CORRELATION BETWEEN VITAMIN D DEFICIENCY AND LOW BODY HEIGHT

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ABSTRACT

The average height of the Indonesians population has increased a few centimeters for the last 50 years, although Indonesians are short. Indonesians adult population is averagely shorter than the modern World Health Organization (WHO) either male or female. Thus, when comparing the height of Indonesian children with several growth measurements, a significant portion of the children is below the critical limit. Nevertheless, associations between nutrition and growth have long been questioned. This review article study has collected several articles related to vitamin D and its effect on the bones developmental. These articles has been reviewed by 3 authors anonymously and distributed randomly to the authors. This study concludes that a low level of vitamin D can decrease calcium level, which in turn leads to inadequate mineralization of bones. Awareness of the significance of vitamin D is important for parents and their children. In Indonesia, deficiency of vitamin D becomes a health problem that threatens children. More further comprehensive reviews are required to provide a better understanding of vitamin D deficiency on skeletal and non-skeletal problems.

KEYWORDS

Children; Deficiency; Indonesian; Low body height; Vitamin D

INTRODUCTION

The average height of the Indonesians population has increased by 5 cm for the last 50 years, although Indonesians are short. Currently, Indonesian adult men are averagely 12 cm shorter than modern WHO reference males. A similar height discrepancy exists for young adult females. Furthermore, Indonesian child growth has been documented since the first half of the 20th century. Indonesian children are shorter than modern European children and also shorter than international standards. Thus, when comparing the height of Indonesian children using some charts (WHO child growth standards, the WHO growth reference for 5-19 years, CDC growth charts, NCHS growth curves, or UK-WHO growth charts), a significant portion of the Indonesian children fall below critical cut-off limits, and are considered “stunted” (1).

Nevertheless, associations between nutrition and growth have long been questioned. There is enough historical evidence from European countries of the late 19th until the early 20th century, from many wars and post-war studies showed that the average of short stature on those European populations was not caused by malnutrition. Leading Indonesian pediatricians question that the average short stature of Indonesian kids results from across the nation undernutrition, health hindrance, or financial disappointment. Utilizing WHO 2006 Growth Standard as the reference, the most recent Indonesian 2013 National Basic Health Survey (NHBS) watched 37.2% pervasiveness of hindered and 12.1% similarity of squandered kids younger than five years. Just 2.5% of the children were both squandered and hindered, a large portion of the kids was either short with typical weight (27.4%) or short yet overweight (6.8%). These immense errors raised doubt on the relationship between poor sustenance and ill health, and development. Indonesian pediatricians contend that a large portion of those alleged "hindered" kids is short for other than dietary or health reasons (1).

New studies of a high similarity of vitamin D inadequacy around the world have heightened the discussion about the appropriateness of current recommendations for ideal levels. An ongoing report applying the Vitamin D Standardized Program (VDSP) convention in 14 European populace examines revealed that 13.0% of the 55 844 people exhibited serum 25-hydroxyvitamin D (25OHD; the proportion

of vitamin D in the blood) all things considered, notwithstanding age group, ethnic blend and latitude. Be that as it may, in sunny countries, because of the since a long time ago held presumption that vitamin D lack is not an issue, populace 25OHD concentrations have not been routinely tried. All things considered, developing examination proposes that vitamin D lack may be a lot greater issue than expected, even in sunny locations. Besides, due to the number of components other than sunlight exposure that may influence vitamin D production, it might never again be suitable to accept that straight scope angle is the most significant determinant of vitamin D status. Those ongoing reports have started discussions with respect to the need to characterize country and ethnic-explicit recommendations for daylight presentation and vitamin D dietary admission in various pieces of the world (2). Furthermore, vitamin D deficiency in school-age children was also reported in Indonesia. This review article aimed to discuss the correlation of vitamin D deficiency with low body height (3).

MATERIALS AND METHODS

This review article study has collected several articles related to vitamin D and its effect on the bones developmental. Most of the recent updates in vitamin D topics are collected and reviewed. These articles has been reviewed by 3 authors anonymously and distributed randomly to the authors. All recent updates about vitamin D and its effect has included in this review. Any additional or new information has been checked and validated using the current theory.

RESULTS

Vitamin D

Vitamin D is as of now probably the hottest point in research and clinics, just as in regular day to day existence. Over the previous decades, researchers assembled overpowering proof showing that the watched worldwide vitamin D deficiency not just negatively affects the human skeletal matrix, yet in addition encourages improvement and movement of numerous ailment of development, including cardiovascular ailments, diabetes, immune system ailment, and malignant growth. This Special Issue, entitled "Vitamin D and Human Health", outlines late advances in the comprehension of pleiotropic action of vitamin D as eight thorough reviews. Besides, eight research papers give a new understanding of vitamin D research and feature new headings (4).

Vitamin D is a fat-dissolvable vitamin that is normally present in not many nourishments and accessible as a dietary enhancement. It is additionally delivered endogenously when bright beams from daylight strike the skin and trigger vitamin D blend. Vitamin D got from sun exposure, nourishment, and enhancements are biologically idle and should undergo two hydroxylations in the body for enactment. The first happens in the liver and changes over vitamin D to 25-hydroxyvitamin D [25(OH)D], otherwise called calcidiol. The second happens essentially in the kidney and structures the physiologically active 1,25-dihydroxyvitamin D [1,25(OH)2D], otherwise called calcitriol (5).

The active type of vitamin D (1,25(OH)2D3, calcitriol) manages calcium–phosphate homeostasis through the cooperation with vitamin D receptor (VDR). It affects the best possible working of the musculoskeletal, immune, nervous, and cardiovascular matrix.. A presentation of diets dependent on profoundly handled nourishment, an indoor way of life, and sun shirking enormously added to the advancement of the worldwide vitamin D insufficiency. A low degree of vitamin D is firmly associated with a diminished calcium level, which thusly prompts insufficient mineralization of bones with resulting improvement of rickets in kids or osteoporosis in grown-ups. It results in bone deformation, yet additionally in the high vulnerability of falls and bone fractures. Consequently, appropriate vitamin D supplementation as per late norms is fundamental for support of the body homeostasis. Regardless of enormous endeavors and aggregating information concerning the effect of vitamin D on human life, there is as yet the requirement for broad studies on molecular systems enacted by vitamin D. Then again, the clinical noteworthiness of vitamin D needs to check through a progression of enormous, randomized, controlled long-term dependent on the comparison of serum levels of 25(OH)D3 as opposed to dosages of supplementations (4).

Vitamin D advances calcium absorption in the gut and keeps up calcium and phosphate concentrations on empowering typical mineralization of bone and on forestalling hypocalcemic tetany. It is additionally required for bone development and bone remodeling by osteoblasts and osteoclasts. Without adequate

vitamin D, bones can turn out to be slim, weak, or misshapen. Vitamin D adequacy forestalls rickets in children and osteomalacia in adults. Together with calcium, vitamin D likewise shields more seasoned grown-ups from osteoporosis (4).

Not many nourishments in nature contain vitamin D. The tissue of greasy fish, (for example, salmon, tuna, and mackerel) and fish liver oils are among the best sources *(Table 1)*. Modest quantities of vitamin D are found in meat liver, cheddar, and egg yolks. Vitamin D in these nourishments is principal as vitamin D3 and its metabolite 25(OH)D3. Mushrooms with improved degrees of vitamin D2 from being presented to bright light under controlled conditions are likewise accessible (4).

Table 1. Several food sources of vitamin D

Food	IUs per serving*	Percent DV**
Cod liver oil, 1 tablespoon	1,360	340
Swordfish, cooked, 3 ounces	566	142
Salmon (sockeye), cooked, 3 ounces	447	112
Tuna fish, canned in water, drained, 3 ounces	154	39
Orange juice fortified with vitamin D, 1 cup (check product labels, as amount of added vitamin D varies)	137	34
Milk, nonfat, reduced fat, and whole, vitamin D-fortified, 1 cup	115-124	29-31
Yogurt, fortified with 20% of the DV for vitamin D, 6 ounces (more heavily fortified yogurts provide more of the DV)	80	20
Margarine, fortified, 1 tablespoon	60	15
Sardines, canned in oil, drained, 2 sardines	46	12
Liver, beef, cooked, 3 ounces	42	11
Egg, 1 large (vitamin D is found in yolk)	41	10
Ready-to-eat cereal, fortified with 10% of the DV for vitamin D, 0.75-1 cup (more heavily fortified cereals might provide more of the DV)	40	10
Cheese, Swiss, 1 ounce	6	2

Types of vitamin D:

- vitamin D2 (ergocalciferol) - present in certain nourishments and dietary enhancements
- vitamin D3 (cholecalciferol) - shaped in skin presented to bright light and present in certain nourishments and dietary enhancements
- 25-hydroxyvitamin D (25[OH]D, calcidol) - a primary flowing type of vitamin D, made through hepatic metabolism of vitamin D2 and D3
- 1,25 dihydroxyvitamin (1,25-[OH]2D3, calcitriol) - biologically active type of vitamin D (it advances intestinal calcium and phosphate assimilation, calcium homeostasis, and skeleton mineralization), made through renal metabolism of 25(OH)D (6).

Serum 25-hydroxyvitamin D (25[OH]D) measurement:
Measure serum 25(OH)D levels utilizing a substantial examination to assess vitamin D status (Strong recommendation).1,25 dihydroxy vitamin D (1,25[OH]2 D3) levels may not precisely reflect all-out body stores (7).

Vitamin D in The Body

The old-style function of vitamin D are to manage calcium-phosphorus homeostasis and control bone metabolism. In any case, vitamin D deficiency has been accounted for in a few chronic conditions related to expanded inflammation and deregulation of the immune system, for example, diabetes, asthma, and rheumatoid joint arthritis. These perceptions, together with exploratory investigations, propose a basic role for vitamin D in the balance of immune function. This prompts the theory of a disease-specific alteration of vitamin D metabolism and fortifies the role of vitamin D in keeping up a healthy immune system. Two key perceptions approve this significant non-old style activity of vitamin D: first, vitamin D receptor (VDR) is communicated by most of the immune cells, including B and T lymphocytes, monocytes, macrophages, and dendritic cells; second, there is a functioning vitamin D metabolism by invulnerable cells that can locally change over 25(OH)D3 into 1,25(OH)2D3, its active structure. Vitamin D and VDR flagging together have a suppressive role in autoimmunity and a calming impact, advancing dendritic cell and administrative T-cell separation and lessening T assistant Th 17 cell reaction and inflammatory cytokines secretion. The review condenses test information and clinical perceptions on the potential immunomodulating properties of vitamin D (8).

The role of vitamin D in the regulation of calcium-phosphate homeostasis and in the control of bone turnover is notable. Vitamin D status essentially influences skeletal health during development and in

grown-up age, its inadequacy during development prompts rickets, though during grown-up age it is dependable of osteomalacia and different level of osteoporo-malacia. Low vitamin D status builds bone turnover, diminishes bone density, and is related to expanded fracture. The most recent updates is the discoveries that vitamin D receptor (VDR) and the vitamin D enacting chemical hydroxylase (CYP27B1) are communicated in a few cells outside the bone and kidney, for example, in the digestive tract, platelets, pancreas, and prostate

A few cells engaged with the immune function express VDR and CYP27B1, this perception recommends that the active form of vitamin D, 1,25(OH)2D3, can control the immune function at various levels. Previous studies on the role of vitamin D in the regulation of the immune system have been published as of late *(Table 2)* (8).

Table 2. Recommended Dietary Allowances (RDAs) for Vitamin D

Age	Male	Female	Pregnancy	Lactation
0–12 months*	400 IU (10 mcg)	400 IU (10 mcg)		
1–13 years	600 IU (15 mcg)	600 IU (15 mcg)		
14–18 years	600 IU (15 mcg)	600 IU (15 mcg)	600 IU (15 mcg)	600 IU (15 mcg)
19–50 years	600 IU (15 mcg)	600 IU (15 mcg)	600 IU (15 mcg)	600 IU (15 mcg)
51–70 years	600 IU (15 mcg)	600 IU (15 mcg)		
>70 years	800 IU (20 mcg)	800 IU (20 mcg)		

* Adequate Intake (AI)

Risk factors that may influence vitamin D synthesis in skin incorporate (9):
• Deficiency of introduction to daylight
• Extensive attire inclusion
• High scopes in winter
• Extensive utilization of sunscreen
• Dark skin pigmentation, (for example, dark grown-ups and Hispanic grown-ups)
• Age

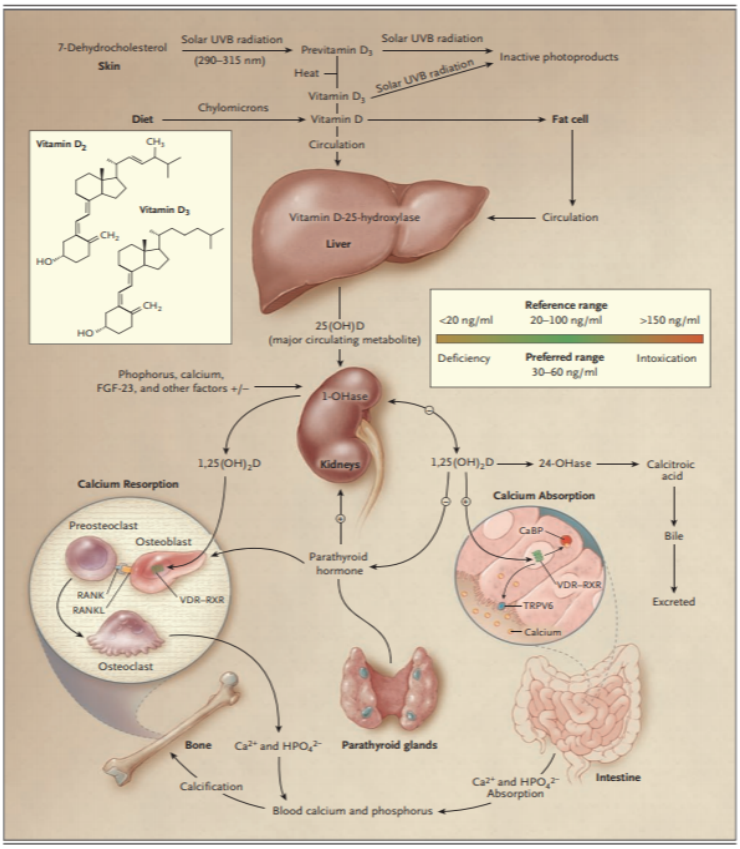
People receive vitamin D from exposure to daylight, from their eating regimen, and from dietary enhancements. An eating regimen high in sleek fish forestalls vitamin D inadequacy. Sunlight based ultraviolet B radiation (frequency, 290 to 315 nm) infiltrates the skin and changes over 7-dehydrocholesterol to pre-vitamin D3, which is quickly changed over to vitamin D3 *(Fig. 1)*. Because any abundance pre-vitamin D3 or vitamin D3 is decimated by daylight *(Fig. 1),* exorbitant exposure to daylight does not cause vitamin D3 inebriation (10). Hardly any nourishments normally contain or are invigorated with vitamin D. The "D" speaks to D2 or D3 *(Fig. 1)*. Both are utilized in over-the-counter vitamin D supplements, yet the structure accessible by solution in the United States is vitamin D2 (10).

Vitamin D from the skin and diet is metabolized in the liver to 25-hydroxyvitamin D *(Fig. 1),* which is utilized to decide a patient's vitamin D status; 25-hydroxyvitamin D is used in the kidneys by the chemical 25-hydroxyvitamin D-1αhydroxylase (CYP27B1) to its active structure, 1,25-dihydroxyvitamin D. The renal creation of 1,25-dihydroxyvitamin D is firmly directed by plasma parathyroid hormone levels and serum calcium and phosphorus levels. Fibroblast development factor 23, emitted from the bone, causes the sodium–phosphate cotransporter to be disguised by the cells of the kidney and small intestine and furthermore stifles 1,25-dihydroxyvitamin D synthesis. The proficiency of the ingestion of renal calcium and of intestinal calcium and phosphorus is expanded within the sight of 1,25-dihydroxyvitamin D *(Fig. 1)*(10).

Without vitamin D, just 10 to 15% of dietary calcium and about 60% of phosphorus is consumed. The connection of 1,25-dihydroxyvitamin D with the vitamin D receptor builds the productivity of intestinal

calcium assimilation to 30 to 40% and phosphorus retention to around 80% *(Fig. 1)* (10). In one investigation, serum levels of 25-hydroxyvitamin D were legitimately identified with bone mineral density in white, dark, and Mexican-American people, with the most extreme density accomplished when the 25-hydroxyvitamin D level arrived at 40 ng for every milliliter or more. At the point when the level was 30 ng for each milliliter or less, there was a huge lessening in intestinal calcium retention that was related to expanded parathyroid hormone. Parathyroid hormone upgrades the rounded reabsorption of calcium and animates the kidneys to deliver 1,25-dihydroxyvitamin D.(2–4,6) Parathyroid hormone likewise initiates osteoblasts, which invigorate the change of preosteoclasts into developing osteoclasts. Osteoclasts break down the mineralized collagen matrix in bone, causing osteopenia and osteoporosis and expanding the risk of fracture (10).

Figure 1. Metabolism of vitamin D



Vitamin D Deficiency

Many health care professionals concluded that the problems of vitamin D deficiency had been settled after the patient's daily diet had been improved with vitamin D and rickets looked to be solved. Nevertheless, rickets is just only the beginning of a bigger problem in vitamin D deficiency. Apparently, it is still common to find children and even adults with vitamin D deficiency. During pregnancy and childhood life, skeletal deformities and growth retardation may occur and amplify the risk of hip fracture later. Moreover, osteopenia and osteoporosis could be worsened in adult life resulting in osteomalacia and muscle weakness, thus increasing the risk of fracture. Fortunately, the discovery of vitamin D receptor and enzymes capable of transforming the inactive form of vitamin D, 25-hydroxyvitamin D, to the active form, 1,25-dihydroxyvitamin D, has been a great benefit in understanding the function of vitamin D. The most important is its ability in reducing the risk of chronic diseases, such as cancers, infection, autoimmune diseases, and cardiovascular diseases (10).

In spite of the absence of consensus on normal levels of 25-hydroxyvitamin D, experts mostly define vitamin D deficiency as a 25-hydroxyvitamin D level of less than 20 ng per milliliter (50 nmol per liter). Calcidiol (25-Hydroxyvitamin D) levels are oppositely related to parathyroid hormone levels until 25-Hydroxyvitamin D reach 30-40 ng per milliliter (75-100 nmol per liter). In addition, calcium transport in the intestine is increased by 45-65% in women when 25-hydroxyvitamin D levels were raised from an average of 20 to 32 ng per milliliter (50 to 80 nmol per liter). Given such information, a degree of 25-

hydroxyvitamin D of 21 to 29 ng for every milliliter (52 to 72 nmol per liter) can be considered to demonstrate an overall deficiency of vitamin D, and a degree of 30 ng for each milliliter or more prominent can be considered to show adequate vitamin D. Vitamin D inebriation is seen when serum levels of 25-hydroxyvitamin D are more prominent than 150 ng for every milliliter (374 nmol per liter) (10).

Deficiency of calcium and vitamin D in utero and in adolescence may forestall the calcium in the skeleton. Like vitamin D deficiency advances, the parathyroid organs are maximally animated, causing auxiliary hyperparathyroidism. Hypomagnesemia blunts this reaction, which implies that parathyroid hormone levels are regularly typical when 25-hydroxyvitamin D levels fall beneath 20 ng for each milliliter. Parathyroid hormone expands the metabolism of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D, which further exacerbates the vitamin D insufficiency. Parathyroid hormone likewise causes phosphaturia, bringing about a low-typical or low serum phosphorus level. Without a satisfactory calcium-phosphorus item, mineralization of the collagen matrix is reduced, prompting exemplary indications of rickets in kids and osteomalacia in adults (10).

Vitamin D deficiency brings variations from the norm in calcium, phosphorus and bone metabolism. In particular, it causes a reduction in the proficiency of intestinal calcium and the phosphorus ingestion of dietary calcium and phosphorus, bringing about an expansion in parathyroid levels. In auxiliary hyperparathyroidism, serum calcium is kept up at the ordinary range to the detriment of preparing calcium from the skeleton and expanding phosphorus squandering in the kidneys. This procedure causes a decline in bone mineral density, like in osteopenia and osteoporosis. The optional hyperparathyroidism additionally causes phosphaturia. This prompts a deficiency in calcium-phosphorus levels and a mineralization deformity in the skeleton. In kids with minimal mineral in their skeleton, this imperfection brings about rickets. In adults, the outcome is osteomalacia. Evaluated by bone mineral thickness scores, osteomalacia gives symptomatically detached or a throbbing painfulness in bones and muscles. In geriatric, vitamin D insufficiency causes expanding influence and successive falls, expanding the risk of fracture. Despite the upgrades in bone density and the anticipation of falls and fracture, vitamin D may have a few other putative advantages, remembering gainful impacts for the immune and cardiovascular systems (11).

Bone Development And Growth

The procedure of bone development is called osteogenesis or ossification. After progenitor cells form osteoblastic lines, they continue with three phases of improvement of cell differentiation, called proliferation, matrix maturation, and mineralization. In light of its embryological origin, there are two sorts of ossification, called intramembranous ossification that happens in mesenchymal cells that separate into osteoblast in the ossification community legitimately without earlier cartilage arrangement and endochondral ossification in which bone tissue mineralization is shaped through cartilage development first. In intramembranous ossification, bone development happens straightforwardly. Right now, cells multiply into regions that have high vascularization in early-stage connective tissue in the development of cell condensation or essential ossification centers. This cell will synthesize bone matrix in the fringe, and the mesenchymal cells keep on separating into osteoblasts. From that point onward, the bone will be reshaped and supplanted by developing lamellar bone. Endochondral ossification will shape the focal point of essential ossification, and the cartilage stretches out by the expansion of chondrocytes and testimony of the cartilage matrix. After this arrangement, chondrocytes in the focal district of the cartilage begin to continue with development into hypertrophic chondrocytes. After the essential ossification place is framed, the marrow cavity starts to grow toward the epiphysis. At that point, the resulting phases of endochondral ossification will occur in a few zones of the bone (12).

Bone keeps on changing its inside structure to arrive at the functional needs and these progressions happen through the action of osteoclasts and osteoblasts *(Table 3)*. The bone seen from its improvement can be separated into two procedures: first is the intramembranous ossification in which bones structure legitimately as crude mesenchymal connective tissue, for example, the mandible, maxilla and skull bones. Second is the endochondral ossification in which bone tissue replaces a previous hyaline osteogenesis 2 cartilage, for instance during skull base development. A similar developmental cell structure two kinds of bone arrangement and the last structure is not much different (12).

Bone development relies upon genetic and environmental components, including hormonal impacts, diet, and mechanical variables. The development rate is not generally equal in all parts, for instance, it

is quicker in the proximal end than the distal humerus in light of the fact that the internal pattern of the spongiosum relies upon the bearing of bone weight. The heading of bone arrangement in the epiphysis plane is dictated by the direction and distribution of the weight line. Expanded thickness or width of the bone is brought about by affidavit of new bone as circumferential lamellae under the periosteum. In the event that bone development proceeds, the lamella will be embedded behind the new bone surface and be supplanted by the Haversian canal system (12).

Table 3. Bone cell, their function, and locations

Cell type	Function	Location
Osteogenic cells	Develop in osteoblast	Deep layers of the periosteum and the marrow
Osteoblast	Bone formation	Growing portions of bone, including periosteum and endosteum
Osteocytes	Maintain mineral concentration of matrix	Entrapped in matrix
Osteoclasts	Bone resoprtion	Bone surfaces and at sites of old, injured, or unneeded bone

Human body must have vitamin D to assimilate calcium and advance bone development. Too little vitamin D brings about delicate bones in kids (rickets) and fragile, distorted bones in grown-ups (osteomalacia). Human need additional vitamin D for other significant body functions (12).

The role of steroid hormone metabolite 1,25-dihydroxyvitaminD (1,25 [OH]2 D) in skeletal development and improvement is essential. Besides, vitamin D metabolites inspire natural reactions through genomic and nongenomic instruments and influence numerous physiological matrix including bone, digestive tract, kidney, immunity, pancreas and metabolic homeostasis, cardiovascular, muscle, and brain system. From the musculoskeletal aspect, increasing bone mass from the earliest stages of life until reach the maximal bone mass at young age is a essential foundation to avoid the osteoporosis. Along these lines, information on the role of vitamin D in the musculoskeletal development in children will take a major role in any milestone to gains a high body height or stature and an increase of the bone mass (13).

Vitamin D is accessible as vitamin D2 from vegetable or as vitamin D3 from meat. In human, vitamin D3 can be combined after the presentation of the skin to daylight in the ultraviolet B spectrum. Be that as it may, endogenous synthesis of vitamin D is lessened by living at a higher scope, winter season, pigmented skin type, and diminished skin territory uncovered from apparel or sunscreen, way of life variety particularly with diminished open air exercises, and even environmental contamination. In this way, for some populaces, the arrangement of exogenous vitamin D is required. Metabolic process and functional impacts are comparable for vitamin D2 or D3, despite the fact that at high portions D3 might be naturally increasingly active and conceivably more toxic (13).

From a clinical point of view, there is a wide scope of plasma 25 OHD concentrations that can keep up great health. Apparently, the edge for the inadequate state is profoundly factor and clinical ill impacts happen presumably at extremely low plasma 25 OHD concentrations. Essentially, clinical signs of poisonous quality at high plasma 25 OHD concentrations additionally demonstrated independent fluctuation (13).

From a pragmatic perspective, it appears to be sensible to keep up plasma concentration over 50 nmol/L except if any high antagonistic or side effects for the skeletal and non-skeletal matrix are reported. Raising the negligible degree of plasma 25 OHD to 75 nmol/L decrease the hazard from vitamin D insufficiency. In any case, it would raise the incidence of vitamin D deficiency and the potential adverse effect from high portion vitamin D supplementation (13).

With the accessibility of 25 OHD models to approve the 25 OHD examines and improved investigation structures utilizing useful results, for example, development and bone mass estimations and considering the confounders that may bring about optional vitamin D inadequacy, it is conceivable that basic 25 OHD concentrations for both inadequate and lethality state can be better characterized with future studies (13).

CONCLUSIONS AND SUGGESTIONS

Fundamental knowledge regarding the relationship of vitamin D deficiency and low body height is important to be understood. Moreover, a low level of vitamin D can decrease calcium level, which in turn leads to inadequate mineralization of bones. In Indonesia, deficiency of vitamin D becomes a health problem that threatens children. Awareness of the significance of vitamin D is important for parents and their children. However, more comprehensive reviews are required to provide a better understanding of vitamin D deficiency on skeletal and non-skeletal problems.

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