Vitamin D Deficiency: Concept, Physiologic Effects and Etiologic Factors

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ABSTRACT
The Objectives of this study are: to determine the etiologic and physiologic factors concerning vitamin D deficiency. Vitamin D deficiency is a global health problem. Every year, more than 254 million children worldwide, suffer from vitamin deficiencies. Vitamin D deficiency, is now an internationally recognized health problem. Vitamin D is a fat-soluble, vitamin that plays an important role in bone health and promotes the absorption and metabolism of calcium and phosphorus. The physiological effects of vitamin D on brain functions, include promoting neurotransmission, neurogenesis, synaptogenesis, amyloid clearance, and preventing neuronal death. Vitamin D originally, acted as an antioxidant, and ancient survival molecule, and later evolved, as a cytokine. Rickets in children, osteomalacia, and osteoporosis are the most commonly mentioned effects of their deficiencies. rickets from vitamin D deficiency in recent decades as a result of multiple factors, which we will discuss in the course of this review.

Keywords: Vitamin D Deficiency, Etiologic Factors, Physiologic effects, Review

INTRODUCTION
Vitamin D deficiency has been linked to several health outcomes, including musculoskeletal (bone fractures, osteomalacia, osteopenia, rickets, osteoporosis and muscle weakness) and non-skeletal complications. Non-skeletal complications include cardiovascular diseases and risk factors such as congestive heart failure, impaired systolic and diastolic function, myocardial infarction, peripheral vascular disease, nonvalvular AF and hypertension. In addition, it was also associated with tuberculosis, rheumatoid arthritis, multiple sclerosis, inflammatory bowel diseases, cancers, schizophrenia, depression, cognitive deficits, (Wong et al., 2013; Demir, Uyan, & Melek, 2014; Küçükazman et al., 2014).
The main possible reasons for this deficiency were a lack of knowledge of vitamin D (lack of exposure to the sun, use of sunscreen, and full body coverage during sun exposure in children). Primary care centers were unable to provide information about the importance of vitamin D for bone health, growth and development, in children. Awareness of the benefits of sunlight needs to be raised, by detailing how often, how long, and how much body should be exposed, for optimal vitamin D intake. Doctors need more nutritional and health information about vitamin D that can be easily transferred to children (Sahay, M., & Sahay, R. 2012). Vitamin D deficiency has been a health problem in the world. The first to describe the condition of vitamin D deficiency is Glisson and his colleagues in London, England, in the mid-17th century. The problem called skeletal deformities. Vitamin D is of great importance in bone growth, so the lack of vitamin D or its metabolism imbalance in the body leads to great problems, especially rickets in children, at this time (Alwadei, Al-Johani, 2018). Therefore, vitamin D supplementation in children could help reverse the increasing trend in the incidence of this disease. It should be noted that the higher serum levels of 25-hydroxyvitamin D are associated with much lower incidence, rates of colon, breast, ovarian, kidney, pancreas, and other cancers. Vitamin D concentrations, above 20 ng/ml have been found, to be associated, with a significant reduction, in the risk, of all cancers, combined. Inadequate vitamin D supply can also, play a role in the pathogenesis of chronic infectious diseases, autoimmune diseases, allergies, and psychiatric disorders, in children (Mondul, & Albanes, D. 2017). Vitamin D deficiency has recently been suggested as a possible environmental risk factor for autism spectrum disorder (ASD). It plays a unique role, in brain homeostasis, embryogenesis, and neurodevelopment, immunological modulation (including the brain's immune system), antioxidation, anti-apoptosis, neuronal differentiation, and gene regulation. Children with ASD had significantly lower serum levels of 25-hydroxyvitamin D (25 (OH) D) than healthy children. Therefore, vitamin D deficiency during pregnancy, and early childhood, can be an environmental trigger for ASD (Duan XY et al., 2013).

Recently, a number of studies have suggested that vitamin D may play a role in ADHD pathogenesis. The mechanisms by which vitamin D can affect a number of neurological disorders, including ADHD (Khoshbakht, Y., Bidaki, R., & Salehi-Abargouei, A. 2018).

Vitamin D supplementation, not only improves some behavior problems, but can prevent some symptoms of the disorder, from getting worse, and reduce impulsiveness (Rao, T. S., Asha, M. R., Ramesh, B. N., & Rao, K. S. 2008).

The vitamin D receptor and the vitamin D metabolizing enzymes, are expressed in the brain. Because pleiotropic function, vitamin D is also involved in signaling, cascades and neurobiological signaling pathways that can impair mental health. Low vitamin D status is linked to a number of adverse, neuropsychiatric outcomes. In particular, population-based epidemiological, and clinical studies, have shown an association between low serum, 25 (OH) vitamin D levels (25 (OH) D) and depressed mood (Föcker, M., et al., 2018).

It is very important, to raise maternal awareness of vitamin D, its importance, for health and well-being, the consequences, of its deficiency and its practices, to
prevent VD. Educating mothers about sources of vitamin D and the importance of sun exposure, as it is not possible to get a sufficient amount of vitamin D from food sources alone. Therefore, a combination of sun exposure and adequate vitamin D supplementation, prevents vitamin D deficiency / insufficiency, for all children (Kamal, 2018). Consequently, continuous maternal vitamin D supplementation, from pregnancy, through breastfeeding, through dietary supplements, and sun exposure, to provide vitamin D to the fetus, and infant and prevent deficiencies (Hollis, B. W., Wagner, et al., 2015).

These commitments, and awareness, of vitamins and minerals, especially vitamin D, were the responsibility of maternal and child nurses who need to begin, raising mothers, through pregnancy and beyond. Nurses, as a subset of health care providers, are in direct contact, with patients, more than other subgroups, and their health, education would affect, the condition, of their patients. Nurses must educate parents about the acquisition of vitamin D through sun exposure and ingesting foods that contain vitamin D or are supplemented, with vitamin D. There are very few nutrients that naturally have enough vitamin D, so the main source of vitamin D is sun exposure. It can therefore, be assumed that insufficient sun exposure, air pollution, winter season, and clothing style are risk factors for vitamin D deficiency. Adding vitamin D to foods is not a common strategy to prevent its deficiency (Fiscaletti, M., Stewart, P., & Munns, C. F. (2017).

During pregnancy, train women, in a life cycle, who are responsible, not only for their own wellbeing and health, but also for that of their developing fetus. While the "right diet" and the "right lifestyle" cannot ensure a healthy, baby at birth 100% of the time, the "wrong diet" and the "wrong lifestyle" are like diets, without folic acid, or iron, lifestyles, with alcohol and cigarettes, not possible are associated, with higher rates, of congenital abnormalities, unfavorable pregnancy outcomes, and direct consequences, in the offspring exposed, to such "false" conditions. Some aspects are more obvious, to us because we are seeing the direct effect, or manifestation of the lack of nutrients, or the excess of an environmental toxin, like cigarette, smoke (with impaired growth of the fetus). The effects, of nutritional deficiencies, can be more subtle and it takes, years to unfold (e.g., vitamin B12 deficiency) (Wagner, Taylor, Johnson, & Hollis, 2012).

**Concept of vitamin D**

Vitamin D deficiency has been linked to several health outcomes, including musculoskeletal (bone fractures, osteomalacia, osteopenia, rickets, osteoporosis and muscle weakness) and non-skeletal complications. Non-skeletal complications include cardiovascular diseases and risk factors such as congestive heart failure, impaired systolic and diastolic function, myocardial infarction, peripheral vascular disease, nonvalvular AF and hypertension. In addition, it was also associated with tuberculosis, rheumatoid arthritis, multiple sclerosis, inflammatory bowel diseases, cancers, schizophrenia, depression, cognitive deficits, (Wong et al., 2013; Demir, Uyan, & Melek, 2014; Küçükazman et al., 2014)

**Epidemiology of vitamin D deficiency**

Vitamin D deficiency is widespread, the lowest vitamin D levels are commonly found in regions such as the Middle East and South Asia and the main risk factors were attributed to elderly women, higher latitude, winter season, less sunlight exposure,
skin pigmentation, dietary intake and low vitamin D fortified foods. It was estimated that the prevalence of vitamin D deficiency is approximately 30–50% of the general population. Furthermore, vitamin D deficiency is still common in sunshine countries. In a large Middle Eastern study of 60,979 patients from 136 countries with yearlong sunlight, 82.5% of studied patients were found to have vitamin D insufficiency (Haq, Svobodová, Imran, Stanford, Razzaque, 2016; Lee, Keefe, Bell, Hensrud, Holick, 2017).

There is an epidemic of vitamin D deficiency worldwide, which represents a major factor of many chronic diseases and has led some authors to suggest annual vitamin D measurement coupled with adequate intake and greater awareness of its consequences. In the United States, there was an increasing prevalence of vitamin D deficiency observed from a sample of 18,158 individuals between 1988 and 1994 compared with a sample of 20,289 individuals between 2000 and 2004 with 5–9 nmol/l decrease in vitamin D levels (Zhang, & Naughton, 2010).

Vitamin D levels were found to be lowest in Blacks, followed by Hispanics and Chinese, and adequate in Whites (Multi-Ethnic Study of Atherosclerosis MESA). Non-Hispanic blacks and Mexican Americans tend to have lower levels of vitamin D in comparison with non-Hispanic whites. Vitamin D to be significantly lower among obese and non-college educated individuals, as well as those with poor health statuses, hypertension, low high-density lipoprotein levels and low milk consumption. Furthermore, the level of vitamin D deficiency was found to be alarmingly lower in winter and spring (Robinson-cohen, Hoofnagle, Ix, Kestenbaum, de Boer, 2013).

**Etiologic Factors of Vitamin D deficiency**

Vitamin D is obtained from several sources: The diet, supplements, or seasonal exposure of skin to adequate solar ultraviolet irradiation via photochemical and thermal conversion of the cholesterol precursor 7-dehydrocholesterol (Mailhot, & White, 2020).

Several factors have significant effects on serum vitamin D levels, including season, sunlight exposure, age and diet. Because of rapid growth in the skeletal system, infants aged 4 months to 2 years are at a high risk for vitamin D deficiency (Çakır, & Demirel, 2014).

The major source of vitamin D for children is exposure to natural sunlight. Children with a naturally dark skin tone have natural sun protection and require at least three to five times longer exposure to make the same amount of vitamin D as children with a white skin tone (Nair, & Maseeh, 2012).

Diet problems, psychological problems, digestive complaints and stomach conditions, lack of food, high food prices and lack of breastfeeding all the main causes of malnutrition. The main causes of malnutrition include changes in nutrient requirements, secondary to disease processes and drug modalities in combination with low or marginal dietary intake. Infections are common and result in anorexia, poor dietary intake, and malnutrition, which predispose the child to another infection. The main causes of malnutrition among the children are insufficient intake of food and lack of nutritional knowledge. The majority of children have no knowledge about the daily caloric intake. As a result, they lead to malnutrition (Khan et al., 2017).
Climate: Food production of many Sub-Saharan Africa countries, which is often affected by environmental conditions (i.e. soil fertility, rainfall, temperature), face the risk of failing food availability as indications of warming climates on current food systems. There is an increasing strain on food resources due to climatic factors as well as due to the decreasing of land area suitable for planting and agricultural production.(Andrew J. Challino et al., 2014)

Food price: From the time of high food prices in the 1870s the world population has amplified more than five times and has attained 6.7 billion today. It is expected to reach nearly 9 billion in 2050. To overcome existing hunger and to provide food to a further 2 billion people, food production has to be increased to double by 2050. An increase in food prices has adversely affected micronutrient deficiencies which gave desirable results on nutrition and health of people.(Christophe Golay.,2010)

Poverty: There is a two-way link between poverty and health. Poverty is one of the most influential risk factors for ill health, and ill health can lead to poverty. Illness impairs learning ability and quality of life has a great impact on productivity and drains family savings. Poor people are more exposed to environmental risks (poor sanitation, unhealthy food, violence, and natural disasters) and less prepared to cope with them, are less informed about the benefits of healthy lifestyles, and have less access to quality health care. They are therefore more at risk of illness and disability (Delisle, & Batal, 2016)

Problems of vitamin D deficiency

1. Malnutrition
Under nutrition is a critical determinant of mortality and morbidity in young children worldwide; it is associated with 45 percent of all deaths in children under five years of age. Approximately 52 million children (7.7 percent of all children under five years of age worldwide) have wasted, and one-third (17 million) have severe acute malnutrition. Many more children (154.8 million; approximately 23 percent) are stunted, reflecting chronic under nutrition. Severe under nutrition is primarily a problem in resource-limited countries. Globally, childhood stunting decreased from 39.7 percent in 1990 to 23.2 percent in 2015 and is expected to decline further. The term "malnutrition" in its traditional sense, referring to under nutrition (wasting, stunting, or micronutrient deficiencies) (Goday, 2020).

2. Cognitive Problems
Vitamin D acts by binding to the nuclear vitamin D receptors (VDR), which are widely distributed throughout the human brain in most neurons and some glial cells. vitamin D deficiency during pregnancy causes extreme alterations in the brain at birth. This provides a biological plausibility for a link between vitamin D status and neurodevelopment (Chowdhury et al., 2020).

The consequences of vitamin D deficiency in early life on neurodevelopmental may not become evident until later in childhood. Furthermore, the predictive ability of early neurodevelopmental assessments is poor, and cognitive assessments in school-aged children have shown to be stable over time (Schneider, Niklas, & Schmiedeler, 2014).
The vitamin D supply to the growing fetus depends on maternal vitamin D status. Therefore, maternal vitamin D deficiency during pregnancy might lead to adverse health outcomes in the offspring. Some studies have observed fetal growth restriction, reduced bone size, and bone mineral content, and recurrent wheeze in the offspring of mothers with vitamin D deficiency. There are poor learning and memory, and alterations in attention, in association with vitamin D deficiency before conception and/or during pregnancy (Walle BM et al., 2020).

The deficiency of vitamin D is associated with various bone and non-bone health hazards. Among non-bone health hazards, in recent decades, growing evidence identified the association of low serum vitamin D levels with neurodegenerative disorders, poor cognition, attention deficit hyperactivity disorder, autism, depression, and schizophrenia in children and adolescents (Wacker, & Holick, 2013; Wrzosek et al., 2013).

3. Immunity problems

Vitamin D plays an important role, not only for bone health, but also in the immune system. Both in vitro and clinical studies have demonstrated that vitamin D is important for the innate and adaptive immune response (Kempker, Han, Tangpricha, Ziegler, Martin, 2010).

In children, vitamin D insufficiency is common in patients who are hospitalized or have a severe infectious process and is associated with increased mortality. Vitamin D enhances the anti-microbial response of adults, suggesting a protective role of vitamin D in infection. Particularly, anti-microbial peptides such as human cathelicidin antimicrobial peptide (hCAP18) and β-defensin are up-regulated in response to vitamin D therapy (Moromizato, Litoniua, Gibbons, Giovannucci, & Christopher, 2014; Hebbar, Wittkamp, Alvarez, McCracken, & Tangpricha, 2014).

4. Cardiovascular problems

There is evolving data about the possible relationship of vitamin D with CVD risk factors. The vitamin D receptor is expressed in cells throughout the vascular system. Many cell types, including vascular smooth muscle cells, endothelial cells, and cardiomyocytes, produce 1α-hydroxylase, which converts 25-hydroxyvitamin D to calcitriol, the natural ligand of the vitamin D receptor. Calcitriol has been shown to inhibit vascular smooth muscle cell proliferation, regulate the renin-angiotensin system, decrease coagulation, and exhibit anti-inflammatory properties (Danik, & Manson, 2012; Norman, & Powell, 2014).

Vitamin D deficiency has been linked to several cardiovascular risk factors. Through increased renin and angiotensin II synthesis, vitamin D deficiency can increase the production of reactive oxygen species and G protein RhoA, resulting in inhibition of the pathways necessary for intracellular glucose transporter and thus the development of insulin resistance and metabolic syndrome. Also, the direct effects of vitamin D upon smooth muscle calcification and proliferation could contribute to their effects on cardiovascular health (Kheiri et al., 2018).

5. Rickets

Vitamin D deficiency results in abnormalities in calcium, phosphorus, and bone metabolism. VDD causes a decrease in the absorption of dietary calcium and
phosphorus, increasing parathyroid hormone (PTH) levels. The PTH-mediated increase in osteoclastic activity creates local foci of bone weakness and causes a generalized decrease in bone mineral density (BMD), resulting in osteopenia and osteoporosis. An inadequate calcium-phosphorus product causes a mineralization defect in the skeleton. In young children who have little mineral in their skeleton, this defect results in a variety of skeletal deformities classically known as rickets. VDD also causes muscle weakness; affected children have difficulty in standing and walking, whereas the elderly have increasing sway and more frequent falls, thereby increasing their risk of fracture. Vitamin D deficiency can lead to a loss of bone density, which can contribute to osteoporosis and fractures (broken bones) (Nair, &Maseeh, 2012; Christodoulou, Goula, Ververidis, &Drosos, 2013; Saglam, Kizildag, Toprak, Alp, &Yalcinkaya, 2017).

Rickets is a skeletal disorder that’s caused by a lack of vitamin D, calcium, or phosphate. These nutrients are important for the development of strong, healthy bones. People with rickets may have weak and soft bones, stunted growth, and, in severe cases, skeletal deformities (Basatemur E Sutcliffe A., 2015).

Rickets is most common in children who are between 6 and 36 months old. They are at the highest risk of rickets because they’re still growing. Children might not get enough vitamin D if they live in a region with little sunlight, follow a vegetarian diet, or don’t drink milk products. In some cases, the condition is hereditary (Choi, 2017)

**Recommendations:**

1. Recommendations for vitamin D supplementation in breastfed.
2. Current recommendations of sun exposure and vitamin D supplementation are limited because of a paucity of studies in children
3. Fortification of commonly used foods with vitamin D are necessary in keeping with various cultural norms of food intake
4. More studies are necessary in children using standard assays to determine safe levels of sun exposure and resultant vitamin D levels, as well as the 25(OH)-D levels below which pathologic changes begin.

**Financial disclosure**

There is no financial disclosure.

**Conflict of interest**

None to declare.

**Ethical Clearance**

All experimental protocols were approved and all experiments were carried out in accordance with approved guidelines.

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