum 25OHD concentration. This was a surprising finding and is difficult to explain. Possible explanations include very low dietary calcium to phosphorous ratio in adolescents from the lower socioeconomic group, high dietary phosphorous may have acted as a potent stimulant to the parathyroid glands, and this rise in PTH was possibly not overcome by the post supplementation increment in serum 25OHD, low dietary calcium intake can result in raised serum PTH concentrations due to reversible end organ resistance to the actions of PTH[45].It is becoming increasingly evident that abundant sunshine does not seem to protect Indians from widespread biochemical vitamin D deficiency.

It has been estimated that 1 billion people

worldwide have Vit D deficiency or insufficiency[46].There is widespread prevalence of varying degrees (50- 90%) of Vit D deficiency with low dietary calcium intake in Indian population according to various studies published earlier[47]. Apart from low dietary intake, people suffering from hepatic, renal, dermatological disorders, alcoholics and inflammatory rheumatological conditions also have Vit D deficiency. Vit D deficiency is a common problem in India due to several factors:

1. Changing food fads and food habits contribute to low dietary calcium and Vit D intake.
2. High fibre diet containing phosphates and phytates which can deplete Vit D stores and increase calcium requirement[48].
3. Genetic factors like having increased 25(OH)D-24-hydroxylase which degrades 25(OH)D to inactivemetabolites[49].
4. It has been shown that increment in serum 25(OH)D in response to treatment depends on the heritability of Vit D binding protein[50].
5. With modernization, the number of hours spent indoor have increased thereby preventing adequate sun exposure. This is particularly true in the urban Indians.
6. Increased pollution can hamper the ultraviolet rays to adequately synthesize Vit D in the skin[51].
7. Cultural and traditional habits prevalent in certain religions like "Burqa" and the "Pardah" system in Muslims have been well known.
8. Repeated and unplanned, unspaced pregnancies in dietary deficient patients can aggravate Vit D deficiency in the mother and the foetus.

Vit D deficiency is not only a problem in India but also in countries like Pakistan, China, middle-East and Africa. It is relatively less common in Japan, USA, Canada and South-east Asia. In USA and Canada, milk is usually fortified with Vit D and the use of vitamin supplements is common[52]. Although we are all aware about the causes of Vit D deficiency, we are still lacking in preventing it. Although, there is adequate sunshine in India, high temperatures during the daytime and sultry and humid climate in many areas are the deterrents to follow the advice about sun exposure. Hence, food fortification with Vit D is a good option to solve this issue. Similarly food fortification and public health policies for Vit D supplementation and dietary guidelines for adequate calcium for Indian population should be formulated and implemented.

Marwaha et al have reported Vit D deficiency in healthy Indians above 50 years from North India[53]. However, there was no correlation of BMD with 25(OH)D in this study. An interesting finding in this study is that more than half of the subjects were taking calcium and Vit D supplements, but there was no difference in serum 25(OH)D levels between the two groups. Most of the subjects were taking between 200-400 IU of Vit D3 (cholecalciferol) which is insufficient to normalize serum 25(OH)D levels in a Vit D deficient population[80]. One study from North India reported requirement of 60,000-120,000 IU per month to achieve Vit D level > 30 ng/ml. This is the level At which calcium absorption from the gut is maximum[81]. Another study by Goswami et al have reported correction of Vit D level to normal after 8 weeks of supplementation with weekly dose of 60,000 IU[54]. Both these studies highlight the need of regular supplementation of at least 2000 IU/day of VitD supplementation to maintain normal Vit D levels[55].

Sex: Prevalence study from south India has shown an increased incidence in females in both rural as well as urban setup[55]. Prevalence rate has been found to be high in girls from north India as well[56]. Studies from different parts of the world also show a similar trend. Different aetiologies, such as insufficient sun exposure, clothing habits, and insufficient intake of vitamin D, may explain high

prevalence of vitamin D deficiency.

**Diet and Nutrition:**

Dietary vitamin D intake is very low in India because of low consumption of vitamin D rich foods, absence of fortification and low use of supplements. All these factors contribute to poor vitamin D status as measured by low circulating levels of 25-hydroxy vitamin D.[57] The RDA for calcium in India recommended by the Indian Council of Medical Research (ICMR) is lower than the recently revised recommendations by the USA and Canada. There is neither a recommendation for dietary intake of vitamin D nor a monitored food fortification program for the intake of calcium or vitamin D by ICMR. there is a strong need to fortify food staples with vitamin D or stimulate public health policies for vitamin D supplementation and dietary guidelines tailored to the Indian diet.

**Recommended Dietary Allowances of calcium in India and USA[58,59]**

| Category | India | USA |
|---|---|---|
| Units | mg/day | mg/day |
| **Infants :** | | |
| 0-6 months | 500 | 500 |
| 6- 12 months | 500 | 750 |
| **Children :** | | |
| 1 - 9 yrs | 400 | 800 |
| 10 - 15 yrs | 500 | 1200 -1300 |
| 16 - 18 yrs | 500 | 1200 -1300 |
| **Men** | 400 | 800 -1000 |
| **Women** | 400 | 800 - 1000 |
| **Pregnant & Lactating mother** | | |
| | 1000 | 1200 - 130 |

**Sun Exposure:**

Traditionally, up to 95% of the body's vitamin D requirement comes from the synthesis in the epidermis on sun exposure. It is the most potent source of vitamin D. (about 3,000 IU vitamin D3 per 5 to 10 min of mid-day, midyear exposure of arms and legs for a light-skinned person) However due to lifestyle changes in the recent times; this has become difficult. Use of sunscreens, playing indoor games, excessive screen time (educational as well as non educational) and clothing are some of the contributory factors. This has definitely contributed to the high prevalence of vitamin D deficiency in India and worldwide. Even if regularly exposed to sunlight, elderly people produce 75% less cutaneous D3 than young adults[60]. Despite of being a tropical country and abundant sun exposure, there is a high prevalence of vitamin D deficiency in India due to above reasons.

**Body Mass Index:**

Obesity is associated with vitamin D insufficiency. Obesity-associated vitamin D insufficiency is likely due to the decreased bioavailability of vitamin D3 from cutaneous and dietary sources because of its deposition in body fat compartments. Because humans obtain most of their vitamin D requirement from casual exposure to sunlight, the >50% decreased bioavailability of cutaneously synthesized vitamin D3 in the obese subjects could account for the consistent observation by us and others that obesity is associated with vitamin D deficiency[61]. It has been postulated that obese individuals may avoid exposure to solar ultraviolet (UV) radiation, which is indispensable for the cutaneous synthesis of vitamin D3[62]. Alternatively, it has been proposed that production of the active vitamin D metabolite 1,25-dihydroxyvitamin D [1,25(OH)2D] is enhanced and thus, its higher concentrations exert negative feedback control on the hepatic synthesis of 25(OH)D.[63] It has also been suggested that the metabolic clearance of vitamin D may increase in

obesity, possibly with enhanced uptake by adipose tissue[64]. Body fat may act as a reservoir for storage of the fat soluble vitamin D, reducing its bioavailability[65]. A negative correlation between serum 25(OH)D levels and magnitude of weight loss in patients after surgical treatment of morbid obesity confirms this theory[66]. A contributing factor to the low vitamin D status among obese people might be lower than average exposure of large body areas to the sun. It is assumed that secondary hyperparathyroidism, observed frequently in overweight and obese population.[67]

**Socioeconomic status:**

Socioeconomic status plays an important role in the diet of a person. It determines the intake of a balanced diet along with adequate intake of all micronutrients and vitamins. Studies in different parts of the world have demonstrated correlation between the living condition and lifestyle and vitamin D status.

**Calcium supplementation:**

It has been shown that calcium absorptive performance of the gut is a function of 25(OH)D status of an individual. When there are low 25 (OH) D concentrations, the effective calcium absorption from the gut is reduced. This is further amplified by the low dietary calcium intake. low dietary calcium converts the 25(OH)D to polar metabolites in the liver and leads to secondary 25(OH)D deficiency.

One study done in rats showed that the rate of inactivation of vitamin D in the liver is increased by calcium deprivation. The effect is mediated by 1,25-dihydroxyvitamin D, produced in response to secondary hyperparathyroidism, which promotes hepatic conversion of vitamin D to polar inactivation products that are excreted in bile. This finding has widespread implications both for understanding the pathogenesis of endemic rickets and in that it provides a unifying mechanism for the development of vitamin D deficiency in many clinical disorders. Furthermore, there is evidence that low calcium intakes might increase vitamin D requirements through another mechanism, as higher levels of 25(OH)D might be required to maintain optimal elevated concentrations of 1,25(OH)2D to ensure maximal absorption of the low intestinal calcium content[68].

**Breastfeeding:**

Breastfeeding will result in vitamin D deficiency in the baby if the mother fails to ensure her own levels are high enough to provide for her baby's needs. When the mother is deficient, the breast-fed child will be deficient due to the low vitamin D content of the mother's breast milk, diet, metabolic abnormalities, liver dysfunction, kidney disease, and exclusively breastfeeding in infants [69].

**Age:**

Many children remain home bound and do not receive as much sun light exposure as those who are younger. When the children do receive sun exposure, vitamin D production is hindered by decreased capability of the skin to utilise the sunlight received. As a person ages, 7-dehydrocholesterol decreases in the skin, which leads to decreased absorption of UVB rays that convert precaliciferol to cholecalciferol[70].

**Diet and Malabsorptive Disorders:**

The amount of vitamin D received in the diet also has an impact on serum levels. Given the body's ability to absorb vitamin D is not compromised, increased intake of foods rich in vitamin D, such as fatty fish and milk, will lead to increased serum levels. In regard to metabolic abnormalities due to the fact that vitamin D is fat-soluble and is best absorbed with dietary fat, if an individual has a condition in which fat absorption is compromised, such as cystic fibrosis, Crohn's disease, or sprue, then less of the vitamin will be absorbed despite the amount of vitamin D and/or dietary fat ingested[1].

**Liver Dysfunction and Kidney Disease:**

In cases of liver dysfunction, the hepatic

enzymes that catalyze the first hydroxylation of cholecalciferol may be inhibited. Additionally, kidney disease or dysfunction leads to an inability of the kidneys to effectively convert vitamin D into its active form. Certain medications may also block the uptake of vitamin D from the gastrointestinal tract[71].

**Vitamin D and Diarrhoeal Diseases:**

The immunomodulatory properties of vitamin D may influence susceptibility to infection. These effects are primarily mediated through the vitamin D receptor (VDR), which is expressed in many cells of the immune system, including T and B lymphocytes, neutrophils, monocytes, macrophages and dendritic cells. Stemming from the immunologic properties of vitamin D, it represents an additional micronutrient that may have a role in the prevention of childhood diarrheal diseases.

Levels of 1,25(OH)2D, the active form of vitamin D, are increased by the enzymatic activities of CYP27B1-hydroxylase and reduced by CYP24A1-hydroxylase. It is postulated that the kinetics of that equilibrium control tissue-specific paracrine activities of vitamin D. Immunologic activation of toll-like receptors on macrophages by pathogens augments intracellular expression of CYP27B1-hydroxylase and vitamin D receptor (VDR) genes. Subsequently, with sufficient cytosolic concentrations of 25-(OH)D, CYP27B1-hydroxylase produces 1,25(OH)2D. Binding of the 1,25(OH)2D-VDR complex to DNA response elements upregulates expression of the antimicrobial peptides cathelicidin and ?-defensin, intracellular modulators that are ubiquitously expressed in the gastrointestinal tract. Thus in vitamin D-deficient individuals innate immune activity may be impaired, thereby enhancing susceptibility to intracellular diarrhoegenic pathogens. Additionally, in vitro research of adaptive immunity has shown that the 1,25(OH)2D-VDR complex induces CCR10 expression in terminally differentiated B cells CCR10 functions in cellular homing of immunoglobulin A-secreting cells to enteric tissues. Given the importance of immunoglobulin A in adaptive mucosal immunity, vitamin D deficiency could result in impaired host abilities to mount pathogen-focused immune responses to diarrhoegenic microbes.[13]

**Vitamin D and Respiratory Infections:**

Recent evidence suggests that vitamin D influences several immune pathways, with the net effect of boosting mucosal defenses while simultaneously dampening excessive inflammation[73]. For example, vitamin D induces the gene encoding the antimicrobial peptide LL-37[74]. This peptide has potent bactericidal capacity against a number of important bacteria and viruses, including M. tuberculosis and influenza-virus [75-76]. In fact, human macrophages rely upon the vitamin D/LL-37-axis to kill mycobacteria, an effect that is abrogated if the LL-37 gene is silenced with RNA-interference [77-78].

In humans, the activation of vitamin D involves two hydroxylation steps, one in the liver and one in the kidney. Notably, the final activation of vitamin D, via 1-alpha hydroxylase (CYP27B1), also occurs in extra-renal tissues, including epithelial and immune cells[122]. In the respiratory tract, CYP27B1 is expressed in bronchial epithelial cells and induced by inflammatory stimuli[79]. Thus, the vitamin D/antimicrobial peptide-circuit may be activated locally upon infection, which further suggests a role for vitamin D in host defense.

Additional evidence supporting a role for vitamin D in respiratory tract infections is provided by observational reports showing an association between low 25-OH vitamin D (25(OH)D) levels and increased risk of infection. A large cross-sectional trial (n = 18883) showed that the risk of RTI increased with lower 25(OH)D levels and that the effect was even stronger in individuals with chronic obstructive pulmonary disease (COPD) or asthma [80-82].

**Epidemiological Studies of Vitamin D :**

Brooke OG et al. conducted a double-blind trial of vitamin D supplements in Asian women (ergocalciferol 1000 IU per day during the last trimester of pregnancy). 59 infants were born to women who had received supplementary vitamin D and 67 to the controls. There were no significant differences in birth weight, length, or head circumference in the two groups. The male: female ratio was 1.3:1 in both groups. The infants were seen at 3, 6, 9, and 12 months, when measurements were made of their naked weight on a well calibrated beam balance, crown-heel length on a horizontal stadiometer and occipitofrontal head circumference. Postnatal vitamin supplements were given and breast-feeding was encouraged. The mean length of breast feeding was 3.2 months in the treated group, whose mothers had received vitamin D during pregnancy, and 3.5 months in the control group ($p > 0.05$). Weights remained approximately equal between the groups at 3 month and began to diverge from 6 month onward, such that by 12 month the infants of control mothers weighed $8.98 \pm 0.62$ kg, compared with $9.39 \pm 0.66$ kg for the treated group. The incremental increase in weight during the 12-month period was $5.92 \pm 0.92$ kg for the infants of control mothers and $6.39 \pm 0.78$ kg for the infants of treated mothers. A similar pattern was observed for length, with divergence from 6 month onward and a difference of 1.2 cm at the age of 1 year ($76.2 \pm 1.9$ cm for infants of treated mothers, compared with $74.6 \pm 1.7$ cm). There was no significant difference in head growth between the two groups [83].

Geeta TK et al. investigated whether vitamin D supplementation can decrease the mortality and morbidity of low birth weight infants in low income countries. In a randomised trial, 2079 low birth weight infants born at term (>37 weeks' gestation) were included. Primary outcome was admission to hospital or death during the first six months of life. Main secondary outcome was growth. Interventions were weekly vitamin D supplements for six months at a dose of one recommended nutrient intake per day (35µg/week). Infants were visited weekly at home for observed supplementation and were brought to the clinic monthly for clinical examination and anthropometric measurements. Between group differences were not significant for death or hospital admissions (92 among 1039 infants in the vitamin D group v 99 among 1040 infants in the placebo group; adjusted rate ratio 0.93, 95% confidence interval 0.68 to 1.29; P=0.68), or referral to the outpatient clinic for moderate morbidity. Vitamin D supplementation resulted in better vitamin D status as assessed by plasma calcidiol levels at six months. In adjusted analyses, vitamin D treatment significantly increased standard deviation (z) scores at six months for weight, length, and arm circumference and decreased the proportion of children with stunted growth (length for age z score ?2) or with arm circumference z scores of 2 or less. They concluded that a weekly dose of vitamin D resulted in better vitamin D status and benefited the classic vitamin D function of bone growth but did not decrease the incidence of severe morbidity or death among young low birth weight infants [84].

Samual A et al. conducted a study to determine whether vitamin D supplementation of breast-fed infants during the first year of life is associated with greater bone mineral content and/or areal bone mineral density (aBMD) in later childhood. The design was a retrospective cohort study. One hundred and six healthy prepubertal Caucasian girls (median age, 8 yr; range, 7-9 yr) were classified as vitamin D supplemented or unsupplemented during the first year of life on the basis of a questionnaire sent to participating families and their pediatricians. Bone area (square centimeters) and bone mineral content (grams) were determined by dual energy x-ray absorptiometry at six skeletal sites. Vitamin D receptor (VDR) 39-gene polymorphisms (BsmI) were also determined. The supplemented (n 5 91) and unsupplemented (n 5 15) groups were similar in terms of season of birth, growth in the first year of

life, age, anthropometric parameters, and calcium intake at time of dual energy x-ray absorptiometry. The supplemented group had higher aBMD at the level of radial metaphysis (mean ± SEM, 0.301 ± 0.003 vs. 0.283 ± 0.008; P = 0.03), femoral neck (0.638 ± 0.007 vs. 0.584 ± 0.021; P = 0.01), and femoral trochanter (0.508 ± 0.006 vs. 0.474 ± 0.016; P = 0.04). At the lumbar spine level aBMD values were similar (0.626 ± 0.006 vs. 0.598 ±0.019; P =0.1). In a multiple regression model taking into account the effects of vitamin D supplementation, height, and VDR genotype on aBMD (dependent variable), femoral neck aBMD remained higher by 0.045 g/cm2 in the supplemented group (P = 0.02). They concluded that Vitamin D supplementation in infancy was found to be associated with increased aBMD at specific skeletal sites later in childhood in prepubertal Caucasian girls [85].

Ghada EK et al. studied the impact of vitamin D deficiency on skeletal health. One hundred seventy-nine girls, ages 10-17 yr, were randomly assigned to receive weekly oral vitamin D doses of 1,400 IU (equivalent to 200 IU/d) or 14,000 IU (equivalent to 2,000 IU/d) in a double-blind, placebo-controlled, 1-yr protocol. Areal bone mineral density (BMD) and bone mineral content (BMC) at the lumbar spine, hip, forearm, total body, and body composition were measured at baseline and 1 yr. Serum calcium, phosphorus, alkaline phosphatase, and vitamin D metabolites were measured during the study. In the overall group of girls, lean mass increased significantly in both treatment groups (P ? 0.05); bone area and total hip BMC increased in the high-dose group (P < 0.02). In premenarcheal girls, lean mass increased significantly in both treatment groups, and there were consistent trends for increments in BMD and/or BMC at several skeletal sites, reaching significance at lumbar spine BMD in the low-dose group and at the trochanter BMC in both treatment groups. There was no significant change in lean mass, BMD, or BMC in postmenarcheal girls. Vitamin D replacement had a positive impact on musculoskeletal parameters in girls, especially during the premenarcheal period [86].

Warren TK et al. investigated the acquisition of bone mass and height of Chinese children with an initial Ca intake of approximately 567 mg/d who were supplemented to about 800 mg/d. Eighty-four 7-year-old Hong Kong Chinese children underwent an 18-month randomized, double-blind, controlled Ca-supplementation trial. The children were randomized to receive either 300 mg elemental Ca or a placebo tablet daily. Bone mass of the distal one-third radius was measured by single-photon absorptiometry, lumbar spine and femoral neck were determined using dual-energy X-ray absorptiometry. Measurements were repeated 6-monthly. Baseline serum 25-hydroxycholecalciferol concentration and physical activity were also assessed. Baseline Ca intakes of the study group and controls were respectively 571 (SD 326) and 563 (SD 337) mg/d. There were no significant differences in baseline serum 25-hydroxycholecalciferol concentration (P = 0·71) and physical activity (P = 0·36) between the study and control groups. After 18 months the study group had significantly greater increases in lumbar-spinal bone mineral content (20·9 v. 16. 34%; P = 0·035), lumbar-spinal area (11·16 v. 8·71%; P = 0.049), and a moderately greater increment in areal bone mineral density of the radius (7·74 0·600%; P = 0.081) when compared with the controls. The results confirm a positive effect of Ca on bone mass of the spine and radius but no effects on femoral-neck and height increase. A longer trial is warranted to confirm a positive Ca effect during childhood that may modify future peak bone mass [87].

Kathryn A et al investigated the association of vitamin D status with morbidity in a prospective study of school-age children from Bogotá, Colombia. Plasma 25-hydroxyvitamin D (25(OH)D) concentrations in a random sample of 475 children (mean ± SD: 8.9 ± 1.6 years) and followed them for an academic year. Caregivers were asked to record daily information on the incidence of morbidity episodes using pictorial diaries. Baseline vitamin D status was classified

according to 25(OH)D concentrations as deficient (<50 nmol/L), insufficient (?50 and <75 nmol/L) or sufficient (?75 nmol/L). Poisson regression was used to estimate incidence rate ratios and 95% confidence intervals for days with diarrhoea, vomiting, diarrhoea with vomiting, cough with fever and earache or discharge with fever, comparing vitamin D-deficient with vitamin D-sufficient children. Estimates were adjusted for child's age, sex and household socioeconomic status. The prevalence of VDD was 10%; an additional 47% of children were vitamin D-insufficient. VDD was associated with increased rates of diarrhoea with vomiting (adjusted incidence rate ratio: 2.05; 95% confidence interval: 1.19, 3.53) and earache/discharge with fever (adjusted incidence rate ratio: 2.36; 95% confidence interval: 1.26, 4.44). VDD was not significantly related to cough with fever. These results suggest that VDD is related to increased incidence of gastrointestinal and ear infections in school-age children. The effect of correcting VDD on reducing risk of these infections needs to be tested in supplementation trials [88].

Naveen TA et al. conducted a cross sectional study aimed to study the association between vitamin D level and recurrent acute diarrhoea. The study was conducted on 80 simple randomly selected children, aged from 4 to 12 years from November 2013 to May 2014, sixty patients were suffering from recurrent acute diarrhoea and twenty were healthy, age and sex matched children taken as a control group. All children were subjected to complete history taking, clinical examination and Laboratory investigations in the form of hemoglobin level, stool analysis and estimation of the serum level of vitamin D by ELISA. There was highly significant decrease in vitamin D levels in patients group than control group. In patients with recurrent acute diarrhoea, vitamin D deficiency was found in 58%, insufficient in 20 % and sufficient in 22%. Vitamin D deficiency was associated with increased rate of diarrheal attacks, vomiting and abdominal pain. Hemoglobin level was decreased below normal in 26.7% of children with recurrent diarrhoea; most of them were vitamin D deficient children. Stool examination in children with recurrent diarrhoea detected Entameba histolytica in 8.3%, Giardia lamblia in 13%, Ascaris lumbricoides in 1.7% and Ancylostoma duodenal in 1.7%, all parasites were detected in vitamin D deficient children, except E. histolytica detected also in vitamin D sufficient child. They concluded that recurrent acute diarrhoea was associated with decreased serum level of vitamin D in preschool and school-age children. Vitamin D deficiency was associated with increased number of diarrheal attacks and Giardia lamblia parasitic infection [89].

Adam AR et al. investigated the effect of vitamin D3 supplementation on the incidence and risk for first and recurrent diarrheal illnesses among children in Kabul, Afghanistan. This double-blind placebo-controlled trial randomized 3046 high-risk 1- to 11-month-old infants to receive 6 quarterly doses of oral vitamin D3 (cholecalciferol 100?000 IU) or placebo in inner city Kabul. Data on diarrheal episodes (?3 loose/liquid stools in 24 hours) was gathered through active and passive surveillance over 18 months of follow-up. Time to first diarrheal illness was analyzed by using Kaplan-Meier plots. Incidence rates and hazard ratios (HRs) were calculated by using recurrent event Poisson regression models. No significant difference existed in survival time to first diarrheal illness (log rank P = .55). The incidences of diarrheal episodes were 3.43 (95% confidence interval [CI], 3.28-3.59) and 3.59 per child-year (95% CI, 3.44-3.76) in the placebo and intervention arms, respectively. Vitamin D3 supplementation was found to have no effect on the risk for recurrent diarrheal disease in either intention-to-treat (HR, 1.05; 95% CI, 0.98-1.17; P = .15) or per protocol (HR, 1.05; 95% CI, 0.98-1.12; P = .14) analyses. The lack of preventive benefit remained when the randomized population was stratified by age groups, nutritional status, and seasons. They concluded that quarterly supplementation with vitamin D3 conferred no reduction on time to first illness or on the risk for recurrent diarrheal disease

in this study [72].

Another small clinical trial assesses the effects of vitamin D supplementation on diarrheal illnesses. In that study children hospitalized with acute diarrhea in Dhaka, Bangladesh were randomized to daily supplementation with 1000 IU vitamin D (n = 27) or placebo (n = 15). Supplementation was not found to reduce stool weight or time to clinical resolution. Although a null study, the small sample size and short duration of follow-up (5 days) make it difficult to draw conclusions from this single work on the role of vitamin D supplementation [90].

Wayse V et al. conducted a hospital-based case-control study to determine whether subclinical vitamin D deficiency in Indian children under 5 y of age is a risk factor for severe acute lower respiratory infection (ALRI). A total of 150 children including 80 cases and 70 controls, aged 2-60 months, were enrolled. Case definition of severe ALRI as given by the World Health Organization was used for cases. Controls were healthy children attending outpatients' service for immunization. Association of serum 25-hydroxyvitamin D3 (25OHD3) with severe ALRI, controlling for demographic and other potential risk factors. Serum 25OHD3 increased with age. Factors significantly associated with decreased risk of severe ALRI in univariate analysis were: exclusive breastfeeding in the first 4 months (cases 35/78 (45%), controls 41/64 (64%); P=0.02); introduction of other dietary liquids than milk only after 6 months (cases 46/70 (66%), controls 31/66 (47%); P=0.03); use of liquid petroleum cooking fuel (cases 32/80 (40%), controls 40/70 (57%); P=0.04); infant not covered in swaddling clothes when exposed to sunlight before crawling (cases 11/52 (21%), controls 25/54 (46%); P=0.006); and serum 25OHD3>22.5 nmol/l (cases 16/80 (20%), controls 48/70 (69%); P<0.001). In multivariate analysis, factors associated with significantly lower odds ratio for having severe ALRI were: serum 25OHD3>22.5 nmol/l (OR: 0.09; 95% CI 0.03-0.24; P<0.001) and exclusive breastfeeding in the first 4 months of life (OR 0.42; 95% CI 0.18-0.99; P=0.046) with age and height/age as significant covariates. They concluded that Subclinical vitamin D deficiency and nonexclusive breastfeeding in the first 4 months of life were significant risk factors for severe ALRI in Indian children [91].

Dayre JM et al investigated a possible association between vitamin D deficiency and respiratory infection by comparing serum 25 hydroxyvitamin D [25(OH)D] levels in a group of young children with ALRI to an age-matched group without respiratory infection. Participants with a diagnosis of bronchiolitis or pneumonia (n?=?55 or 50, respectively), as well as control subjects without respiratory symptoms (n?=?92), were recruited at the Royal University Hospital, Saskatoon, Saskatchewan, Canada from November 2007 to May 2008. 25(OH)D levels were measured in patient serum using a competitive enzyme linked immunoassay. The mean vitamin D level for the entire ALRI group was not significantly different from the control group (81?±?40 vs. 83?±?30?nmol/L, respectively). The mean vitamin D level for the ALRI subjects admitted to the pediatric intensive care unit (49?±?24?nmol/L) was significantly lower than that observed for both control (83?±?30?nmol/L) and ALRI subjects admitted to the general pediatrics ward (87?±?39?nmol/L). Vitamin D deficiency remained statistically related to pediatric intensive care unit admission in the multivariate analysis. They concluded that No difference was observed in vitamin D levels between the entire ALRI group and control groups; however, significantly more children admitted to the pediatric intensive care unit with ALRI were vitamin D deficient. These findings suggest that the immunomodulatory properties of vitamin D might influence ALRI disease severity [92].

Karatekin G at el. conducted a study determine the association of serum 25-hydroxy vitamin D (25(OH)D) concentrations in newborns with acute lower respiratory infection (ALRI) and

without clinical signs of rickets, and their mothers. The design comprises a hospital-based case-control study. The study group consisted of 25 newborns with ALRI who were admitted to neonatal intensive care unit and their mothers. Controls were 15 healthy newborns of the same age as the study group and their mothers. A commercial radioimmunoassay was used to measure 25(OH)D concentrations in serum for assessing vitamin D status. The two groups were similar in gestational week, birth weight, birth height, head circumference, age and gender. The mean serum 25(OH)D concentrations in the study group newborns were lower than those of the control group (9.12±8.88ng/ml and 16.33±13.42?ng/ml, respectively) (P=0.011). Also, mean serum 25(OH)D concentrations in the mothers of the study group were lower than those in the mothers of the control group (13.38±16.81?ng/ml and 22.79±16.93?ng/ml respectively) (P=0.012). In 87.5% of all newborns and 67.5% of all mothers, serum 25(OH)D concentrations were lower than 20?ng/ml. The 25(OH)D concentrations of newborns were highly correlated with mothers' serum 25(OH)D concentrations. They concluded that newborns with subclinical vitamin D deficiency may have an increased risk of suffering from ALRI. The strong positive correlation between newborns' and mothers' 25(OH)D concentrations shows that adequate vitamin D supplementation of mothers should be emphasized during pregnancy especially in winter months[93].

Carlos A et al. conducted a randomised trial with hypothesis that hypothesized that vitamin D supplementation of children with vitamin D deficiency would lower the risk of ARIs. By using cluster randomization, classrooms of 744 Mongolian schoolchildren were randomly assigned to different treatments in winter (January-March). This analysis focused on a subset of 247 children who were assigned to daily ingestion of unfortified regular milk (control; n = 104) or milk fortified with 300 IU of vitamin D3 (n = 143). This comparison was double-blinded. The primary outcome was the number of parent-reported ARIs over the past 3 months. At baseline, the median serum 25(OH)D level was 7 ng/mL (interquartile range: 5-10 ng/mL). At the end of the trial, follow-up was 99% (n= 244), and the median 25(OH)D levels of children in the control versus vitamin D groups was significantly different (7 vs 19 ng/mL; P < .001). Compared with controls, children receiving vitamin D reported significantly fewer ARIs during the study period (mean: 0.80 vs 0.45; P = .047), with a rate ratio of 0.52 (95% confidence interval: 0.31-0.89). Adjusting for age, gender, and history of wheezing, vitamin D continued to halve the risk of ARI (rate ratio: 0.50 [95% confidence interval: 0.28-0.88]). Similar results were found among children either below or above the median 25(OH)D level at baseline (rate ratio: 0.41 vs 0.57; Pinteraction = .27). They concluded that Vitamin D supplementation significantly reduced the risk of ARIs in winter among Mongolian children with vitamin D deficiency[94].

Laaksi I et al. conducted a randomized, double-blinded trial among young Finnish men to assess the role of Vitamin D supplementation for the prevention of acute respiratory tract infection. Of a total of 400 men entering the unit, 164 (41%) volunteered to participate in the study and met the inclusion criteria. The subjects were randomly assigned to the intervention group, which received 400 IU (10 μg; n = 80) vitamin D3 (Minisun; Verman) daily, or the control group (n = 84), which received placebo (Pharmia; a capsule identical in size and form to the active preparation). The main outcome variable, which was the number of days absent from duty due to respiratory tract infection, did not differ between groups. Mean number of days absent (±SD) was 2.2 ± 3.2 days in the intervention group and 3.0 ± 4.0 days in the placebo group (P = .096). There was an effect during the first 6 weeks of the study, with a mean (±SD) of 0.7 ± 2.1 days of absence in the intervention group and 1.4 ± 2.6 days absent in the placebo group (P = .060). After the first 6 weeks, there tended to be no difference between groups (Table 2). Nevertheless, the proportion of men remaining healthy

throughout the 6-month study period was greater in the intervention group (41 [51.3%] of 80) than in the placebo group (30 [35.7%] of 80; P = .045). In a Cox regression analysis with adjustments for smoking and influenza vaccination, the adjusted hazard ratio (HR) for absence from duty due to respiratory tract infection was lower in the intervention group (HR, 0.71; 95% confidence interval [CI], 0.43-1.15). The number needed to treat, calculated from the proportion of men without any days absent from duty, was 6.4 (95% CI, 3-257). Self-reported cough (65% in the intervention group vs 57% in the placebo group; P = .30), runny nose (74% vs 75%; P = .86), sore throat (48% vs 45%; P = .77), fever (31% vs 38%; P = .36), and common cold symptoms (56% vs 52%; P = .40) did not differ between the groups. The mean number of hospital days (±SD) was 0.31 ± 1.21 per subject in the intervention group and 0.90 ± 2.22 in the placebo group (P = .06). Mean plasma PTH concentrations (±SD) did not significantly differ between the 58 individuals in the intervention group (4.3 ± 1.3 ng/L) and the 50 individuals in the placebo group (4.4 ± 1.4 ng/L) (P = .55) [95].

**Bibliography :**


1. Glisson, F. A treatment of the Rickets being a disease common to children.London 1-373(1668)
2. Steenbock H, Black A Fat-soluble vitamins. XVII. The induction of growth-promoting and calcifying properties in a ration by exposure to ultraviolet light. J BiolChem 1924; 61:405-422
3. "Adolf Windaus - Biography". Nobelprize.org. 2010-03-25. Retrieved 2010-03-25
4. McCollum EV, Simmonds N, Becker JE, Shipley PG An experimental demonstration of the existence of a vitamin which promotes calcium deposition. J BiolChem 1922; 53:293-298
5. Holick MF, Schnoes HK, Deluca HF, Suda T, Cousins RJ (1971). "Isolation and identification of 1,25-dihydroxycholecalciferol. A metabolite of vitamin D active in intestine".Biochemistry 10 (14): 2799-804.
6. Holick MF, Deluca HF, Avioli LV (1972). "Isolation and identification of 25-Hydroxyl cholecalciferol from human plasma". Archives of Internal Medicine 129 (1): 56-61.
7. .Holick MF. The vitamin D epidemic and its health consequences.J of Nutr.2005;135: 2739S-2748S.
8. 8.Gropper S, Smith J, Groff J. Advanced Nutrition and Human Metabolism. 4th ed.Belmont, C.A.: Wadesworth Publishing, 2004.
9. 9.Reese RW. Vitamin D and bone health. J of Lancaster General Hospital.2006; 1:78-87.
10. Arnold, Christine N., "Vitamin D Deficiency in the United States: How Common is it?" (2010). Undergraduate Honors Theses.Paper39.
11. Holick MF, Garabedian M. Vitamin D: photobiology, metabolism, mechanism of action, and clinical applications. Favus MJ, ed. Primer on the metabolic bone diseases and disorders of mineral metabolism. 6th ed. Washington, D. American Society for Bone and Mineral Research; 2006:129/37
12. Harkness LS, Cromer BA. Vitamin D deficiency in adolescent females.J Adolesc Health.2005; 37 (1):75
13. Holick MF. Vitamin D: importance in prevention of cancers, type 1 diabetes, heart disease, and osteoporosis. Am J of Clinical Nutrition. 2004; 79: 362-371.
14. Wang TJ, Pencina MJ, Booth SL, Jacques PF, Ingelsson E, Lanier K, Benjamin EJ, D'Agostino RB, Wolf M, Ramachandran SV. Vitamin D deficiency and risk of cardiovascular disease. 2008; 117: 503-511. M, Fernandez-Martin J, Diaz-Lopez J, Fernandez-Coto M, Cannata-Andia J. Vitamin D status and secondary hyperparathyroidism: the importance of 250hydroxyvitamin D cut-off levels. Kidney International. 2003; 63: S44-S48. .
15. Holick MF. Vitamin D deficiency.N Engl J Med.

2007;357(3): 266-281.

16. 16.Liu BA, Gordon M, Labranche JM, et al. Seasonal prevalence of vitamin D deficiency in institutionalized older adults. J Am Geriatr Soc. May 1997;45(5):598-603.

17. Koutkia P, Lu Z, Chen TC, Holick MF. Treatment of vitamin D deficiency due to Crohn's disease with tanning bed ultraviolet B radiation. Gastroenterology. Dec 2001; 121(6):1485-8.

18. 18.HolickMF.The vitamin D epidemic and its health consequences. JNutr. 2005 Nov; 135(11):2739S-48S.

19. Apperly FL. The relation of solar radiation to cancer mortality in North America.Cancer Res1941;1:191-195.

20. Grant WB. An estimate of premature cancer mortality in the U.S. due to inadequate doses of solarultravioletBradiation.Cancer2002;94:1867 -75.

21. Grant WG, Garland CF. The association of solar ultraviolet B (UVB) with reducing risk of cancer: multifactorial ecologic analysis of geographic variation in age-adjusted cancer mortality rates. Anticancer Res2006;26:2687-700.

22. Giovannucci E, Liu Y, Rimm EB, et al. Prospective study of predictors of vitamin D status and cancer incidence and mortality in men. J Natl Cancer Inst2006;98:451-9.

23. Garland CF, Garland FC, Gorham ED, et al. The role of vitamin D in cancer prevention.Am J Public Health2006;96:252-61.

24. Ahonen MH, Tenkanen L, Teppo L, Hakama M, Tuohimaa P. Prostate cancer risk and prediagnostic serum 25-hydroxyvitamin D levels (Finland). Cancer Causes Control2000;11:847-52.

25. Harinarayan CV, Gupta N, Kochupillai N. Vitamin D status in primary hyperparathyroidism in India. ClinEndocrinol (Oxf). 1995; 43: 351-8.

26. Gibson RS, Bindra GS, Nizan P, Draper HH. The vitamin D status of East Indian Punjabi immigrants to Canada. Br JrNutr 1987; 58 (1): 23-9.

27. Ahonen MH, Tenkanen L, Teppo L, Hakama M, Tuohimaa P. Prostate cancer risk and prediagnostic serum 25-hydroxyvitamin D levels (Finland). Cancer Causes Control2000;11:847-52.

28. Stene LC, Ulriksen J, Magnus P, Joner G. Use of cod liver oil during pregnancy associated with lower risk of type I diabetes on the offspring. Diabetologia2000;43:1093-8.

29. Ponsonby A-L, McMichael A, van der Mei I. Ultraviolet radiation and autoimmune disease: insights from epidemiological research. Toxicology2002;181-182:71-8.

30. Embry AF, Snowdon LR, Vieth R. Vitamin D and seasonal fluctuations of gadolinium-enhancing magnetic resonance imaging lesions in multiple sclerosis. Ann Neurol2000;48:271-2

31. Hypponen E, Laara E, Jarvelin M-R, Virtanen SM. Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. Lancet2001;358:1500-3.

32. Munger KL, Zhang SM, O'Reilly E, et al. Vitamin D intake and incidence of multiple sclerosis. Neurology2004;62:60-5.

33. Merlino LA, Curtis J, Mikuls TR, Cerhan JR, Criswell LA, Saag KG. Vitamin D intake is Inversely associated with rheumatoid arthritis.Arthritis Rheum2004;50:72-7.

34. Krause R, Buhring M, Hopfenmuller W, Holick MF, Sharma AM. Ultraviolet B and blood pressure.Lancet1998;352(9129):709-10.

35. McGrath J, Selten JP, Chant D. Long-term trends in sunshine duration and its association with schizophrenia birth rates and age at first registration-data from Australia and the Netherlands. Schizophr Res2002;54:199-212.

36. Gloth FM III, Alam W, Hollis B. Vitamin D vs. broad spectrum phototherapy in the treatment of

seasonal effective disorder. J Nutr Health Aging1999;3:5-7.

37. Bodnar LM, Catov JM, Simhan HN, Holick MF, Powers RW, Roberts JM. Maternal vitamin D deficiency increases the risk of preeclampsia. J ClinEndocrinolMetab2007;92:3517-22.

38. Chan TYK. Vitamin D deficiency and susceptibility to tuberculosis.Calcif Tissue Int 2000;66:476-8.

39. Wolpowitz, Deon, and Barbara A. Gilchrest. "The vitamin D questions: how much do you need and how should you get it?." Journal of the American Academy of Dermatology 54.2 (2006): 301-317.

40. Vitamin D Deficiency in Adults: When to Test and How to Treat. Mayo Clin Proc. 2010 August; 85(8): 752-758.

41. Khadilkar A, Das G, sayyed M, Sanwalka N, BhandariD,Khadilkar V, et al.Low calcium intake and hypovitaminosis D. Arch Dis Child 2007;92; 1045.

42. Awumey EM, Mitra DA, Hollis BW, Kumar R,Bell NH. Vitamin D metabolism is altered in Asian Indians in the southern United States: a clinicalresearch center study. J ClinEndocrinol Metab1998; 83: 169-173.

43. Fu L, Yun F, Oczak M, Wong BY, Vieth R, ColeDE. Common genetic variants of the vitamin Dbinding protein (DBP) predict differences in responseof serum 25-hydroxyvitaminD [25(OH)D]to vitamin D supplementation. ClinBiochem 2009;42: 1174-1177.

44. Marwaha R, Tandon N, Agarwal N, PuriS,Agarwal R, Singh S, et al. Impact of two regimens of vitamin D supplementation on calcium - vitamin D-PTH axis of schoolgirls of Delhi."Indian pediatrics 47.9 (2010): 761-769.

45. Khadilkar A, Mughal MZ, Hanumante N, SayyadM, Sanwalka N, Naik S, et al. Oral calcium supplementation reverses the biochemical patternof parathyroid hormone resistance in underprivilegedIndian toddlers. Arch Dis Child 2009;94: 932-937.

46. Hollick MF. Vitamin D deficiency.N Engl J Med 2007;357:266-281.

47. Harinarayan CV, Joshi SR. Vitamin D status in India-Its implications and Remedial Measures. J Assoc Physicians India 2009;57:40-48.

48. Khadilkar AV. Vitamin D deficiency in Indian Adolescents. IndianPaediatr2010;47:756-757.

49. Awumey EM, Mitra DA, Hollis BW, et al. Vitamin D metabolismis altered in Asian Indians in the southern United states: a clinical research center study. J ClinEndocrinolMetab1998;83:169-173.

50. Fu L,Yun F, Oczak M, et al. Common genetic variants of the vitaminD binding protein (DBP) predict differences in response of serum 25-hydroxyvitamin D[ 25(OH)] to vitamin D supplementation. CliBiochem2009;42:1174-1177.

51. Babu US, Calvo MS. Modern India and the vitamin D dilemma:evidence for the need of a national food fortification program. MolNutr Food Res 2010;54:1134-47.

52. Heaney RP. Vitamin D depletion and effective calcium absorption. J Bone Min Res 2003;18:1342 .

53. Marwaha RK, Tandon N, Garg MK, et al. Vitamin D status inhealthy Indians aged 50 years and above. J Assoc Physicians India2011;59:703-707.

54. Goswami, Ravinder, et al. "Pattern of 25-hydroxy vitamin D response at short (2 month) and long (1 year) interval after 8 weeks of oral supplementation with cholecalciferol in Asian Indians with chronic hypovitaminosis D." British journal of nutrition 100 (2008): 526-529.

55. Harinarayan et al.Prevalence of VDD in children. IJMR; 2008.

56. S. Puri et al.Vitamin D status of schoolgirls British Journal of Nutrition (2008); 99: 876-

882.

57. High prevalence of low dietary calcium and low vitamin D status in healthy south Indians. Asia Pac J ClinNutr 2004;13 (4):359-365

58. Ross AC, Taylor CL, Yaktine AL Del Valle HB (2011).Dietary Reference Intakes for Calcium and Vitamin D. Washington, D.C: National Academies Press. ISBN 0-309-16394-3.

59. Nutrient requirements and recommended dietary allowances for indiansnational institute of nutrition Indian Council of Medical Research Jamai-Osmania PO, Hyderabad - 500 604. P.303-304

60. Lee, John H., et al. "Vitamin D deficiency: an important, common, and easily treatable cardiovascular risk factor?." Journal of the American College of Cardiology. 2008;52(24):1949-1956.

61. Wortsman J, Matsuoka LY, Chen TC, Lu Z and Holick MF: Decreased bioavailability of vitamin D in obesity. Am J ClinNutr72: 690-693, 2000

62. Compston JE, Vedi S, Ledger JE, Webb A, Gazet JC, Pilkington TRE. Vitamin D status and bonehistomorphometry in gross obesity.Am J ClinNutr1981;34:2359-63.

63. Bell NH, Epstein S, Greene A, Shary J, Oexmann MJ, Shaw S. Evidence for alteration of the vitamin D-endocrine system in obese subjects. J Clin Invest1985;76:370-3.

64. Liel Y, Ulmer E, Shary J, Hollis BW, Bell NH. Low circulating vitamin D in obesity.Calcif Tissue Int1988;43:199-201.

65. Wortsman J, Matsuoka LY, Chen TC, Lu Z and Holick MF: Decreased bioavailability of vitamin D in obesity. Am J ClinNutr72: 690-693, 2000.

66. Abbasi AA, Amin M, Smiertka JK, Grunberger G, MacPherson B, Hares M, Lutrzykowski M and Najar A: Abnormalities of vitamin D and calcium metabolism after surgical treatment of morbid obesity: a study of 136 patients. EndocrPract13: 131-136, 2007.

67. Adiposity in relation to vitamin D status and parathyroid hormone levels: a population based study in older men and women. J ClinEndocrinolMetab90: 4119-4123, 2005.

68. Clements, M. R., L. Johnson, and D. R. Fraser. "A new mechanism for induced vitamin D deficiency in calcium deprivation." (1987): 62-65.

69. Vandana Jain, Nandita Gupta, Mani Kalaivani, Anurag Jain, Aditi Sinha & Ramesh Agarwal Vitamin D deficiency in healthy breastfed term infants at 3 months & their mothers in India: Seasonal variation & determinants Indian J Med Res 133, March 2011, pp 267-273

70. Thacher TD, Fischer PR, Isichei CO, Pettifor JM. Early response to vitamin D(2) in children with calcium deficiency rickets. J Pediatr 2006; 149: 840-844.

71. Reese RW. Vitamin D and bone health. J of Lancaster General Hospital. 2006; 1:78-87

72. Aluisio, Adam R., et al. "Vitamin D3 Supplementation and Childhood Diarrhea: A Randomized Controlled Trial." Pediatrics 132.4 (2013): e832-e840.

73. Pfeffer PE, Hawrylowicz CM (2012) Vitamin D and lung disease. Thorax 67: 1018-1020.

74. Barlow PG, Svoboda P, Mackellar A, Nash AA, York IA, et al. (2011) Antiviral activity and increased host defense against influenza infection elicited by the human cathelicidin LL-37. PLoS One 6: e25333.

75. Rivas-Santiago B, Rivas Santiago CE, Castaneda-Delgado JE, Leon-Contreras JC, Hancock RE, et al. (2012) Activity of LL-37, CRAMP and antimicrobial peptide-derived compounds E2, E6 and CP26 against Mycobacterium tuberculosis. Int J Antimicrob Agents.

76. Liu PT, Stenger S, Li H, Wenzel L, Tan BH, et al. (2006) Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. Science 311: 1770-1773.

77. Liu PT, Stenger S, Tang DH, Modlin RL (2007) Cutting edge: vitamin Dmediated human antimicrobial activity against Mycobacterium tuberculosis is dependent on the induction of cathelicidin. J Immunol 179: 2060-2063.

78. Hewison M (2011) Antibacterial effects of vitamin D. Nat Rev Endocrinol 7: 337-345.

79. Hansdottir S, Monick MM, Hinde SL, Lovan N, Look DC, et al. (2008) Respiratory epithelial cells convert inactive vitamin D to its active form: potential effects on host defense. J Immunol 181: 7090-7099.

80. Ginde AA, Mansbach JM, Camargo CA Jr (2009) Association between serum 25-hydroxyvitamin D level and upper respiratory tract infection in the Third National Health and Nutrition Examination Survey. Arch Intern Med 169: 384-390.

81. Jolliffe DA, Griffiths CJ, Martineau AR (2012) Vitamin D in the prevention of acute respiratory infection: Systematic review of clinical studies. J Steroid Biochem Mol Biol. 136 (2013): 321-329.

82. Charan J, Goyal JP, Saxena D, Yadav P (2012) Vitamin D for prevention of respiratory tract infections: A systematic review and meta-analysis. J Pharmacol Pharmacother 3: 300-303.

83. Brooke OG, Butters F, Wood C. Intrauterine vitamin D nutrition and postnatal growth in Asian infants. Br Med J (Clin Res Ed) 1981;283:1024.

84. Geeta TK et al. Effect of weekly vitamin D supplements on mortality, morbidity, and growth of low birthweight term infants in India up to age 6 months: randomised controlled trial. Br Med J 2011;342:2975.

85. Samual A Zamora. Vitamin D Supplementation during Infancy Is Associated with Higher Bone Mineral Mass in Prepubertal Girls. The Journal of Clinical Endocrinology & Metabolism 84.12 (1999): 4541-4544.

86. Ghada El. Effect of Vitamin D Replacement on Musculoskeletal Parameters in School Children: A Randomized Controlled Trial. The Journal of Clinical Endocrinology & Metabolism 91.2 (2006): 405-412.

87. Lee, Warren TK, et al. "A randomized double-blind controlled calcium supplementation trial, and bone height acquisition in children." British Journal of Nutrition 74.01 (1995): 125-139.

88. Thornton, Kathryn A., et al. "Vitamin D deficiency associated with increased incidence of gastrointestinal and ear infections in school-age children." The Pediatric infectious disease journal 32.6 (2013): 585-593.

89. Abed, Neveen Tawfik, et al. "Vitamin D status in children with recurrent acute diarrhea." Int. J. Curr. Microbiol. App. Sci 3.11 (2014): 858-868.

90. Alam NH, Ashraf H, Gyr NE, Meier RF. Efficacy of L-isoleucine supplemented food and vitamin D in the treatment of acute diarrhea in children. Gastroenterology. 2011;140(5 suppl 1):S571.

91. Wayse, V., et al. "Association of subclinical vitamin D deficiency with severe acute lower respiratory infection in Indian children under 5 y." European Journal of Clinical Nutrition 58.4 (2004): 563-567.

92. McNally, J., et al. "Vitamin D deficiency in young children with severe acute lower respiratory infection." Pediatric pulmonology 44.10 (2009): 981-988.

93. Karatekin G, Kaya A, Salihoglu O, Balci H, Nuhoglu A. Association of subclinical vitamin D deficiency in newborns with acute lower respiratory infection and their mothers. Eur J Clin Nutr. 2007 (in press)

94. Camargo, Carlos A., et al. "Randomized trial of vitamin D supplementation and risk of acute respiratory infection in Mongolia." Pediatrics 130.3 (2012): e561-e567.

95. Laaksi I, Ruohola JP, Tuohimaa P, et al. An association of serum vitamin D concentrations < 40 nmol/L with acute respiratory tract infection in young Finnish men. Am J Clin Nutr.2007;86(3):714-717.