Vitamin D: An Essential Micronutrient for Bone Health

Somchit Jaruratanasirikul, M.D.

Department of Pediatrics, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla 90110, Thailand.

ABSTRACT

Vitamin D is an essential micronutrient in children for bone mineralization and bone growth. There are two forms of natural vitamin D, vitamin D2 and vitamin D3. Natural vitamin D is obtained from 2 main sources, dietary vitamin D intake and cutaneous vitamin D synthesis from sunlight exposure. Natural vitamin D requires a 2-step enzymatic hydroxylation process to be turned into active form of 1,25-dihydroxyvitamin D, firstly, 25-hydroxylation in the liver, and secondly, 1α-hydroxylation in the kidneys. Although breast milk is highly nutritive containing adequate amounts of most important vitamins, it contains only a small amount of vitamin D, approximately 15–50 IU/L, which does not reach the recommended daily requirement of 400 IU for infants. Exclusively breastfed infants are at risk to develop vitamin D deficiency if sunlight exposure is limited. Despite the excess of sunshine for the whole year in Southeast Asian countries including Thailand, various studies have found that more than 30.0% of children and adolescents had vitamin D insufficiency. The factors associated with vitamin D insufficiency in children include maternal vitamin D deficiency, exclusively breastfed as infants, insufficient daytime outdoor activities, use of sunscreens, extensive skin coverage by clothing, and lack of vitamin D supplementation and dietary fortification. To prevent vitamin D deficiency in infants, a global consensus in 2016 recommended that vitamin D supplementation should be included in routine national health care programs along with other essential micronutrients and immunizations.

Keywords: vitamin D; vitamin D in breastmilk; vitamin D deficiency; vitamin D insufficiency

INTRODUCTION

Vitamin D is an essential micronutrient in children for bone mineralization and bone growth by regulation of calcium and phosphate metabolism. There are two forms of vitamin D which have nearly identical biochemical structures from different natural sources: vitamin D2 (or ergocalciferol, C28H44O) and vitamin D3 (or cholecalciferol, C27H44O). The native forms of vitamin D2 and D3 are...
inactive and have no biological effect. The natural sources of native vitamin D2 are from some dietary plants by synthesis from ergosterol found in shiitake mushrooms and that ergosterol converts to ergocalciferol by ultraviolet (UV) irradiation. The natural sources of native vitamin D3 are from direct sunlight ultraviolet B (UVB) exposure at wavelengths of 290–315 nm by cutaneous synthesis from 7–dehydrocholesterol in the skin, and from some kinds of animal foods such as oily fish (sardines, tuna, mackerel, salmon), cod liver oil, egg yolks, organ meats (liver, kidney). When native vitamin D enters the circulation, it requires a 2-step enzymatic hydroxylation process to become an active form of vitamin D (Figure 1), firstly by 25-hydroxylation in the liver to 25-hydroxyvitamin D [25(OH)D], and secondly, further by 1α-hydroxylation in the kidneys to the active form, 1,25-dihydroxyvitamin D [1,25(OH)₂D].

FUNCTIONS OF VITAMIN D

The active forms of both vitamin D2 and vitamin D3 have equivalent physiological functions in maintaining the serum calcium and phosphate levels in the normal ranges of 8.5–10.5 and 3.5–5.5 mg/dL, respectively. The physiological actions of 1,25(OH)₂D are on the vitamin D receptors which are located in 3 organs (Figure 2), 1) the duodenal epithelium, to promote intestinal calcium and phosphate absorption, 2) the proximal renal tubules, to increase renal tubular calcium and phosphate reabsorption, and 3) 2 different types of bone cells, osteoblasts, to promote calcium and phosphate accretion (or bone mineralization), and osteoclasts, to promote calcium and phosphate mobilization from bone (bone resorption) (the different functions of vitamin D in different bone cells are for bone modeling and bone remodeling to maintain normal bone shape during bone growth in children). When serum calcium is lower than the acceptable ranges from either inadequate calcium or vitamin D intake, the low level of ionized serum calcium then activates the parathyroid glands to increase the parathyroid hormone level (secondary hyperparathyroidism) in which the parathyroid hormone stimulates 1α-hydroxylase in the kidneys to produce 1,25(OH)₂D from circulating 25(OH)D. The elevated level of 1,25(OH)₂D then increases intestinal calcium absorption, enhances bone resorption, and increases renal tubular calcium reabsorption. (Figure 3)
Figure 2 Physiological action of active form of vitamin D

Figure 3 Physiologic function of vitamin D in maintaining calcium homeostasis
This physiologic loop of vitamin D function in maintaining calcium homeostasis indicates that sufficient 25(OH)D is essential to maintain adequate 1,25(OH)\(_2\)D synthesis and serum calcium levels. Hence, the sensitive serum parameters for early detection of vitamin D deficiency are a low level of serum 25(OH)D and an elevated parathyroid hormone (PTH) level.

As 1,25(OH)\(_2\)D functions as an active form, its half-life is short, only 4–6 hours, and its circulating level very low whereas 25(OH)D functions as a reservoir of 1,25(OH)\(_2\)D with a much longer half-life of 14–21 days and a circulating level about 1,000 times greater than 1,25(OH)\(_2\)D. Moreover, 1,25(OH)\(_2\)D is tightly regulated to keep it at a normal level even when total body vitamin D is insufficient due to secondary hyperparathyroidism, thus its serum level does not reflect vitamin D reserves.\(^1\)-\(^4\) Therefore, 25(OH)D, the major form of circulating vitamin D, is recommended as a marker for assessment of vitamin D status.\(^5\) According to the American Academy of Pediatrics (AAP)\(^6\) in 2008, and more recently the Global Consensus\(^7\) in 2016, the classification of vitamin D status as assessed by the 25(OH)D levels is summarized in Table 1.

### SOURCES OF VITAMIN D

Humans get natural vitamin D from 2 main sources, dietary vitamin D intake and cutaneous vitamin D synthesis from sunlight exposure.\(^1\)-\(^4\) Adequate endogenous synthesis from a natural form (or native form) of vitamin D to an active form of vitamin D is essential to normal bone growth, to maintain bone mineralization, and to prevent vitamin D insufficiency and rickets.

#### Dietary sources of vitamin D

Natural dietary sources of vitamin D2 include only a few kinds of plants, and vitamin D3 is naturally obtained only from some oily fish, cod liver oil, egg yolks, liver and kidneys of beef and pork. The most vitamin D3–rich food is oily fish such as salmon, sardine and mackerel which contain vitamin D3 of 100–300 IU per 100 g, cod liver oil with 400–1,000 IU per teaspoon, beef or pork liver and kidneys containing 0–500 IU per pound, and egg yolk at approximately 20 IU per yolk. The main source of vitamin D2 is from the Shiitake mushroom which contains 600–1,000 IU per 100 g.\(^8\) Fortified milk and infant formula contain vitamin D3 in amount of 200–400 IU per liter.\(^5\)

---

**Table 1** Classification of vitamin D status, based on 25–hydroxyvitamin D level\(^6\)-\(^7\)

<table>
<thead>
<tr>
<th></th>
<th>American Academy of Pediatrics 2008*</th>
<th>Global Consensus Recommendation 2016†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ng/mL</td>
<td>nmol/L</td>
</tr>
<tr>
<td>Vitamin D deficiency</td>
<td>&lt;15.0</td>
<td>&lt;37.5</td>
</tr>
<tr>
<td>Vitamin D insufficiency</td>
<td>15.0–20.0</td>
<td>37.5–50.0</td>
</tr>
<tr>
<td>Vitamin D sufficiency</td>
<td>20.1–100.0</td>
<td>50.1–250.0</td>
</tr>
<tr>
<td>Vitamin D excess</td>
<td>&gt;100.0</td>
<td>&gt;250.0</td>
</tr>
<tr>
<td>Vitamin D intoxication</td>
<td>&gt;150.0</td>
<td>&gt;375.0</td>
</tr>
</tbody>
</table>

*1 ng/mL = 2.5 nmol/L
Therefore, natural food sources of vitamin D are relatively minimal and not enough to reach the daily requirement of 400 IU/day. Even considering fortified vitamin D in dairy products, infants would have to take over 1 liter per day of infant formula to reach their requirement of 300–400 IU vitamin D. 

**Vitamin D from sunlight exposure**

As either vitamin D2 or D3, is found in limited amounts in only some kinds of foods, even fortified milk or dairy products, dietary sources of vitamin D have little impact on overall vitamin D status. Thus, the major source of vitamin D for infants and children is from natural sunlight exposure. 

The cutaneous synthesis of vitamin D3 depends on the amount and the duration of sunlight exposure of UVB radiation at wavelengths between 290 and 315 nm, the time of day the exposure occurs, the percentage of skin exposed to sunlight (not covered by clothing), skin pigmentation, and the use of topical sunscreen. 

The best time to achieve the highest efficiency of UVB radiation for vitamin D synthesis is between 10.00 and 15.00 o’clock with a minimum 15-minute sunlight exposure on at least one-fourth of the body area (over arms and face, or arms and legs/hands), which can produce adequate vitamin D synthesis in light-skinned populations. 

Infants and young children require shorter durations of sunlight exposure than adults to produce adequate quantities of vitamin D because of the relatively greater surface area compared to volume ratio and better capacity to produce vitamin D. A review by the AAP in 2008 found that 30 minutes of sunlight exposure per week for infants in diapers or 2 hours of sunlight exposure per week in fully clothed infants without a hat can maintain a sufficient vitamin D level of >11 ng/mL in white infants. 

Individuals or infants with heavier skin pigmentation need longer durations to sunlight exposure to achieve equivalent amount of cutaneous vitamin D synthesis. Various studies have found that Asian skin types require 3–4 times duration of sunlight exposure than Caucasians and African skin types need 6–10 times more. Skin fully covered by clothing with a veil and the use of topical sunscreens can block effective dermal vitamin D synthesis and is the main risk factor for vitamin D deficiency. 

It has been proven that topical sunscreen use can reduce cutaneous vitamin D production. 

**Vitamin D in breast milk**

Breast milk is highly nutritive containing adequate amounts of most important vitamins and immunological and growth factors. The World Health Organization recommends exclusively breastfeeding for the first six months of life. The Academy of Nutrition and Dietetics agrees that exclusively breastfeeding provides the best nutrition and health protection for the first six months of life, and that breastfeeding with complementary foods from six months until at least 12 months of age is the ideal feeding pattern for infants. 

However, human breast milk has been found to be low in certain nutrients such as vitamin D, iodine, iron, and vitamin K. Human breast milk contains little vitamin D, approximately 15–50 IU/L, and even lower amounts in vitamin D–deficient nursing mothers. Therefore, exclusively breastfed infants receive much lower amounts of vitamin D than the recommended dietary intake and are at higher risk to develop vitamin D deficiency if sunlight exposure is also limited. 

The amount of vitamin D that is transferred from mother to infant through human breast milk varies depending on the maternal dietary intake and serum 25(OH)D concentration. Maternal supplementation with 400–2,000 IU of vitamin D per day can increase the level of vitamin D in breast milk, but cannot achieve a sufficient 25(OH)D level in the infant. Several trial studies of supplementing 4,000–6,400 IU vitamin D3 daily for 6 months in nursing mothers found that this is safe for mothers and provides adequate maternal vitamin D intake and higher maternal circulating 25(OH)D levels to
meet infant requirements without adverse events. The Endocrine Society recommends a daily intake of 4,000–6,000 IU of vitamin D for lactating mothers to satisfy the vitamin D requirement in breastfed infants.

**Pregnancy and vitamin D in fetus**

Maternal health and nutritional status are positively correlated with fetal growth during pregnancy, and also infant growth during lactation by breastmilk nutrient composition. During pregnancy, the main source of fetal calcium is placental transfer from the mother independently of vitamin D, and only 25(OH)D crosses the placenta into the fetus while native vitamin D and 1,25(OH)₂D do not cross the placenta. Thus, the newborn is dependent on the maternal supply of only 25(OH)D during pregnancy. As the half-life of 25(OH)D is 14–21 days, its circulating level decreases rapidly within 2–3 months after birth. If vitamin D status is insufficient in breastfeeding mother, the 25(OH)D concentration in the neonate decreases rapidly into the deficient range. Thereafter, either exogenous vitamin D supplementation or cutaneous vitamin D synthesis through sunlight exposure is necessary to maintain vitamin D sufficiency.

**VITAMIN D INSUFFICIENCY AND DEFICIENCY**

Vitamin D is essential in maintaining bone health and bone growth. Young children, particularly infants, are a high risk age group for vitamin D deficiency as rapid bone growth occurs during this period. Over the last 20 years, prevalence of infantile nutritional rickets have been reported in many regions, both in developing and developed countries. Current global estimates suggest that 1 billion people worldwide have vitamin D deficiency or insufficiency, and since the clinical manifestations of vitamin D deficiency in infancy are not obvious or may be absent in cases with mild nutritional rickets, many studies have further suggest that this figure may be an underestimate. Despite an excess of sunshine for the whole year in many Southeast Asian countries located near the equator, various studies have found that more than 30.0% and may be up to 50.0% of children and adolescents in these countries had hypovitaminosis D including Thailand. The high prevalences of vitamin D insufficiency in those study populations could have resulted from several factors such as maternal vitamin D deficiency, exclusive breastfeeding, higher skin pigmentation, inadequate sunlight exposure due to decreased daytime outdoor activities, use of sunscreens, extensive skin coverage by clothing especially in Islamic women, and lack of vitamin D supplementation and dietary fortification.

Rickets is the clinical consequence of a long duration of defective mineralization from vitamin D deficiency in the growing skeleton. In vitamin D–deficient individuals, intestinal calcium absorption is poor resulting in hypocalcemia. In the early stage of vitamin D deficiency, hypocalcemia activates secondary hyperparathyroidism and parathyroid hormone stimulates 1α–hydroxylation in kidneys to produce more 1,25(OH)₂D resulting in increased intestinal calcium absorption, enhanced bone resorption, and increased renal tubular calcium reabsorption. Despite some degree of bone demineralization at this early stage of vitamin D insufficiency, radiographic studies do not show the typical features of rickets. When vitamin D deficiency continues, the individual will have further defective chondrocyte maturation and widening of the costochondral junctions resulting in the clinical feature of beading along the rib cage known as the classic rachitic rosary. (Figure 4) With progression of the disease, further decrease in bone mineralization occurs, particularly at the growth plates of the metaphysis and epiphysis, and later results in widening between the metaphysis and epiphysis and an irregular metaphysis border (flaring and fraying signs on radiograph). Moreover, the disorganization of the spongy bone in the metaphysis results in the protrusion of some non–mineralized bone cells into the metaphyseal plate causing cupping of the metaphysis. (Figure 5)
The diagnosis of nutritional rickets is made on the basis of history, physical examination, radiographs and biochemical measurements of calcium, phosphate, alkaline phosphatase, and parathyroid hormone levels, and is confirmed by low serum 25(OH)D concentration. Routine screening of 25(OH)D levels is not recommended for most children, except for those at a higher risk for vitamin D deficiency, including young infants, or in children who present with poor growth, or those who are hospitalized or institutionalized with limited sun exposure.\textsuperscript{6-8,30,31}

**PREVENTION OF VITAMIN D DEFICIENCY**

Vitamin D insufficiency is preventable in neonates and infants by supplementing pregnant and lactating women with vitamin D or by sufficient sunlight exposure of both mothers and infants, or by supplementing exclusively breastfed infants with vitamin D. As mentioned above, infants can get adequate amounts of vitamin D by sunlight exposure of 30 minutes per week wearing only a diaper or 2 hours per week when fully clothed without a hat.\textsuperscript{6,23}

However, due to the concern of sunburn and possible risk of skin cancer later in life, the AAP recommendations in 1999 suggest that infants younger than 6 months should be kept away from direct sunlight exposure.\textsuperscript{6,37} Traditional guidelines suggest that mothers with high amounts of vitamin D of 4,000–6,400 IU per day during pregnancy and lactation are required to increase both maternal and infant serum 25(OH)D concentrations to adequate levels\textsuperscript{27-29}, however, recent studies have reported that infants of mothers supplemented with vitamin D >2,000 IU per day had similar serum 25(OH)D concentrations as infants receiving 400 IU per day\textsuperscript{27-29}, and therefore, AAP 2008\textsuperscript{6} and recently, the global consensus 2016\textsuperscript{7} recommend that exclusively or partially breastfed infants should be given 400 IU vitamin D daily beginning within the first week of life regardless of being supplemented with formula, and this 400 IU vitamin D daily supplementation should be continued until the infant takes more than 1,000 mL per day of 400 IU vitamin D–fortified formula.\textsuperscript{5,7} Also, the global consensus 2016 recommends that lactating women should take dietary vitamin D supplementation 600 IU per day for their own needs rather than a high daily dose of 4,000–6,400 IU vitamin D for the needs of both the mothers and their infants.\textsuperscript{7} For universal prevention of vitamin D deficiency in infants, the AAP 2008 and the global consensus 2016 recommend that vitamin D supplementation should be incorporated in routine national health care programs along with other programs ensuring adequate essential micro-nutrients and immunizations.\textsuperscript{6,7}
CONCLUSION

Vitamin D is an essential micronutrient in children for bone mineralization and bone growth. Due to the rapid bone growth in the first year of life, the recommended daily requirement of vitamin D in infants is 400 IU per day. Although breast milk is highly nutritive and suitable for infants, it contains only 15–50 IU/L of vitamin D which is not adequate for bone mineralization, leaving the child at risk of vitamin D insufficiency. Factors associated with vitamin D insufficiency include maternal vitamin D deficiency, exclusive breastfeeding, insufficient daytime outdoor activities, use of sunscreen, extensive skin coverage by clothing, and lack of vitamin D supplementation. To prevent vitamin D deficiency, it is recommended that exclusively or partially breastfed infants should be supplemented with 400 IU vitamin D daily regardless of being fed vitamin D supplemented formula, and this 400 IU vitamin D daily supplementation should be continued until the infants take more than 1,000 mL of fortified formula per day. Vitamin D supplementation should be included in routine national health care programs to prevent the unrecognized vitamin D insufficiency.

ACKNOWLEDGEMENT

The authors thank Mr. David Patterson from the International Affairs Office of the Faculty of Medicine, Prince of Songkla University, for English editing of the manuscript.

REFERENCES

10. Itkonen ST, Erkkola M, Lamberg–Allardt CJE. Vitamin D fortification of fluid milk products and their contribution to vitamin D intake and vitamin D status in observational studies – A review. Nutrients 2018;10:1054.
28. Roth DE. Maternal postpartum high-dose vitamin D3 supplementation (6400 IU/day) or conventional infant vitamin D3 supplementation (400 IU/day) lead to similar vitamin D status of healthy exclusively/fully breastfeeding infants by 7 months of age. Evid Based Med 2016;21:75.