The pleiomorphic actions of vitamin D and its importance for children

Se Young Kim, MD, PhD
Department of Pediatrics, Bundang Jesaeng General Hospital, Daejin Medical Center, Seongnam, Korea

Knowledge regarding the physiological role and dietary requirements of vitamin D has dramatically expanded over the past several decades. The "new" vitamin D is not only a mediator of calcium homeostasis, it also has important immunomodulatory, antimicrobial, and antiproliferative actions. In spite of the interest in vitamin D as a mediator in many chronic diseases of adulthood such as cancer and type II diabetes, less attention has been given to the implications of the new understanding of vitamin D for child and adolescent health. Recently, rickets caused by vitamin D deficiency is resurging in developed countries. Therefore, pharmacokinetic studies and epidemiologic research that incorporates clinical and functional outcomes are needed to clarify the role of vitamin D in growth and development in Korean children and adolescents and to determine vitamin D dietary requirements.

Keywords: Vitamin D, Vitamin D receptor, Child, Growth

Introduction

Vitamin D is not just for preventing rickets and osteomalacia. Recent findings, primarily in animals studies but also in a number of epidemiologic studies and a few clinical trials, indicate that adequate vitamin D levels are important for normal growth and puberty, cancer prevention, controlling hormones such as parathyroid hormone (PTH), insulin, fibroblast growth factor 23 (FGF23), and renin, and regulation of the immune response. 25-hydroxyvitamin D (25(OH)D) levels above 10 ng/mL may suffice to prevent rickets and osteomalacia, but these levels are not sufficient to provide for these more recently discovered clinical benefits. The recent report indicate that a level of 20 ng/mL was adequate for maintenance of skeletal health, but the evidence was insufficient to make recommendations for the nonskeletal actions, but determination of the optimal levels of 25(OH)D and thus amount of vitamin D supplementation required to reach these levels for the numerous actions of vitamin D will only be established with additional prospective trials. The objectives of this review are to understand the basic metabolism and mechanisms of action of vitamin D, including its pleiomorphic actions in multiple tissues. And to assess the quality of the data supporting the current recommendations for serum 25(OH)D levels, and the know where the gaps in our knowledge exist regarding optimal vitamin D levels. Last, to determine the appropriate means of achieving vitamin D sufficiency with supplementation, while appreciating some of the pitfalls regarding monitoring those levels deemed sufficient.

The background of physiology of vitamin D

The large amount of work by a number of laboratories near 10 decades demonstrated that vitamin D not only was essential for bone health but also was a hormone mediating a wide range of homeostatic functions. The physiology of vitamin D from its synthesis in the skin to its active form...
1,25-dihydroxyvitamin D (1,25(OH)₂D), was fully defined by the mid-1970s (Fig. 1). The cloning of the vitamin D receptor (VDR) occurred by 1987. After that, in all tissues, further basic and clinical studies uncovered subsequent actions and led to the surprisingly abundant physiological role of vitamin D. Simultaneously, vitamin D as a therapeutic modality for the prevention of chronic diseases was rising. In a recent 2-year, there were more than 500 publications centered on vitamin D. In 2012, an Endocrine Society Scientific Statement was published in Endocrine Review. The evidence that defines

Fig. 1. (A) Production of vitamin D from the skin via ultraviolet (290–330 nm) in a nonenzymatic manner. (B) The synthesis of vitamin D metabolites including the inactive form, 24,25-dihydroxyvitamin D, and the active form, 1,25-dihydroxyvitamin D (1,25(OH)₂D). The process is controlled at several levels, including the liver, kidney, and peripheral tissues, and is regulated by systemic hormones including parathyroid hormone (PTH), 1,25(OH)₂D, and fibroblast growth factor 23 (FGF23). Calcium and phosphorus are also major modulators of 1-hydroxylase and 24,25-hydroxylase activity through their effects on PTH and FGF23. 25(OH)D₃, 25-hydroxyvitamin D₃. Adapted from PubChem, National Center for Biotechnology Information, U.S. National Library of Medicine (www.ncbi.nlm.nih.gov/pc complication).
the effects of vitamin D on epidermal, neuromuscular, cardiovascular, metabolic, immunological, maternal/fetal, and neoplastic tissues. In Fig. 2, the metabolic pathway of vitamin D, including the various steps in its activation and degradation, are depicted. It was assumed that exposure of the skin to ultraviolet (UV) radiation drove the conversion of 7-dehydrocholesterol to cholecalciferol (Fig. 2, step 1). The photo-production is subject to a variety of factors including amount of UV exposure (latitude, season, and use of sunscreen and clothing), ethnicity (skin pigmentation), and age. After the photochemical conversion of 7-dehydrocholesterol to previtamin D3 and its thermal isomerization to vitamin D3, it binds to the vitamin D-binding protein (DBP), and is transported to the liver where a hydroxyl group is attached at the carbon-25 atom (i.e., C-25) to generate 25(OH)D (Fig. 2, step 2). A number of 25-hydroxylases have been reported including cytochrome P450 CYP27A1 and CYP2R1. CYP2R1 is probably the major enzyme required for 25-hydroxylation of vitamin D3, at least in humans. Much remains unknown about the 25-hydroxylase enzymes including the significance of their reported presence in skin, kidney, and intestine. In the absence of severe hepatic dysfunction, 25-hydroxylation of vitamin D is not usually rate limiting. However, in mild to moderate liver impairment, the associated fat malabsorption can cause vitamin D deficiency. In contrast, 1α-hydroxylation is the major rate-limiting step in synthesis of 1,25(OH)_2D (Fig. 2, step 3). Synthesis of 1,25(OH)_2D is tightly regulated and is mediated by the enzyme 1α-hydroxylase. Factors regulating 1α-hydroxylase in kidney are shown. Due to its sequence similarity to CYP27A1, the gene encoding 1α-hydroxylase was called CYP27B1. Its role was demonstrated in 1998 by the development of rickets and reduced circulating 1,25(OH)_2D levels in four patients with gene mutations for this enzyme. Cyp27B1-null mice also develop rickets with reduced levels of circulating 1,25(OH)_2D. CYP27B1 mRNA is expressed in a number of vitamin D target tissues including kidney, skin, intestine, macrophages, and bone. Although its expression is relatively high in skin, the kidney is thought to be primarily responsible for circulating levels of 1,25(OH)_2D. This is supported by 1,25(OH)_2D deficiency in people with renal failure. However, this has not been conclusively proven with renal-specific CYP27B1 deletion. The presence of CYP27B1 in other cell types, especially macrophages, is demonstrated by the fact that people with granulomatous diseases can have elevated 1,25(OH)_2D levels.

Entry of 25(OH)D into the proximal renal tubular cells requires receptor-mediated uptake of DBP plus 25OHD at the brush border, degradation of DBP by legumain, and endocytic internalization and translocation of 25(OH)D to mitochondria. Megalin, a member of the low-density lipoprotein receptor family, is required for reabsorption of filtered DBP-bound 25OHD. It is in the mitochondria that 1α-hydroxylation of 25(OH)D into its biologically active form, 1,25(OH)_2D, occurs. A number of factors contribute to the tight regulation of 1α-hydroxylase enzyme expression and activity in the kidney (Fig. 2). These include calcium, PTH, calcitonin,
growth hormone (GH), insulin-like growth factor-I (IGF-I), and FGF23. In addition, 1,25(OH)2D negatively regulates its own synthesis by suppressing 1α-hydroxylase expression in kidney and bone. There is also evidence to suggest that estrogen, progesterone, and prolactin may regulate 1α-hydroxylase activity. In macrophages, regulation of CYP27B1 is primarily cytokine mediated. The final important enzyme in the vitamin D endocrine system is 24-hydroxylase (CYP24A1). Found in nearly all cells and highly expressed by the kidney, CYP24A1 limits the amount of 1,25(OH)2D in target tissues by converting 1,25(OH)2D to inactive metabolites, including 1,24,25(OH)3D and calcitriol acid and by converting 25D to 24,25(OH)2D (Fig. 2, step 4). In addition to 24-hydroxylation, this multicatalytic enzyme is able to catalyze side-chain hydroxylations at the C23 and C26 positions. Recently, mutations in CYP24A1 were reported in six children with infantile hypercalcemia, thereby providing conclusive evidence of the importance of this enzyme in the in vivo regulation of vitamin D metabolism.

**VDR structure**

VDR is a member of a large family proteins (> 150 members) that includes receptors for the steroid hormones, T4, the vitamin A family of metabolites (retinoid), fatty acids, and eicosanoids. A large number of family members have no known ligands and are called orphan receptors. VDR is widely, although not universally, distributed throughout different tissues of the body. The human VDR has two potential start sites. A common polymorphism (Fok I) alters the first ATG start site to ACG. This polymorphism has been correlated with reduced bone mineral density (BMD) in some studies, whereas other genome-wide association studies have not found a strong signal for polymorphisms in the VDR gene and bone mass or fractures. The most conserved domain in VDR from different species and among the nuclear hormone receptors in general is the DNA-binding domain. This domain consists of two zinc fingers. The proximal (N-terminal) zinc finger confers specificity for DNA binding to the VDR, whereas the second zinc finger and the region following provide at least one of the sites for heterodimerization of the VDR to the RXR. The second half of the molecule if the ligand-binding domain (LBD), the region responsible for binding 1,25(OH)2D, but also contains regions necessary for heterodimerization to RXR.
At the C-terminal end is the major activation domain, AF2, which is critical for the binding to coactivators such as those in the steroid receptor coactivator and VDR-interacting protein (also known as Mediator) families. In mutation studies of the homologous thyroid receptor, corepressors were found to bind in overlapping regions with coactivators in helices 3 and 5, a region blocked by helix 12 (the terminal portion of the AF2 domain) in the presence of ligand. Deletion of helix 12 promoted corepressor binding while preventing that of coactivators. The LBD for VDR has been crystallized, and its structure solved. It shows a high degree of structural homology to other nuclear hormone receptors. It comprises 12 helices joined primarily by β-sheets. The ligand 1,25(OH)2D is buried deep in the ligand-binding pocket and covered with helix 12 (the terminal portion of the AF2 domain). Assuming analogy with the unliganded LBD of RXRα and the ligand-bound LBD of RXRγ, the binding of 1,25(OH)2D to the VDR triggers a substantial movement to helix 12 from open position to a close position, covering the ligand-binding pocket and putting helix 12 in position with critical residues from helices 3, 4, and 5 to bind coactivators.

**Nongenomic actions of vitamin D**

A variety of hormones that serve as ligands for nuclear hormone receptors also exert biologic effects through membrane receptors or the VDR situated outside of the nucleus. Examples include estrogen, progesterone, testosterone, corticosteroids, and thyroid hormone. 1,25(OH)2D also have rapid effects that be mediated by a distinct receptor which is on the membrane receptor. 1,25(OH)2D also has been shown to regulate calcium and chloride channel activity, protein kinase C activation and distribution, and phospholipase C activity in a number of cells including osteoblasts, liver, muscle, and intestine. A putative membrane receptor for 1,25(OH)2D—i.e., 1,25(OH)2D membrane-associated rapid response steroid-binding protein (1,25D-MARRSBP), also known as endoplasmic reticulum stress protein 57—has purified from the intestine, cloned, and sequenced, and blocking antibodies have been prepared that block the rapid actions of 1,25(OH)2D. However, these rapid actions of 1,25(OH)2D appear to require the VDR (ineffective in VDR null mice), which suggests that 1,25D-MARRSBP and VDR cooperate in mediating these acute actions of 1,25(OH)2D but without the need for new protein synthesis. In the latter case, analogs of 1,25(OH)2D that do not support genomic actions of 1,25(OH)2D do support these nongenomic actions, which suggests that the membrane VDR may have a different three-dimensional structure with a different binding pocket for its activating ligands.

**Growth and development**

Maternal vitamin D status regulates skeletal growth and development during fetal life. These effects partly persist in early childhood, as has been suggested in a longer prospective study. In these reports, tibia cross sectional area, bone mineral content or BMC remained larger in infants whose mothers had better vitamin D status during pregnancy. Besides genetic background, bone size is affected by various hormones and it has been shown that GH-IGF-I axis is responsible for bone size and periosteal expansion. Leptin may favor stem cell differentiation towards osteoblasts rather than adipocytes in infancy. Furthermore, vitamin D stimulates osteoblastogenesis in human mesenchymal stem cells and production of IGF-I in osteoblasts. In infants with rickets vitamin D supplementation increased serum IGF-I and accelerates linear growth.

**Obesity**

Obesity is a strongly correlated with vitamin D deficiency. The nature of this association is not yet clear, it may be that vitamin D deficiency contributes to fat accumulation by suppression of certain key enzymes in adipose tissue differentiation (e.g., lipoprotein lipase, fatty acid synthase). Vitamin D deficiency may also be a consequence of obesity. Vitamin D may be "sequestered" in fat tissue. This term has used as a possible explanation for why obese individuals had a smaller vitamin D increase than leaner individuals after UV exposure. The term "sequestration" means that vitamin D is tightly bound within fat tissue, but there is no evidence that this is the case. In contrast, lower vitamin D levels among larger individuals are better explained by total body weight than adipose tissue weight. This suggest that "dilution" may be a better word than "sequestration" to explain the lower vitamin D values of obese people. The study of 242 girls of the Bogota School Children Cohort, Colombia, their vitamin D levels were adjusted for baseline body mass index (BMI)-for-age z score, a measure that reflects larger weight for a given height and age, not absolute weight or body pool size. This finding could reflect residual confounding by body size. Larger girls could have lower 25(OH)D concentrations due to increased tissue dilution of vitamin D over their larger pool size and reach menarche earlier because their greater size reflects greater maturity and/or adiposity.

**Age at menarche**

A geographic north-south gradient in age at menarche was described; girls who live at higher latitudes appear to have an earlier menarche than girls who live closer to the equator. This pattern might be explained by differences in temperature, light-darkness rhythms, and socioeconomic conditions, it also corresponds with a geographic gradient on sun exposure that coincided with vitamin D status. Vitamin D deficiency is associated with the development of adiposity in children, and childhood obesity could be a risk factor for early puberty. Vitamin D might play a role in the timing of puberty. To investigate the relation between vitamin D and early puberty, by Villamor et al. used a subset of 242 girls (mean...
age, 8.8±1.6 years) from the Bogota School Children Cohort, which was comprised of 3,202 students (aged 5–12 years) who were representative of the population enrolled in the public school system in Bogota, Columbia (latitude 4°43′N). The cohort was followed for 2.5 years to determine associations between nutrition and health. The subset included girls in whom serum 25(OH)D had been measured at baseline in February 2006. Baseline vitamin D status was categorized as < 50 nmol/L (deficient, < 20 ng/mL), 50 and < 75 nmol/L, and 75 nmol/L (sufficient, > 30 ng/mL). Follow-up assessments were conducted, twice in 2006 and once yearly in 2007 and 2008, to determine menarcheal status. Baseline 25(OH)D deficiency was correlated with a decreased age of menarche. This relationship was partially attenuated after adjustments for age at baseline and BMI-for-age a score. Except this report, no prior studies have directly examined the association of age at menarche with vitamin D level. And a gradient effect has not been observed consistently worldwide. In Europe, the more northern latitudes are associated with later menarche, though this could be due to the stronger influence of genetic factors over environmental factors. Twin studies indicate that as much as 68% of the variance in age at menarche may be generally determined, and polymorphisms in the VDR gene may be involved. VDR knockout mice show both impaired ovarian development and alterations in vitamin D metabolite levels compared to wild-type mice. In humans, the A allele of the VDR Apal locus and the t allele of the VDR Taq 1 locus, which are linked, may be associated with earlier menarche.

Musculoskeletal development

The clinical and radiographic signs of rickets due to severe vitamin D deficiency have been well described. Bone mineral accretion may be compromised by vitamin D insufficiency (VDI), and vitamin D influences prenatal and postnatal linear growth. Vitamin D may also affect musculoskeletal development, as high-dose supplementation (50 μg/day) of schoolchildren aged 10–17 year-old in Beirut was found to increase lean tissue mass compared with children receiving lower-dose vitamin D (5 μg/day) after 1 year.

Regulation of immune responses and inflammatory diseases

The association of VDI with immune dysregulation is compelling, because 1,25(OH)₂D potentially modulates the activity of leukocytes and cytokine production. Many of the actions of 1,25(OH)₂D are anti-inflammatory and antiproliferative, including the downregulation of proinflammatory tumor necrosis factor-α synthesis and nonspecific reduction of T cell responsiveness. The clinical implications for children and adolescents are unclear, yet there is evidence that VDI in adults predisposes to obesity-related conditions such as insulin resistance, possibly related to the role of vitamin D in modulating chronic inflammatory responses. In vitro observations suggest that 1,25(OH)₂D suppresses T helper lymphocyte type 1 (Th1) cytokine production in favour of Th2 cytokines (Fig. 5). Administration of 1,25(OH)₂D prevented and arrested the Th1-mediated immune response implicated in diabetes pathogenesis in nonobese diabetic mice. Epidemiologic studies in Finland have found that vitamin D supplementation during infancy was associated with a reduced risk of type I diabetes, but an increased risk of atopic disease (Th2 mediated) in adulthood, suggesting that the effect of vitamin D on T cell development during infancy may have longterm clinical implications. Clinical trials to clarify these associations have not yet been reported.

Vitamin D status and the risk of lower respiratory tract infection

Rickets commonly co-occurs with pneumonia, yet few studies have explored the possibility of a direct causal role of VDI in susceptibility or severity of childhood acute lower respiratory infection (ALRI). Accumulating evidence points towards antimicrobial properties of vitamin D; for example, the expression of an innate antimicrobial peptide, cathelicidin antimicrobial peptide is dependent on 1,25(OH)₂D activity. A case-control study conducted in India showed that vitamin D deficiency was a significant independent risk factor for severe ALRI in children under 5 years of age. Among children aged 1–24 months in Edmonton, they did not find vitamin D deficiency alone to be associated with the risk of ALRI (mostly viral bronchiolitis) in a relatively vitamin D repleted group, but the combination of a hypofunctional polymorphic variant of the VDR and 25(OH)D concentration < 80 nmol/L was significantly associated with the risk of ALRI. In Northern Aboriginal communities at high risk of VDI, where an extraordinarily high incidence of severe infantile bronchiolitis requiring hospitalization has been reported, it remains possible that moderate to severe VDI contributes to immune dysregulation, which predisposes to over-exuberant host responses to viral pathogens.

Dietary vitamin D requirements of the child and adolescent

Dietary intake of vitamin D is necessary if endogenous synthesis is limited (e.g., northern latitude, clothing habits, or sedentary lifestyles that limit sunlight exposure). However, adequate vitamin D nutriture often depends on the consumption of commercially fortified products because vitamin D naturally occurs in foods that are scarce or infrequently consumed. Vitamin D₂ (ergocalciferol) is found primarily in UV-exposed fungi and some vitamin D supplements; vitamin D₃ (cholecalciferol) is found in some animal tissues (i.e., liver, sea fish oils, and egg yolks), is used in most fortified products (e.g., milk) and is the form produced...
endogenously in human epidermis.

Hollis and Wagner\(^\text{74}\) have convincingly contended that a 70 kg adult and a 1 kg premature infant have the same absolute dietary vitamin D requirements. In fact, doses of at least 50 μg/day (2,000 IU/day) may be required to maintain vitamin D sufficiency in adults\(^\text{75}\). A daily dose of 100 μg/day (4,000 IU/day) for 2–5 months was shown to be safe in adult.

The level of 25(OH)D in the blood is the best indicator of vitamin D status. There is consensus that levels below 25 nmol/L (10 ng/mL) qualify as deficient\(^\text{76}\), but beyond this is currently no standard definition of ‘optimal’ 25(OH)D levels\(^\text{77}\). There is also lack of standardization of methods used to measure 25(OH)D status, with different tests producing very different results\(^\text{78}\). Some scientists suggest that levels above 50 ng/mL (20 ng/mL) are ‘sufficient’, while 70–80 nmol/L (28–32 ng/mL) is ‘optimal’\(^\text{79}\). However, raising the definition of ‘deficiency’ or ‘sufficiency’ is currently inappropriate since no results from randomized trials suggest that maintaining such levels of 25(OH)D prevents chronic diseases. It is also unclear whether these levels are practical for all individuals. Given that various studies have found that that 25(OH)D levels plateau at around 70–80 nmol/L, with wide variation across individuals\(^\text{79}\). For example, a Hawaiian study found that half of healthy, young surfers had levels below 75 nmol/L despite extensive unprotected outdoor exposure and tanned complexions\(^\text{79}\). Most recommendations are daily 10 microgram vitamin D supplement for those at risk of vitamin D deficiency, including all pregnant and breastfeeding women, older people and those at risk of inadequate sun exposure. A daily vitamin D supplement of 7 micrograms is also recommended for all children aged 6 months to 5 years\(^\text{80}\). The importance of maintaining adequate vitamin D during pregnancy and breastfeeding suggests that women may choose to take up to 10 μg of vitamin D a day during these periods\(^\text{81}\).

**Vitamin D requirements for infant**

25(OH)D concentration of between 40 and 50 nmol/L should be considered for vitamin D sufficiency. For toddlers and
children older than 1 year of age. Estimated average requirement is 400 IU/day (10 μg/day). Dietary Allowance of 600 IU/day (15 μg/day) are proposed for infants less than 1 year. Breast milk contains limited amounts of vitamin D, so lactating mothers with high levels of vitamin D (2,000–4,000 IU/day) may maintain vitamin D sufficiency. Breastfed infants should be supplemented with 400 IU/d of vitamin D. In United Kingdom, infants up to 6 months of 320 IU/day (8 μg/day) for infants and children aged 6–36 months of 280 IU/day (7 μg/day).

Conclusions

Vitamin D is not only essential for bone health and growth, but also hormone mediating nonskeletal effects across a wide range of homeostatic functions. Pharmacokinetic studies and epidemiologic research that incorporates clinical and functional outcomes are needed to clarify the role of vitamin D in growth and development and the specific dietary vitamin D requirements among Korean children and adolescents.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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