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Review Article

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Recent Updates on Vitamin D and Pediatric Gastrointestinal Diseases

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The clinical importance of vitamin D has been recently highlighted, due to non-skeletal effects of vitamin D and the fact that vitamin D receptors are observed in many kinds of cells. Vitamin D deficiency or insufficiency results in the development of gastrointestinal diseases, including obesity, hepatitis B, chronic hepatitis C, and inflammatory bowel disease in children. The prevalence of vitamin D insufficiency in 188 Korean adolescents, aged 12-13 years, was 98.9% for boys and 100% for girls. This article reviews recent publications, regarding vitamin D deficiency and childhood gastrointestinal diseases, and introduces new treatment and prevention guidelines for vitamin D deficiency. **(Pediatr Gastroenterol Hepatol Nutr 2012; 15: 138～144)**

Key Words: Vitamin D, Vitamin D deficiency, Gastrointestinal diseases

INTRODUCTION

Vitamin D is a fat-soluble vitamin that is important for maintaining calcium homeostasis through actions in the intestine, bone, kidney, and parathyroid gland [1]. Vitamin D is acquired through nutritional supplements (10-20%) and by the cutaneous synthesis from exposure to sunlight (80-90%) [2].

Vitamin D deficiency in children causes rickets, which is the failure of mineralization during the growth of bone and cartilage. Nutritional rickets has almost disappeared since the discovery that exposure to sunlight and consumption of cod liver oil can both prevent and treat rickets [3,4]. In pediatric patients, causes of rickets have changed from low exposure to sunlight and intake of vitamin D to inappropriate supplementation or metabolic disorders, including hepatic disease, renal disease, and metabolic problems with calcium or phosphorus. However, vitamin D deficiency and nutritional rickets are re-emerging as a major public health problem throughout the world [5-8]. Since the late 1990s, vitamin D has become increasingly recognized in the literature for possessing extraskeletal functions, including effects

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on the adaptive immune system, innate immune system, insulin secretion by pancreatic cells, multifactorial heart functions, blood pressure regulation, and brain and fetal development [9,10]. Moreover, the vitamin D receptor is present in most tissues and cells in the body. Therefore, the purpose of this review is to discuss recent updates in research of vitamin D and extraskeletal diseases, including gastrointestinal diseases and vitamin D deficiency in children.

DEFINITION OF VITAMIN D DEFICIENCY AND VITAMIN D INSUFFICIENCY

Vitamin D deficiency has been defined as a 25-hydroxyvitamin D [25(OH)D] concentration less than 20 ng/mL, and vitamin D insufficiency has been defined as a 25(OH)D concentration of 21-29 ng/mL [11]. The cut-off value of 20 ng/mL is based on studies that have shown that levels below this value may be associated with rickets and impaired bone development. The cut-off value of 30 ng/mL is based on vitamin D levels below which parathyroid hormone levels begin to increase in adults, thereby affecting calcium absorption.

THE PREVALENCE OF VITAMIN D DEFICIENCY OR INSUFFICIENCY IN KOREA

The prevalence of vitamin D deficiency in normal healthy individuals is high in many countries [6,7]. In the Korean National Health and Nutrition Examination Survey from 2008, 47.3% of males and 64.5% of females were found to have a vitamin D insufficiency [12]. Vitamin D insufficiency was most prevalent in the age range of 20-29 years, with an incidence of 65.0% in males and 79.9% in females [12]. In 188 Korean adolescents aged 12-13 years who participated in a general health check-up, vitamin D insufficiency and deficiency was found in 98.9% of boys and 100% of girls [13]. A higher prevalence of vitamin D insufficiency in Korea is most likely related to decreased outdoor activities, because adolescents tend to limit outdoor activities as they study and prepare for entrance into high-ranking schools [14]. In particular, girls often prefer fair skin and therefore apply topical sunscreen. Notably, in a 2003 study, 48% of white girls aged 9-11 years living in Maine had 25(OH)-D levels less than 50 nmol/L (20 ng/mL) at the end of the winter season, and 17% continued to have vitamin D insufficiency at the end of summer due to the use of sunscreen and practice of complete sun protection [15].

RISK FACTORS OF VITAMIN D DEFICIENCY

The main cause of vitamin D deficiency is inadequate exposure to sunlight [16]. Risk factors for vitamin D deficiency and rickets in infants include breastfeeding without vitamin D supplementation, dark skin pigmentation, and maternal vitamin D deficiency [17]. Children younger than 2 years of age as well as those who were breastfed or tested in the winter or spring were more likely to have a vitamin D deficiency [18]. In 31 infants with high alkaline phosphatase levels, 58% had a vitamin D insufficiency or deficiency as well as all of the infants who had been breastfed [19]. Other risk factors for vitamin D deficiency in children include the use of a topical sunscreen, obesity, a fat malabsorption syndrome, and a wide variety of medications, such as anticonvulsants and medications to treat acquired immunodeficiency syndrome (AIDS)/human immunodeficiency virus (HIV) and chronic granuloma- forming disorders, certain lymphomas, and primary hyperparathyroidism.

The serum levels of 25(OH)D is also influenced by genetic factors [20-22]. Genome-wide association studies and candidate gene studies have revealed that several vitamin D-related genes, including *VDR, GC, NADSYN1, CYP2R1, CYP24A1, CYP27B1*, and *C10orf88*, contribute to variations in serum 25(OH)D levels. However, the involvement of genetic factors in vitamin D deficiency should only be considered after ruling out other common causes.

EXTRASKELETAL DISEASES AND VITAMIN D DEFICIENCY

The active form of vitamin D, $1,25(OH)_2D$, is considered to be a steroid hormone because it interacts with its cognate vitamin D receptor [23]. Vitamin D deficiency or insufficiency has resulted in significant contributions to the development of a variety of diseases, including infectious diseases (influenza and tuberculosis), psychiatric disorders, inflammatory disease, and cancer. In particular, several childhood diseases have been shown to be associated with vitamin D deficiency.

Obesity and metabolic syndrome

Vitamin D deficiency is common among obese children and adolescents, and low vitamin D levels in obese individuals may accelerate the development of metabolic syndrome, type 2 diabetes mellitus, and cardiovascular disease by further increasing insulin resistance [24]. There is a positive correlation between 25(OH)D concentrations and some lipid profiles, such as total cholesterol, apolipoprotein A1, apolipoprotein B, and triglycerides in children and adolescents [25]. A study in Korean adolescents showed that serum 25(OH)D levels were significantly correlated with diastolic blood pressure, total cholesterol, triglycerides, low density lipoprotein-cholesterol, insulin concentrations, and homeostasis models of assessment of insulin resistance [13]. Serum 25(OH)D levels were inversely associated with homeostasis models of assessment of insulin resistance, triglycerides, and low density lipoprotein-cholesterol levels. Vitamin D is believed to directly affect the action of insulin by improving glucose transportation through the expression and stimulation of the insulin receptor, or indirectly by regulating calcium concentrations outside and inside the cell by transporting calcium across the cell membrane when needed [26]. In addition, infants in Finland who received at least 2000 IU/d of vitamin D during the first year of life had a reduction in the risk of developing type 1 diabetes in the ensuing 31 years by 88%, without any reports of toxicity [27].

Hepatitis

Certain polymorphisms in the vitamin D receptor have been associated with occult hepatitis B infection, greater severity of hepatitis B associated liver disease, and a higher viral load [28-31]. The tumor necrosis factor-alpha (TNF)-α 308 allele and VDR *Apa*I A allele tend to occur more frequently in children with chronic hepatitis B virus infection, suggesting that the TNF-α and vitamin D pathways may be involved in the susceptibility to and outcome of hepatitis B virus infection acquired early in life [31].

A relationship between Vitamin D deficiency and hepatitis C has also been reported. In 42 patients with recurrent hepatitis C who received interferon-α and ribavirin for a 48 week period, patients taking oral vitamin D_3 supplements and those with higher vitamin D levels had a greater sustained antiviral response to treatment [32]. Lower vitamin D levels in patients with chronic hepatitis C are associated with necrosis and inflammation, and predict severe fibrosis and a poor antiviral response to interferon-based therapy [33]. Severe liver disease may increase the risk of vitamin D deficiency and *vice versa*, as there may be a relationship between vitamin D deficiency and fibrosis [34]. Vitamin D deficiency also frequently occurs before liver transplantation in 51-92% of cases [34]. Early vitamin D supplementation was shown to be independently associated with a lack of acute liver allograft cellular rejection [35]. However, additional studies are necessary to confirm these associations.

Inflammatory bowel disease (IBD)

The environment contributes to IBD development, and there is reason to believe that vitamin D may be an environmental factor affecting IBD. The prevalence of IBD has been shown to be highest in northern climates, such as North America and Northern Europe. These areas receive less sunlight, and therefore individuals in these regions produced lower levels of vitamin D [36,37]. Vitamin D deficiency may compromise the mucosal barrier, leading to increased susceptibility to mucosal damage and increased risk of IBD [38] Vitamin D deficiency exacerbates the symptoms of enterocolitis in interleukin-10 knock-

out mice, and 1,25$(OH)_2D_3$ treatment for as little as 2 weeks ameliorated IBD symptoms in these mice [39] The *Taq*I polymorphism at codon 352 of exon 8 among patients with Crohn's disease is frequently found in patients with ulcerative colitis [40]. Studies assessing the vitamin D status of children with IBD have shown that vitamin D deficiency may be related to the onset and severity of IBD. Vitamin D deficiency was found in 62% of the patients aged 1-18 years with newly diagnosed IBD [41]. In addition, another study found that the prevalence of vitamin D deficiency was 34.6% in 130 children and young adolescents aged 8-22 years with IBD [42]. IBD could lead to vitamin D deficiency, because patients may have decreased exposure to sunlight, decreased vitamin D intake, malabsorption, or gastrointestinal loss [42] However, the relationship between vitamin D status and IBD in children remains controversial [43-45], and therefore additional studies exploring this association are needed.

RECOMMENDED DIETARY INTAKE OF VITAMIN D FOR PATIENTS AT RISK FOR VITAMIN D DEFICIENCY

The prevalence of nutritional rickets has increased in the United States, Canada, Australia, and other countries since 1990s. In 2003, the American Academy of Pediatrics (AAP) recommended a vitamin D supplement for (1) breastfed infants who do not consume at least 500 mL of a vitamin D-fortified formula/beverage, and (2) non-breastfed infants who do not consume more than 500 mL of vitamin D-fortified liquids [46]. Supplementation should start during the first 2 months of life and continue throughout childhood and adolescence.

The AAP and the Canadian Pediatric Association both recommend 400 IU/d of vitamin D supplementation [47]. The Institute of Medicine (IOM) recommends that the adequate intake and recommended dietary allowance (RDA) of vitamin D for children aged 0-1 and 1-18 years should be 400 and 600 IU/d, respectively [48]. According to Korean Dietary Reference Intakes , the adequate intake of vitamin D is 200 IU/d in children [49] (Table 1).

Based on recent guidelines for vitamin D management in IOM [11], infants and children aged 0-1 year require at least 400 IU/d of vitamin D and children 1 year and older require at least 600 IU/d of vitamin D for maximal bone health. However, it is currently unknown whether these recommendations are sufficient for providing all of the potential nonskeletal health benefits associated with vitamin D for maximization of bone health and muscle function. In addition, at least 1,000 IU/d of vitamin D may be required to consistently increase serum levels of 25(OH)D above 30 ng/mL. Obese children and children on certain medications, such as anticonvulsants, glucocorticoids, antifungals (i.e. ketoconazole) and HIV medications are currently given at least two to three times more vitamin D in order to satisfy the vitamin D requirement. The tolerable upper limit of vitamin D maintenance supplementation, which is not to be exceeded without medical supervision,

Table 1. Vitamin D Recommended Intakes by the Institute of Medicine (IOM) [11], the American Academy of Pediatrics (AAP) [46], and Korean Dietary Reference Intakes (DRIs) [49]

Age	IOM (IU/day) [11]			AAP (IU/day) [46]			DRIs (IU/day) [49]	
	AI*	RDA†	UL‡	AI	RDA	UL	AI	UL
0-5 mo	400		1,000	400		1,000	200	1,000
6-11 mo	400		1,500	400		1,500	200	1,000
1-3 yr		600	2,500		400	2,500	200	2,500
4-8 yr		600	3,000		400	2,500	200	2,500
9-13 yr		600	4,000		400	3,000	200	2,500
14-18 yr		600	4,000		400	3,000	200	2,500

*AI: adequate intake, †RDA: recommend dietary allowance, ‡UL: tolerable upper limit.

should be 1,000 IU/d for infants up to 6 months of age, 1,500 IU/d for infants aged from 6 months to 1 year, at least 2,500 IU/d for children aged 1-3 years, 3,000 IU/d for children aged 4-8 years, and 4,000 IU/d for children over 8 years of age. However, higher levels of vitamin D supplementation, including 2,000 IU/d for children aged 0-1 year and 4,000 IU/day for children aged 1-18 years, may be required to correct vitamin D deficiency.

The major source of vitamin D is exposure to natural sunlight [16]. The application of sunscreen with a sun protection factor of 30 reduces vitamin D synthesis in the skin by more than 95% [50].

CONCLUSION

Vitamin D deficiency and insufficiency is common in normal healthy children according to a national nutritional survey conducted in Korea. However, vitamin D deficiency is often symptom free and not associated with any disorders. In addition, there is controversy on the use of vitamin D supplementation in healthy newborns and children. Currently, no study has assessed the serum levels of vitamin D in normal healthy children less than 12 years of age in Korea. To prevent rickets, vitamin supplementation and outdoor activity should be encouraged for children. Appropriate guidelines for the use of topical sunscreen in children should also be established in order to minimize the effect on serum vitamin D levels. Outdoor activity is recommended for children in order to maintain normal or higher levels of vitamin D.

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