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Chapter 9

Vitamin D Deficiency

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http://dx.doi.org/10.5772/63638

Abstract

Previously, known actions of vitamin D were confined to skeletal health, but accumulating evidence has consistently suggested that vitamin D has pleomorphic roles in overall human physiology. Hence, no other micronutrient deficiency in the modern times has gained as much global attention as vitamin D deficiency. In this chapter, the author reinforces what is already known in vitamin D and highlights several important findings in vitamin D research, with a special focus on one of the most vitamin D-deficient regions in the world, the Middle East, and Saudi Arabia, in particular.

Keywords: vitamin D, deficiency

1. Vitamin D physiology

Vitamin D plays an essential role in the regulation of calcium and phosphorus absorption and metabolism for bone health. Nevertheless, the influence of vitamin D is more than just mineral and skeletal homeostasis. The existence of vitamin D receptors (VDR) in several tissues and organs implies that vitamin D physiology encompasses beyond bone maintenance [1]. Furthermore, the enzyme responsible for the conversion of 25[OH]D to its biologically active form [Vitamin D (1, 25$[OH]_2$D)] has been recognized in several other tissues aside from kidneys with evidence growing that extra renal synthesis of 1, 23$[OH]_2$D may be just as important in regulating the cell growth of cellular differentiation via paracrine or autocrine regulatory mechanisms [2–4]. **Figure 1** shows the schematic overview of vitamin D metabolism that starts in the liver, where vitamin D is hydroxylated to 25(OH)D, the main circulating vitamin D metabolite used for vitamin D deficiency diagnosis [5]. Further hydroxylation of 25(OH)D to 1, 25(OH)D is catalyzed by 1α-hydroxylase which is expressed in multiple tissues and binds to vitamin D receptors that in turn regulates various genes [5].

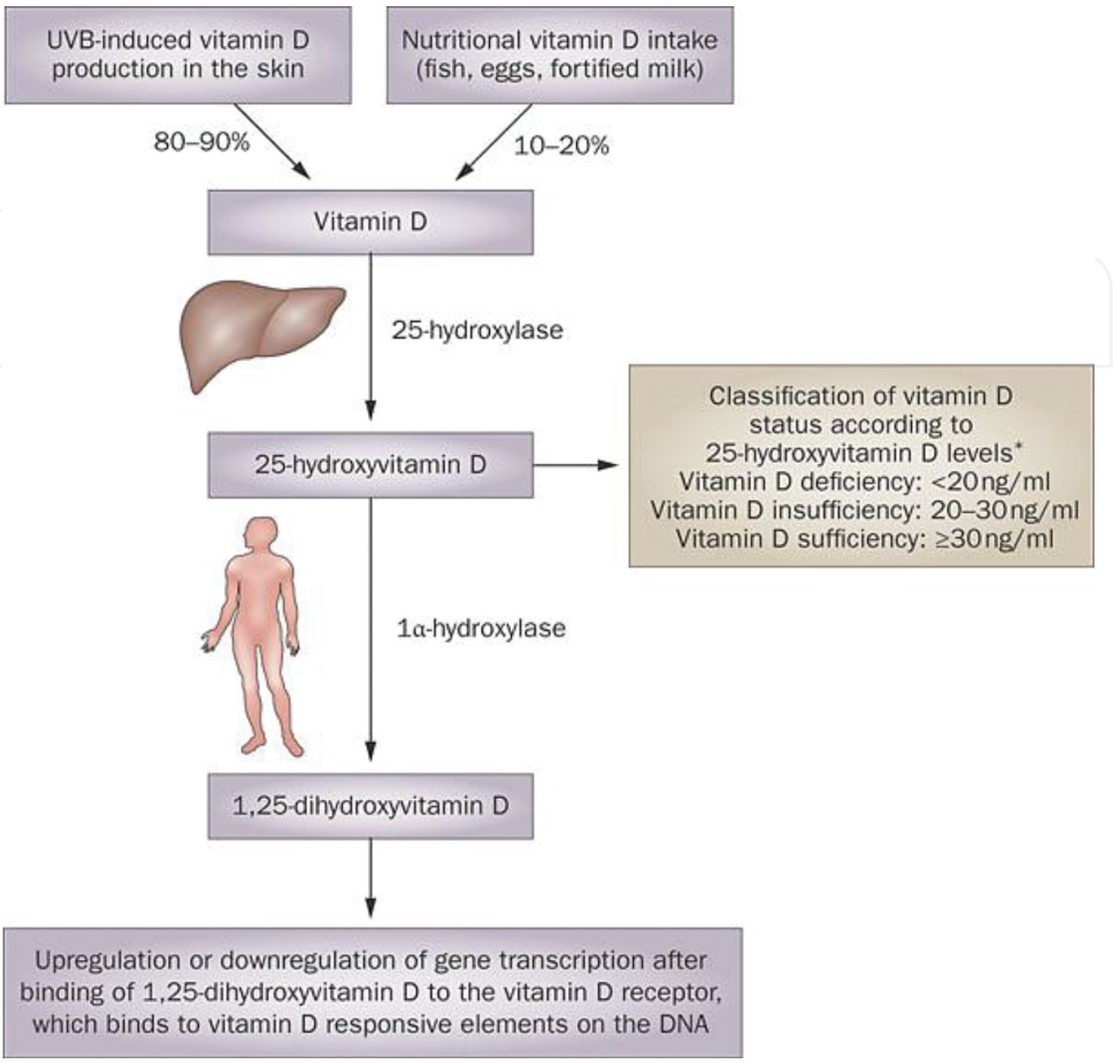

Figure 1. Vitamin D metabolism overview (figure reprinted from Pilz et al. [5]).

Vitamin D's etymology was obtained in the early part of the twentieth century after the discovery of the antirachitic effect of cod liver oil [6]. Then, the unidentified vitamin in cod liver oil was labeled as "D," similar to vitamins A, B, and C, which have been already identified. Synthesis of vitamin D from the skin provides most of the vitamin to the body (80–100%) and with adequate sunlight exposure, dietary vitamin may be unnecessary. However, time spent outdoors or the amount of incidental sun exposure on a regular basis, latitude, age, and skin color influence the cutaneous production of vitamin D and therefore affect vitamin D status. Foods rich in vitamin D include high-fat content fish (sardines, salmon, herring, and mackerel) that are meager and costly, since the study site is situated far from the coast, meat and egg, and fortified milk, juice and margarine. Even in some countries where certain foods are fortified with vitamin D, dietary intake of vitamin D is usually insufficient to maintain adequate levels of 25-hydroxyvitamin D [7]. Currently, there are three treatment modalities for vitamin D deficiency: sunlight, artificial ultraviolet B (UVB) radiation, and vitamin D supplementation [7]. Ideal 25-hydroxyvitamin D [25(OH)D] levels continue to be debated in

http://dx.doi.org/10.5772/63638

scientific circles and the definition of vitamin D deficiency changes almost yearly and ranges become higher than previously thought. As of this writing, the most commonly accepted definition of vitamin D deficiency is the one endorsed by the US Endocrine Society, that is, circulating serum 25(OH)D levels <50 nmol/l (<20 ng/ml) [8].

2. Vitamin D deficiency prevalence

Globally, vitamin D deficiency is widespread and is considered as an epidemic [9]. In a systematic literature review done by Hilger et al. in 44 countries involving more than 168,000 participants, 37.3% of the studies reported mean values <50 nmol/l, with the highest values reported in. Furthermore, it was only in the Asia/Pacific and Middle East/African regions where they observed age-related differences [10]. The recent study of Haq et al. also measured vitamin D deficiency prevalence in a single laboratory in United Arab Emirates, and this time involved 60,979 patients coming from 136 countries and revealed severe vitamin deficiency (25(OH)D <25 nmol/l) in 23% of the subjects tested and another 37% falling under mild deficiency (25(OH)D <50 nmol). This study is unique among other large-scale epidemiologic studies since it involved several nationalities in one setting and using only one laboratory, minimizing the need to adjust for known vitamin D cofactors such as geographical location and variability between measurements [11]. The Middle East and North African (MENA) region in general has a very high prevalence of vitamin D deficiency and is most prominent in women of varying ages [12]. The Kingdom of Saudi Arabia (KSA), being part of the MENA region, is not spared from vitamin D deficiency, despite the sunlight-rich environment.

Sedrani [12] was the first to document vitamin D deficiency in KSA, and this was observed among apparently healthy student males of King Saud University, Riyadh, KSA. Since then and in the same year [12], other studies using different healthy subpopulations have emerged, mostly women of child-bearing age [13–16]. In all studies, henceforth, vitamin D deficiency ranged from one out of five Saudis, to almost 100%. Consequently, at this time, rapid industrialization was taking place at KSA. Environmental risk factors in lifestyle such as daytime sleep and night time activities, work environments, which are sedentary and extreme weather conditions, may have been contributory [17]. Certain groups, such as the elderly, dark skinned, and/or veiled women and their children, are at particular risk of hypovitaminosis D [7, 18]. But more importantly, urbanization and tremendous socioeconomic growth has resulted in profound changes in the way of life during the last three decades, resulting in an increased and sustained incidence of obesity and type-2 diabetes mellitus [19], diseases known to elicit depressed circulating levels of vitamin D. As time passed, and with advancing technology and faster dissemination of information, epidemiologic studies on vitamin D deficiency across KSA has emerged. Through the initiatives of HRM, King Abdullah bin Abdulaziz Al-Saud, and the thrust for a knowledge-based economy, the research industry in KSA exponentially flourished and with it, several large scale studies paved way for exposing the worsening vitamin D deficiency in KSA [20, 21]. Furthermore, debilitating diseases associated with vitamin D

deficiency have started to emerge and become more prominent, including osteoporosis [22], type-2 diabetes mellitus [23, 24], and systemic lupus erythematosus [25] to name a few.

3. Diseases associated with vitamin D deficiency

Vitamin D deficiency has been consistently associated with hypertension, diabetes mellitus, cardiovascular disease, stroke, multiple sclerosis, inflammatory bowel disease, osteoporosis, periodontal disease, macular degeneration, mental illness, propensity to fall, and chronic pain and various cancers [26]. Most tissues have not only vitamin D receptors, but also hydroxylase enzyme that is required to convert 25(OH)D to the active form, 1α,25-dihydroxyvitamin D3 [27]. Therefore, vitamin D can affect tissues that are not involved in calcium homeostasis and bone metabolism. Almost all tissues in the body possess vitamin D receptors including brain, heart skeletal muscle, smooth muscle cells, pancreas, activated T and B lymphocytes, and monocytes [28].

The major diseases associated with vitamin D deficiency in KSA are listed in **Table 1**. Among these, the most widely documented include vitamin D deficiency rickets among Saudi children and type-1 diabetes mellitus and osteoporosis in adults. It is expected that with the increasing elderly Saudi population, the prevalence of chronic noncommunicable diseases, including osteoporosis in KSA, will increase if not remain steady, and uncorrected vitamin D deficiency being a risk factor for these diseases will play a major role in the progression of these diseases. It is worth to note that among these diseases, the emergence of increasing incidence of fibromyalgia or chronic muscle pain is mostly experienced by Saudi women, which showed significant improvement after treatment of high-dose vitamin D [52, 53], and reversal of metabolic syndrome manifestations among Saudi adults by mere increased sun exposure [54]. Several intervention studies are further required for the rest of the nonskeletal diseases where vitamin D is involved to determine whether vitamin D status correction will provide major beneficial effect.

Diseases	References
Chronic low back pain	[29]
Fibromyalgia	[30, 31]
Hyperparathyroidism	[32, 33]
Obesity and the metabolic syndrome	[21, 23, 24, 34, 35]
Osteoporosis/osteopenia/osteomalacia	[20–22, 36–44]
Sickle cell disease	[45, 46]
Systemic lupus erythematosus	[25]
Type-1 diabetes mellitus	[47–49]
Type-2 diabetes mellitus	[39, 50, 51]

Table 1. List of major diseases associated with vitamin D deficiency in Saudi Arabia.

4. Treatment

The two commonly available forms of vitamin D supplements are ergocalciferol (vitamin D_2) and cholecaleiferol (vitamin D_3). Some, but not all, studies suggest that vitamin D_3 increase serum 25[OH]D more efficiently than does vitamin D_2 [55–57]. The best indicator of vitamin D status is 25-hydroxyvitamin D because it is the major circulating form of vitamin D; it reflects cutaneous and dietary intake [58]. A nonfasting sample taken at any time of the day is suitable for the measurement of 25-hydroxyvitamin D status. Although calcitriol 1,25 dihydroxycholecalciferol is the active form of vitamin D, it is not an appropriate indicator of vitamin D status. It is usually normal or even elevated in patients with vitamin D deficiency. Although reliable and consistent evaluation of serum 25[OH]D level remains an issue, reliable laboratories currently exist, and efforts are in progress to improve and standardize assays to enhance accuracy and reproducibility at other laboratories.

Adults with 25 OHD 50–75 nmol/L require treatment with 800 to 1000 IU of vitamin D_3 daily. This intake was hypothesized to increase the vitamin D status to 7 nmol/L over a three-month period, but still, many individuals might require higher doses. In malabsorptive states, oral dosing and treatment duration depend on the individual patient's vitamin D absorptive capacity. Mega doses of vitamin D (10,000 to 50,000 IU daily) may be essential for postgastrectomy patients or patients with malabsorption. In cases where such patients remain deficient/insufficient despite such doses, they should be treated with hydroxylated vitamin D metabolites (since they are more readily absorbed) or with sun or sun camp exposure. All patients should maintain a daily calcium intake of at least 1000 mg (for ages 31 to 50 years) to 1200 mg (>51 years old) per day [59].

Since vitamin D is a fat-soluble vitamin, there are concerns about toxicity from excessive supplementation. Widespread fortification of food and drink from the 1930s to 1950s in the United States and Europe led to reported cases of toxicity. Increased levels of vitamin also raise calcium levels. Most of the symptoms of vitamin D toxicity are secondary to hypercalcemia. Early symptoms include, but are not limited to, gastrointestinal disorders like anorexia, diarrhea, constipation, nausea, and vomiting. Other reported symptoms include bone pain, drowsiness, continuous headaches, irregular heartbeat, loss of appetite, muscle, and joint pain are other symptoms that are likely to appear within a few days or weeks; frequent urination, especially at night, excessive thirst, weakness, nervousness and itching, and kidney stones [60].

5. Conclusion

This chapter provides a glimpse on the essential knowledge about this micronutrient vitamin D, as it is one of the most clinically important nutritional deficiencies. It is by no means comprehensive but nevertheless equips the reader with vital information on vitamin D with special attention in the Middle East and Saudi Arabia.

Conflict of interest

The author declares no conflict of interest.

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