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Vitamin D Deficiency and its Relation with Cancer in Children

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Abstract
Vitamin D deficiency is known as the most common nutritional deficiency. It is created during infancy due to different factors, including decreased dietary intake, decreased dermal synthesis, malabsorption, enzyme-inducing medications, and exclusive breastfeeding. Vitamin D deficiency is associated with poor bone health such as rickets and osteomalacia in children. Despite vitamin D plays an important role in bone health, its role in pediatric cancer is not detected and remained unknown; therefore, the aim of this study was to evaluate the role of vitamin D deficiency and its relation with cancer in children. Vitamin D in cancer children has been considered as a contributory factor for skeletal pathologies. Children with cancer may be at increased risk of vitamin D deficiency due to side effects which are induced by the disease and multiple treatments, given that chemotherapy and clinical radiation play a main role in decreased bone mineral density. Therefore, possible role of vitamin D deficiency in cancer pathogenesis and progression is well defined. It seems that these patients should be taken sufficient amount of calcium and vitamin D during chemotherapy and afterward.
Key words: Cancer, Children, Vitamin D Deficiency

Introduction

Childhood cancers are found in less than 1% of all cancers diagnosed each year (1). Cancer is the second cause of death in children. Vitamin D deficiency is known as the most common nutritional deficiency in all age groups (2). There are numerous cases of rickets in infants that are related to inadequate vitamin D intake and decreased exposure to sunlight in the United States and other Western countries (3). This event is seen especially in infants with darker skin pigmentation and breastfed infants (4-11) because breast milk includes inadequate vitamin D. Therefore, supplementations with high dose of vitamin D are needed to increase maternal breast milk concentrations (12). Since few studies have been done about the role of vitamin D in the etiology of pediatric cancer, this study reviewed the role of vitamin D deficiency in pediatric cancer patients.

Vitamin D and its metabolites

Vitamin D exists in two forms, including vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). The principal origin of vitamin D in human is vitamin D3 synthesized in the skin in the presence of UV-*B*. (13). Following absorption, vitamin D2 or vitamin D3 are converted to 25-hydroxyvitamin D2 (25(OH) D2) or 25-hydroxyvitamin D3 (25(OH) D3) metabolites in the liver and then they may activate to 1, 25-dihydroxyvitamin D (1, 25(OH) 2D) (14) in kidneys, placenta, and other tissues (15). 1, 25 (OH) D increases calcium via intestine and bone using different mechanisms.

Vitamin D 25(OH) D and 1, 25 (OH) D binds to vitamin D binding protein (DBP). Then, they are transported to target tissues (16, 17). Concentration of DBP in plasma

might be decreased during disease process (17).

1 α ,25(OH) 2 D (active form of vitamin D) performs its action via binding to nuclear receptor (the vitamin D receptor) as a member of the steroid and thyroid hormone receptor superfamily (18). Then, it binds to specific DNA sequences named vitamin D response elements and modulates specific gene expression in a tissue-specific manner (19).

Vitamin D deficiency

Vitamin D deficiency in adults is defined as concentration of 25-OH-D < 50 nmol/L and vitamin D insufficiency as concentration of 25-OH-D of 50 to 80 nmol/L (19-26). There is no accurate definition about vitamin D insufficiency in infants and children (3) (27). American Academy of Pediatrics suggested infants and children to take at least 400 IU/day through supplementation or diets to prevent vitamin D deficiency (28). Moreover, 400 IU of vitamin D per day caused serum 25-OH-D concentrations > 50 nmol/L in exclusively breastfed infants (3). Consumption of 200 400 IU of vitamin D per day cannot retain 25-OH-D concentration > 50 nmol/L in infants (3). Vitamin D supplement of 400-800 IU/day should be consumed in preterm infants from birth to compensate for insufficient transfer of maternal vitamin D. Moreover, preterm infants suffer from prematurity symptoms, including poor feeding, gastrointestinal difficulties, impairing absorption, and sometimes liver and kidney impairments. Therefore, vitamin D supplement, especially in breastfed infants, has been suggested (29). Vitamin D intoxication diagnosis is based on elevated level of serum 25OHD. Children with vitamin D intoxication showed hypercalcemia symptoms, including poor appetite, weight loss, abdominal pain, vomiting, constipation, polyuria, polydipsia, and dehydration (30-38).

Measurement of vitamin D levels

Evaluation of 25(OH) D includes measuring both D2 (ergocalciferol) and D3 (cholecalciferol) derivatives. The level of total 25(OH) D is measured via high performance liquid chromatography (HPLC) or tandem mass spectrometry as the gold standard assay. Other methods for 25 (OH) D measurements are radio-immune assay using monoclonal antibody and chemiluminescent protein binding assay (2).

Relation between vitamin D and calcium ion (Ca^{2+})

There is inverse relation between the level of circulating 1, 25(OH) 2 D and calcium intake (39). Inadequate intake of calcium leads to increased production of 1, 25(OH) 2 D (activated form) (19). It also motivates absorption of Ca^{2+} from intestine and regulates serum calcium to reserve a sufficient mineralization of the skeleton (40). On the other hand, vitamin D is necessary for metabolism of phosphate and magnesium (41). Therefore, vitamin D plays a main role in metabolism and absorption of minerals (41) and maintenance of bone health in the body (27) and its deficiency is associated with poor bone health, including rickets and osteomalacia in children (27). It seems that calcium and vitamin D deficiency can induce rickets (42).

Vitamin D and immunity

The role of vitamin D deficiency in the pathogenesis of immunomediated diseases has been highlighted (43). On the other hand, positive effect of vitamin D on immune system has been documented. 1, 25(OH) 2 D 3 acts as a powerful suppressor of IFN-γ stimulated macrophage activation (18). Therefore, it motivates phagocytosis and kills bacteria through macrophages (43). It also has a main role in shaping immune response by T and B cells. Enhancement of 1, 25 (OH) 2 D 3 to CD4+ T cells suppresses reproduction of T-helper-1 cells and cytokine production. Therefore, 1, 25 (OH)

2 D 3 induces differentiation of monocytes and decreases inflammatory cytokines and chemokines released by these cells (43). In addition, the role of vitamin D in macrophages maturation like macrophase-specific surface antigens, lysosomal enzyme acid phosphatase, and hydrogen peroxide secretion are determined. Moreover, properties of antimicrobial action are destroyed in case of vitamin D deficiency (43).

The role of vitamin D deficiency in infants and children

Deficiency of vitamin D is important for health of the fetus and the newborn. Moreover, maternal vitamin D deficiency is a risk factor for vitamin D deficiency in infants and childhood.Gartner et al., reported that human milk includes vitamin D at concentration of 25 IU/L or less (44). Therefore, sufficient intake of vitamin D can't be provided by human milk as the sole origin of vitamin D for the breastfeeding infant (45). It seems that infants who are breastfed and don't get vitamin D supplement or sufficient sunlight are at increased risk of vitamin D deficiency and rickets (45-49). The peak incidence of rickets is between 3 - 18 months of age (3) and it is related to vitamin D deficiency (15). Furthermore, children, particularly infants, may need less sun exposure than adults for producing sufficient vitamin D concentration due to greater surface area to volume ratio and increased ability to produce vitamin D than older people (27). According to Specker et al., if infants have exposure to sunlight for 30 min/week in diaper and 2 hour /week for fully clothed, vitamin D levels will get greater than 11ng/dL(2). Another Study showed that limited sunlight exposure can prohibit rickets in most of breastfed infants (50, 51). Lee reported risk factors for vitamin D deficiency in infants as follows: decreased dietary intake, malabsorption, dark skin, and inadequate sunlight exposure, (e.g., anticonvulsants, glucocorticoids), sedentary lifestyle and obesity (28), premature infants, enzyme-inducing medications, and exclusive breastfeeding (27).

Relation between vitamin D deficiency and geographical positions

Vitamin D deficiency is created during infancy due to different factors (2). Sun exposure can be a major source of vitamin D for most children and adults (43). Wanger et al., showed vitamin D insufficiency in 6 -10 years old children in Pittsburgh (52). Scheimberg et al., evaluated the effect of vitamin D deficiency in infants in London, England, and concluded that abnormalities due to vitamin D deficiency can start in the first days of life (53).

Relation between vitamin D deficiency and other disease

Vitamin D deficiency and insufficiency are nutrition problems worldwide (54). In adults, vitamin D has a main role in retaining innate immunity and preventing several diseases , including multiple sclerosis (55-58), rheumatoid arthritis(38), some types of cancer (e.g. breast, ovarian, colorectal, prostate cancers) (59-61) , type 2 diabetes mellitus(3, 62,63), and infectious diseases (2). Serious complication of vitamin D deficiency leads to heart failure, arrhythmia, cardiogenic shock, and even death (15).

Moreover, using supplements in infants and early childhood may reduce the incidence of type 1 diabetes mellitus (3). Children with increased risk of vitamin D deficiency, including patients with chronic fat malabsorption and those who take anti-seizure medications have vitamin D deficiency in spite of vitamin D intake of 400 IU/day. It seems that higher doses of vitamin D may be essential to gain vitamin D to normal status in these children (3).

Relation between vitamin D deficiency and cancer in children

There is little evidence about 25(OH) D insufficiently in pediatric cancer patients (64). Although vitamin D plays an important role in pediatric and adult bone health (65, 66), its impact on cancer therapy of children is not examined and remains unknown (65); however, some studies have shown prevalence of vitamin D deficiency in these patients (64). Children with cancer may be at increased risk of vitamin D deficiency due to side effects which are induced by both the disease and the multiple treatments (64). Children with cancer had lack of appetite and insufficient sun exposure during chemotherapy (65). Fuleihan et al., held that children with cancer are faced with decreased bone mineral density (BMD). Moreover, they reported vitamin D inadequacy at different stages of the disease (64).

The prevalence of 25 (OH) D deficiencies in children diagnosed with hematological malignancies is 24% (64). Most studies evaluated the status of vitamin D in children and young people with hematological malignancies and few studies investigated the status of vitamin D in patients with solid tumors, brain tumors, and benign tumors (64).

High level of 25OHD and vitamin D intake are associated with improved overall and recurrence-free survival in pediatric patients (68). On the other hand, prevalence of vitamin D deficiency and insufficiency in pediatric patients is associated with malignancy (68). Moreover, the negative effects of chemotherapy with drugs such as steroids and methotrexate (MTX) as well as clinical radiation play a main role in decreasing bone mineral density (67). In a nutshell, patients with cancer are recommended to take sufficient amount of calcium and vitamin D during chemotherapy and afterward (67).

Conclusion

The result of this study showed that prolonged sun exposure and consumption of vitamin D can provide sufficient level of vitamin D. On the other hand, chemotherapy can decrease bone mineral density in cancer patients. Therefore, patients with cancer are recommended to take sufficient amount of calcium and vitamin D during chemotherapy and afterward.

Conflict of interest

The authors report no conflict of interest.

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