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Vitamin D Deficiency in Childhood: A Review

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***Abstract*— Vitamin D is a type of molecule that can be dissolved in fats. It acts like a steroid hormone. There are two precursors of vitamin D, and both of them contain the steroid structure. One of them, 7-dehydrocholesterol, is in the lipids of animals , and the second one, ergosterol, is in plants Vitamin D is essential for the health of young children and their growth: it is responsible for calcium absorption and ensures bone and tooth strength. In addition, it plays a significant role in the functioning of the immune system and improves mental health and nervous development. Direct sunlight contains UVB rays needed for the skin to produce vitamin D. Children's skin produces it quickly, but the body also uses its level quickly. Depending on the latitude, season, availability of clothes, and cream, which protects the skin from the sun, a person produces vitamin D in10 to 15 minutes to an hour. Areas that have limited sunlight or have children with darker skin or a medical condition may need more. The daily intake in a day may range from 400 to 1000 IU depending on the age and income level. However, Monitoring vitamin D status through blood tests and adjusting supplementation is essential to ensure adequate intake.**

Keywords— Vitamin D deficiency, Childhood, Screening, Bone health, Supplements of vitamin D.

I. INTRODUCTION

Vitamin D, a fat-soluble vitamin, is crucial for bone health, growth, differentiation, and immune regulation. It is sourced from both endogenous sources like sun exposure and exogenous sources like vitamin D preparations and dietary supplements [1]. Vitamin D is crucial for children's growth and development, but people lack awareness and can't provide adequate dietary nutrition. Increased homework and reduced outdoor activities lead to insufficient vitamin D levels in children, increasing the risk of disease due to insufficient sunlight exposure [2].

The following are the reasons why vitamin D (VD) research has become more and more important: The study focuses on three main areas: 1) the characterization of VD receptors, both nuclear and cytosolic; 2) the role of the enzymatic machinery involved in the metabolism of VD in various tissues, such as muscle, pancreas, and adipose tissue; 3) the potential risks associated with the presence of multiple diseases and the suboptimal range of 25(OH)D (3)Because of this, it is crucial to talk about the functions of vitamin D in the bones and to think about the steps that should be taken to prevent vitamin D deficiency (VDD) in the pediatric population [3, 4]. This article reviews the relationship between vitamin D deficiency and the growth of children and its treatment and prevention, aiming to increase public and medical awareness of vitamin D and promote healthy child growth.

II. VITAMIN D SOURCES

A. Sunlight

Vitamin D synthesis in the skin depends on various factors such as season, latitude, weather, air pollution, time spent outside, time of day, skin color, lifestyle, and sunscreen use. The UK's critical wavelength of sunlight reaches between April and September, and less is synthesized on cloudy days. Air pollution reduces the necessary UV light waves available for skin synthesis. For children to synthesize vitamin D through the skin, they need to go outdoors. Toddlers of African, African-Caribbean, and South Asian descent are likelier to have lower amounts of vitamin D, and darker skin types need longer time in the sun to manufacture the nutrient. Lifestyle, such as clothing or religious and cultural traditions, also affects vitamin D synthesis. Excessive sunshine exposure does not result in vitamin D excess [5].

B. Food

Meat and eggs are the next best sources of vitamin D, which varies according to the mother's vitamin D status. Oily fish is the rarest food source of vitamin D. Margarine, formula milk evaporated milk, some morning cereals, and several yogurt brands are among the foods fortified with vitamin D. Since the Second World War, fortification of baby, follow-on, and growing-up milk has been permitted [6].

C. Breast Milk

Vitamin D in breast milk is very low, with an average of 22 units/L and a range of 15 to 50 units/L concentrations

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depending on the volume of the mother's vitamin D status. Recent reports suggest that supplementing the mother with amounts exceeding the upper limits of the recommended daily intake of vitamin D may give enough of the vitamin to the infant from breast milk. However, this isn't encouraged. Given the low concentrations of vitamin D ingested in breast milk, the most recent suggestion for infants who are only breastfed is to be given a supplement of 400 units per day rather than 200 units per day [7-11].

D. Supplements of Vitamin D

Because it's hard to obtain enough vitamin D from a diet taking a supplement is usually the best way to get enough for most people. Vitamin D3 (also called cholecalciferol) and vitamin D2 (sometimes called ergocalciferol or pre-vitamin D) are the two forms of vitamin D supplements. Although D2 is produced in fungi and plants and D3 in mammals, including humans, both forms of vitamin D are naturally occurring substances that are synthesized in the presence of ultraviolet-B (UVB) rays from the sun. This is why vitamin D is known as "the sunshine vitamin." The skin produces vitamin D naturally, but many people don't get enough of it because they live in places with limited winter sunshine or because they spend much time inside because it's hard to obtain enough vitamin D from a diets taking a supplement is usually the best way to get enough for most people. Vitamin D3 (also called cholecalciferol) and vitamin D2 are the two forms of vitamin D supplements that are often used [12, 13]. The Institute of Medicine (IOM) advises persons between the ages of 19 and 70 should take a daily supplement containing 400 IU or more of vitamin D, with a recommended dietary requirement of 600 IU or more, as shown in **Table (1)** to address and prevent vitamin D deficiency, obese persons may need two to three times the amount of vitamin D deficiency [14].

Table (1): Daily intake of vitamin D according to IOM

Age groups	IOM recommendations		Recommendations from the committee for patients who may be at risk of vitamin D deficiency (IU)
	EAR (IU)	RDA (IU)	
Infants (0-12 M)	400	600	400-1000
Children (1-8 yr)	400	600	600-1000
Adolescents (9-18 yr)	400	600	600-1000
Adults (19-70 yr)	400	600	1500-2000
Elderly (>70 yr)	400	600	1500-2000
Pregnancy and lactation	400	600	1500-2000

** EAR: Estimated Average Requirement; RDA: Recommended Dietary Allowance; IOM: Institute of Medicine

III. Metabolism of Vitamin D

A class of fat-soluble secosteroids known as Calciferols popularly sounds like "D vitamins". For practical use, two forms are important: plant-derived – vitamin D2 or ergocalciferol, and animal-derived cholecalciferol. Thus, vitamin D2 and cholecalciferol or vitamin D3 can be ingested from various foods; the second compound is also synthesized in the skin when exposed to ultraviolet-B rays **(Figure 1)**. Because ergocalciferol and cholecalciferol are physiologically inert, they must first undergo a sequence of hydroxylation processes in the liver before they can be used by kidneys to 'convert' into active forms. Thus, 25-hydroxyvitamin D2 and 25-hydroxyvitamin D3, respectively, are produced first. For vitamin D to be biologically active, it acquires an additional hydroxyl group via the enzyme 1-alpha hydroxylase, thus 1,25(OH)2D, an alteration regulated by the parathyroid glands [15, 16]. In the cells mentioned above the active vitamin D isoform is also produced. The active vitamin D type circulates in the bloodstream and is mainly attached to vitamin D-binding protein (VDBP), a circulating albumin superfamily protein. [17, 18]. When it gets to its target organs, it behaves as a hormone It connects cytosolic vitamin D receptors that occurs almost universally and may explain the wide variety of mechanisms regulated by vitamin D. The active metabolite of vitamin D binds VDR, goes into the cell nucleus thereby activating gene expression [19-21] . It has been calculated that 1,25(OH)2D directly or indirectly regulates at least 1,250 genes. The body uses 1,25(OH)2D for a variety of purposes. For example, it increases the intestinal absorption of calcium and phosphorus, encourages bone resorption, and lowers the amount of calcium and phosphorus excreted by the kidneys to preserve bone health. In concert with calcitonin and parathyroid hormone (PTH), 1,25(OH)2D preserves normal plasma calcium levels. Additionally, it affects the host's immune system by controlling the inflammatory cascade and innate and adaptive immunity [22-25].

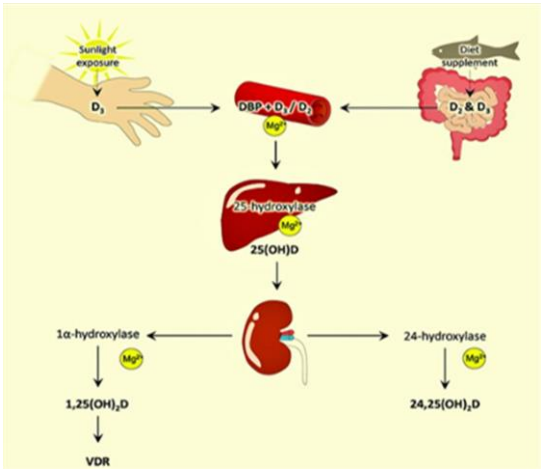

Figure (1): A diagram that shows the various stages of vitamin D metabolism in a simplified manner.

IV. Vitamin D Deficiency

While the body can produce vitamin D3, several obstacles might prevent this from happening. Too little sunshine on the skin prevents adequate skin synthesis, which is the main cause of vitamin D insufficiency. Season and high latitude are two possible causes of this restricted

exposure to sunlight. The months of October through March in the northern hemisphere at latitudes higher than 40° north and April through September in the southern hemisphere above latitude 40° south have low sunshine intensity insufficient for sufficient vitamin D production; (ii) increased amount of skin pigment melanin [26-28]; (iii) whole-body attire influenced by a culture's customs or environment; and (iv) limited mobility. Sunscreen with as little as a 15-sun protection factor inhibits the skin's capacity to produce vitamin D by 98%. Since vitamin D is taken orally and absorbed from the stomach, GI problems may cause malabsorption of vitamin D and deficiency after that the liver is important for vitamin D metabolism because bile acid production required for its absorption has to take place in the liver, and then 25-hydroxylation follows [29-32] Obstructive liver disease, food allergies, celiac sprue, cholestasis, biliary obstructions, inflammatory bowel disease, and cystic fibrosis are a few examples of these gastrointestinal disorders. Patients may also experience a vitamin D deficiency following a gastrectomy due to the loss of acidity and dysfunction of the proximal portion of the small intestine [32]. Moreover, since the kidneys are the primary site of vitamin D activation because of CYP27B1 loss and decrease of this enzyme by hyperphosphatemia, there is a low rate of activation of vitamin D in chronic renal disorders. Patients with Nephrotic Syndrome may experience Hypovitaminosis D as a result of elimination in the urine of 25(OH)D connected with vDBP. A severe deficiency at present can be arbitrarily considered as defined when 25(OH)-D levels are <12.5nmol/l (5ng/ml). In one study, rickets was found among 86% of children with levels below 20 nmol/L (8 ng/mL), while 94% of hypocalcemia children had levels of <20 nmol/L (8 ng/ mL), vitamin D status showed in **Table 2** [33-35].

Table (2): Vitamin D Status according to 25(OH)-D Levels [36]

Vitamin D status	25(OH)-D Level, nmol/L (ng/mL)
Severe deficiency	≤ 12.5 (5)
Deficiency	≤ 37.5 (15)
Insufficiency	37.5–50.0 (15–20)
Sufficiency	50–250 (20–100)
Excess	> 250 (100)
Intoxication	> 375 (150)

V. Vitamin D Is Essential for Preserving Good Health

For human health to be maintained, vitamin D is essential. It is in charge of controlling the body's levels of calcium phosphate, which is necessary for immunological, neurological, musculoskeletal, and cardiovascular processes. Decreased blood calcium levels have been associated with low vitamin D levels, which raises the risk of osteoporosis and rickets. The advantages of vitamin D in strengthening the immune system, avoiding pregnancy-related diseases , including pre-eclampsia, and lowering the risk of complications from acute respiratory infections have been the subject of several research. [37-40]. Vitamin D also acts as a hormone that helps regulate the immune system and protects against upper respiratory tract infections [41-43].
The benefits of taking Vitamin D supplements include the ability to postpone the onset of age-related illnesses. As per the Unified Parkinson's Disease Rating Scale (UPDRS), a lack of Vitamin D can worsen the severity and progression of Parkinson’s Disease, increasing the risk of falls. Researchers have been studying the link between Vitamin D and cancer for many years and have found a negative correlation between the incidence of two forms of cancer and vitamin D levels. Additionally, Na et al. emphasized the significance of vitamin D for the microbiota and immune system, indicating that it may be able to prevent colorectal cancer [44-46].

A. Vitamin D and Its Effects on Bone Health

Several proteins that are reliant on vitamin D regulate the absorption of calcium into the stomach, which is essential for the best possible formation of bone mineral matrix. When blood levels of 25-hydroxyvitamin D reach 32 ng/ml, calcium absorption is at its peak. Research by Boonen and colleagues found that hip fracture risk decreased by approximately 18% after taking supplements of vitamin D. In a nationwide health survey, there was a high association between 25-hydroxyvitamin D levels and bone mineral density (BMD). They increase the concentration of 25-hydroxyvitamin D from 20 to 90 nmol/L produced in a 0.06 g/cm2 increase in BMD [47, 48].
In a study in New Zealand, adults ages 50 to 84 saw a 0.5% increase in BMD of the femoral neck after 2 years of monthly vitamin D supplementation. It was recommended by Alison et al. to combine vitamin D and calcium supplements to reduce non-vertebral fractures by 14% and any type of fracture by 5%. Vitamin D supplementation is effective in improving bone health and preventing diseases like rickets and osteoporosis. Under a vitamin D supplementation program, the prevalence of rickets in children under three years old in Turkey dropped from 6% to 0.1% [49-51]. Recent research has investigated the correlation between low levels of 25-hydroxyvitamin D and the quality of bones, occurrences of fractures, and changes in body measurements in children who are in good health [52].

B. The Role of Vitamin D in Women's Health and Pregnancy

Vitamin D plays a crucial role in the development of babies before they are born. When pregnant women lack enough vitamin D, it can cause problems for their child's health, like asthma and cognitive issues. Pregnant women with a vitamin D deficiency are also more likely to experience complications such as pre-eclampsia, early delivery, and gestational diabetes. To assess a pregnant woman's vitamin D status, doctors measure her levels of a protein called vitamin D binding protein (VDBP) [52, 53].
A preliminary Infertile group exhibited lower amounts of VDBP and lower levels of free and accessible vitamin D

than fertile groups, according to 2017 research. According to research by Badr et al., VDBP levels were low in all infertile patients, with VDBP being a contributing factor to endometriosis (35, 54). Women who have infertility frequently battle diseases including endometriosis and polycystic ovarian syndrome (PCOS) [54, 55] [56]. In 2020, a more recent study found that women who had spontaneous miscarriages had lower levels of VDBP expression in their placentas. Moreover, infants and newborns born to mothers with low maternal VDBP levels in the final trimester of pregnancy had an increased risk of developing type 1 diabetes mellitus. Research shows a potential link between vitamin D and fertility in both men and women. Studies have found that low levels of testosterone are associated with low levels of vitamin D, but . Still, there is not enough evidence to conclusively show that vitamin D supplements can increase testosterone levels. Akhavizadegan and colleagues discovered that men with Sperm counts were considerably lower in those with vitamin D levels < 20 ng/mL [57]. A tertiary care center's investigation discovered a significant link. (r = 0.94) between vitamin D levels and follicular fluid levels, which can impact the success of in vitro fertilization. Pilz and his team demonstrated that vitamin D supplementation can lead to increased birth rates [58-63].

C. The Role of Vitamin D in Reducing the Risk of Respiratory Infections and COVID-19

Recent research has focused on the relationship between systemic infection and vitamin D deficiency. Studies have shown that vitamin D plays a crucial is crucial in enhancing innate immunity by producing peptides that help fight against viruses. According to a meta-analysis done in 2019, those with low vitamin D levels were 64% more likely to have pneumonia. Sustaining sufficient amounts of vitamin D has the potential to enhance both innate and acquired immunity. The frequency of COVID-19 cases per million people and vitamin D levels were shown to be significantly correlated in research by Lips et al. The number of COVID-19 fatalities per million people and vitamin D levels, however, did not show any discernible relationship. Remarkably, in contrast to control groups, COVID-19 patients did not see a decline in their clinical status [64-67].

D. Vitamin D and its effects on heart health

A recent study conducted in northern India found that a large percentage of adults with high blood pressure also had low levels of vitamin D. This deficiency in vitamin D may be linked to an increased risk of heart disease. An imbalance in blood vessel dilatation and constriction, which is impacted by hereditary and epigenetic factors, results in hypertension or high blood pressure. These epigenetic processes may be disturbed by vitamin D deprivation, which would especially impact the renin-angiotensin-aldosterone pathway [67, 68]. While there is a shortage of worldwide research assessing the prevalence of cardiovascular problems in patients with vitamin D deficiency, multiple regional studies have been conducted to evaluate this occurrence [68, 69]. In one such study, which included 100 patients with chronic stable angina and 100 matched controls, it was shown that 75 angina patients (75%) had a significantly higher frequency of vitamin D insufficiency than 10 (10%) in the control group [70]. According to Framingham's research, individuals with heart failure and low 25(OH)D levels had a 60% increased risk of passing away [65].

E. The Relationship between Vitamin D and Autoimmune Diseases

Vitamin D is essential for boosting the immune system and fighting off diseases. It helps produce mportant neurotransmitters and neurotrophins like dopamine and acetylcholine. The vitamin receptor (VDR) Performs a critical role in the growth of macrophages and the synthesis of interleukin-1 (IL-1), which is involved in both innate and adaptive immunity. Numerous studies have demonstrated that autoimmune illnesses can result from a lack of vitamin D; yet, supplementation has been reported to raise the number of T-regulatory cells in MS patients [71-73].
Women who took more than 4000 IU of vitamin D had a decreased chance of getting multiple sclerosis, according to two studies.. Rheumatoid Arthritis (RA) is a condition where the immune system attacks the joints, leading to joint damage and disability. Interestingly, there is a connection between RA activity and levels of vitamin D in the blood. Vitamin D also helps regulate blood sugar levels in patients with type 1 diabetes [74].

F. The Relationship between Vitamin D and Cancer

Studies have shown that vitamin D plays a crucial role in preventing and fighting cancer. A lack of vitamin D has been strongly linked to a higher risk of developing cancer, particularly colorectal, prostate, and breast cancer. 1,25-hydroxyvitamin D has been found to have properties that can help slow the growth of cancer cells in the breast. Vitamin D also works to inhibit the prostaglandin pathway and repairs damaged DNA. It also regulates certain proteins to prevent cell death and help with cell differentiation. Research has also suggested a potential link between cancer rates and exposure to sunlight, further highlighting the importance of vitamin D in cancer prevention [74].
In their study, Lin and colleagues found that calcium and vitamin D supplementation reduced the risk of breast cancer in premenopausal women [73]. Additionally, they found that low blood 25 (OH)D levels and vitamin D deficiency were present in 63% of patients with advanced or metastatic colorectal cancer [74, 75]. Increasing blood 25(OH)D levels by 8 ng/mL reduced overall and disease-specific death rates, according to research by Na et al. [46]. A correlation between a reduced incidence of stomach cancer and increased vitamin D consumption was found in a case-control study conducted in Vietnam. All these results point to the possible benefits of vitamin D supplementation [75].
According to a meta-analysis of databases, those with high blood levels of 25(OH)D had a 37% reduced risk of ovarian

cancer compared to those with low levels. This conclusion was drawn from 15 observational studies. Nevertheless, the overall vitamin D consumption had a feeble negative correlation, while case-control studies revealed a more pronounced negative correlation. The study indicates that measuring serum 25(OH)D levels could be a more accurate way to predict the outcome of ovarian cancer. [76]. Glioblastoma, the predominant form of brain cancer originating in the brain, can be effectively treated with small molecule analogues of Vitamin D. These analogues can impede the cell cycle, trigger programmed cell death, and hinder the migration of cancer cells [76, 77]. A study discovered that Vitamin D and calcipotriol can hinder osteosarcoma growth by altering the functioning of NMD and SNAI2-mediated EMT genes. This alteration impacts various outcomes, such as fibrosis and delayed cell migration. This research has the potential to be implemented in human patients, as well as potentially having wider applications for the aging population [78, 79]. Glioblastoma, the most common primary brain cancer, can be treated with small molecule analogues of Vitamin D, which inhibit the cell cycle, induce programmed cell death, and inhibit migration [80, 81].

G. Vitamin D and Its Effects on Dental Health

According to research, dental cavities are caused by bacteria in dental plaque that produce acidic secretions leading to the breakdown of teeth. Early childhood tooth decay has been related to vitamin D insufficiency throughout pregnancy and infancy. Dental caries and vitamin D insufficiency are related, according to a 2013 systematic review and meta-analysis [82-84]. The research discovered that vitamin D supplementation led to a 47% reduction in the incidence of cavities after analyzing 24 studies with 2827 children. Nevertheless, there were differences in the outcomes from trial to trial and some evidence of bias, which resulted in a conclusion that was not very clear. However, the difference in trial outcomes decreased when high-quality research was only examined, indicating that vitamin D is extremely beneficial in reducing caries. Additionally, the projected reduction in caries increased from 47% to 54% as a result of the rigorous study [85]. Having enough Vitamin D in the body may help prevent cavities by supporting tooth development and molar-incisor mineralization [86]. The correlation between vitamin D insufficiency and dental caries in youngsters indicates that insufficient vitamin D levels can result in tooth issues. Ensuring optimal vitamin D levels throughout a child's development prevents both permanent and primary tooth decay [87].

H. Vitamin D has various other impacts on the body

Studies have shown that vitamin D deficiency can impact more than just bone health; it can affect various tissues like the brain, skin, gastrointestinal tract, prostate, papilla, colon, kidneys, and immune cells. Additionally, vitamin D deficiency has been linked to conditions such as multiple sclerosis, rheumatoid arthritis, osteoarthritis, type 1 diabetes, hypertension, and cardiovascular disorders [88-94].

VI. TREATMENT AND PREVENTION OF VITAMIN D INSUFFICIENCY

Pregnant and breastfeeding women often engage in fewer outdoor activities, do not spend enough time in the sun, and experience significant fluctuations in hormone levels and metabolism. This makes them more susceptible to vitamin D deficiency, which can have a direct impact on the health of both the fetus and newborn. Research on vitamin D recommendations in China and other countries has indicated this issue [95]. All recommendations for vitamin D suggest pregnant and nursing women should take supplements to maintain proper levels of 25-(OH)D3. In 2018, the Italian consensus advised all pregnant and breastfeeding women to take 600 IU/d of vitamin D at the start of pregnancy. China recommends pregnant women take 800 IU/d of vitamin D supplements daily during the perinatal period for –themselves and their babies. Ensuring children have enough vitamin D is important for their health [96]. This can be achieved through sunlight, a balanced diet, and vitamin D supplements. However, too much sun exposure can harm children's health. Research indicates that the earlier children are exposed to sunlight, the higher their risk of developing skin cancer. To protect babies under 6 months, it is advised to avoid direct UV rays. Children should also use sunscreen and wear protective clothing when outdoors. If children cannot get enough vitamin D from sunlight and food, they may need vitamin D supplements. After three months of consistent vitamin D supplementation, the guidelines were updated to recommend a daily intake of 400 to 800 IU. The Global Consensus Recommendation for Nutritional Rickets Control (2016) suggested giving infants at least 400 IU of vitamin D daily, and children over 12 months old at least 600 IU daily. A small daily dose of vitamin D (400 IU for infants aged 0 to 1 year, and 600 IU for those older than 1 year). They also advised high-dose supplementation three times a year (1000 IU daily for 0-6 months, 1500 IU daily for 6 months to 1 year, 2500 IU daily for 1-3 years, 3000 IU daily for 4-8 years, Despite differences in vitamin D supplementing methods between China and other countries, it is feasible to keep the 25-(OH)D3 blood levels within the normal range for children aged 0 to 12 by taking 400 IU/d of vitamin D (and 4000 IU daily for those aged 8 and over)[97, 98, 99, 100].

VII. CONCLUSIONS

Vitamin D is important for building strong bones and supporting the immune and cardiovascular systems. It may also help protect against diseases like cancer and degenerative conditions. Vitamin D deficiency is common worldwide, especially in the Mediterranean region. During children's development, it is crucial to focus on providing adequate vitamin D supplementation and regularly monitoring their 25-(OH)D3 levels to prevent vitamin D

insufficiency or deficiency. Future studies should prioritize creating personalized vitamin D supplementation plans for children and exploring the relationship between growth and development indicators monitoring. This will ensure that children receive optimal health services and promote healthy growth.

CONFLICT OF INTEREST

Authors declare that they have no conflict of interest.

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