

Vitamin D Deficiency in a Sunny Country: The Missing Chain

Review Article

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Abstract

Vitamin D deficiency continues to be an important health problem around the world. It has been reported in healthy children, young adults, middle age adults and elderly, and common among both males and females. Recent studies have shown that Vitamin D deficiency or insufficiency are associated with other pathologic conditions. Vitamin D plays an important role in skeletal development and bone health maintenance. Because the symptoms and signs of Vitamin D deficiency are insidious, or nonspecific, it often goes unrecognized and therefore untreated. In Saudi Arabia, with abundant sunshine, Vitamin D deficiency remains a major public health problem, due to lack of exposure to sun in the appropriate times.

This review, highlights the history of vitamin D and its deficiency in Saudi Arabia, causes, risk factors, pathophysiology, clinical presentation, and diagnosis and suggests strategies for its prevention and treatment.

Keywords: Deficiency; Vitamin D; Rickets; Sunny Country; Saudi Arabia.

Introduction

Vitamin D deficiency is an important health problem in bone development World wide [1-19].

Vitamin D deficiency results in a failure of osteoid to calcify in a growing person (Rickets), while failure of osteoid to calcify in adults is called osteomalacia. The term rickets comes from the old English word "wricken" meaning to twist or bend. Rickets occurred in humans as early as the second century AD. The disease was not considered a significant health problem until the industrialization of Northern Europe. In the 17th century, Whistler, De Boot and Glissen independently recognized that many of the children who lived in the crowded and polluted cities in Northern Europe developed a severe bone-deformity disease characterized by enlargement of the epiphyses of the long bones and rib cage, bowing of the legs, bending of the spine, and weak and toneless muscles. Figure 1 & 2.

Much debate has taken place over the definition of vitamin D deficiency. Most agree that a 25 (OH)D in concentration of

less than 50 nmol/L or 20 ng/ml is an indication of vitamin D deficiency, whereas a 25 (OH) D concentration of 51-74 nmol/L, or 21-29 ng/ml, is considered to be indicative of insufficiency. Concentrations of >30 ng/ml or >75 nmol/L are considered to be sufficient. Since 1650, scientists and physicians throughout Europe began to search for the cause of childhood rickets. In 1822, Sniadecki observed that children living in Warsaw had a high incidence of rickets, whereas children living in rural areas outside Warsaw did not have such an observation. He advocated exposure to sunlight as a means of curing the disease. The major breakthrough in understanding rickets was in the period (1910-1930) where the chemical structures of Vitamin D were determined [20-25].

Recent reports on the extra skeletal effects of vitamin D deficiency or insufficiency of vitamin D are increasing. It has been associated with autoimmunity, systemic lupus erythematosus (SLE), psoriasis, diabetes mellitus, multiple sclerosis, Crohn's disease, hypertension, dental caries, psychological disorders such as depression and Schizophrenia, cardiovascular disorders, many common cancers [6, 19, 23-35] and others.

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Figure 1. Photograph of the hand and wrist of a patient with rickets, showing swollen wrist (A) with the classical cupping and fraying of the humerus on X-ray (B).

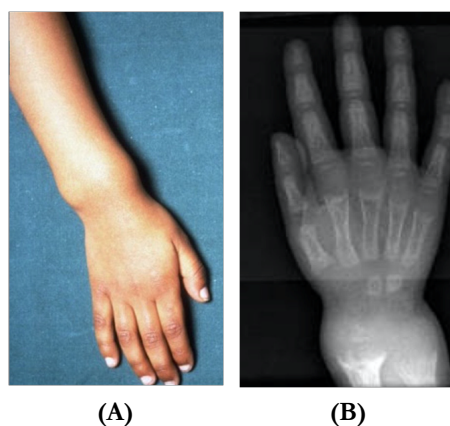


Figure 2. Photograph of a patient with rickets showing bowing of the legs (A) with classical radiological findings (B) of rickets.



Vitamin D Metabolism

Under ultraviolet radiation, solar ultraviolet B radiation, wavelength 290 to 315 nm penetrate the skin and convert, pro vitamin D₃ correct (7-dehydrocholesterol) in the skin to provitamin D₃ (Figure 3). Provitamin D₃ thermally isomerizes to Vitamin D₃ in the skin. A slow process (24 hours), a carrier globulin in the blood, Vitamin D binding protein, transports Vitamin D₃ from the skin to liver. In the liver, vitamin D₃ is hydroxylated to 25-hydroxy-vitamin D₃, which in turn is hydroxylated in the kidney to 1,25-dihydroxy vitamin D₃. The final hydroxylation process is facilitated by decreased calcium, decreased phosphorous or increased parathyroid hormone.

1, 25 Dihydroxy Vitamin D₃ increases intestinal calcium and phosphorous absorption, mobilizes calcium and phosphorous from bone, and possibly retains calcium and phosphorous through its renal effect. The combined effects of 1,25 dihydroxy vitamin D₃ are to increase calcium and phosphorous retention and enhance the conditions for bone mineralization. 1, 25 dihydroxy vitamin D₃ fulfills the criteria for classification as a hormone.

In the kidney, 24, 25 dihydroxy vitamin D (24,25 (OH)₂ D) is also produced from 25 hydroxy vitamin D₃. This metabolite is produced in conditions and phosphorous and its production is stimulated by 1,25 dihydroxy vitamin D₃. Possible functions of 24, 25 dihydroxy vitamin D₃ are intestinal calcium transport, chondrocyte protein synthesis, and bone mineralization [20, 22, 25, 36-38].

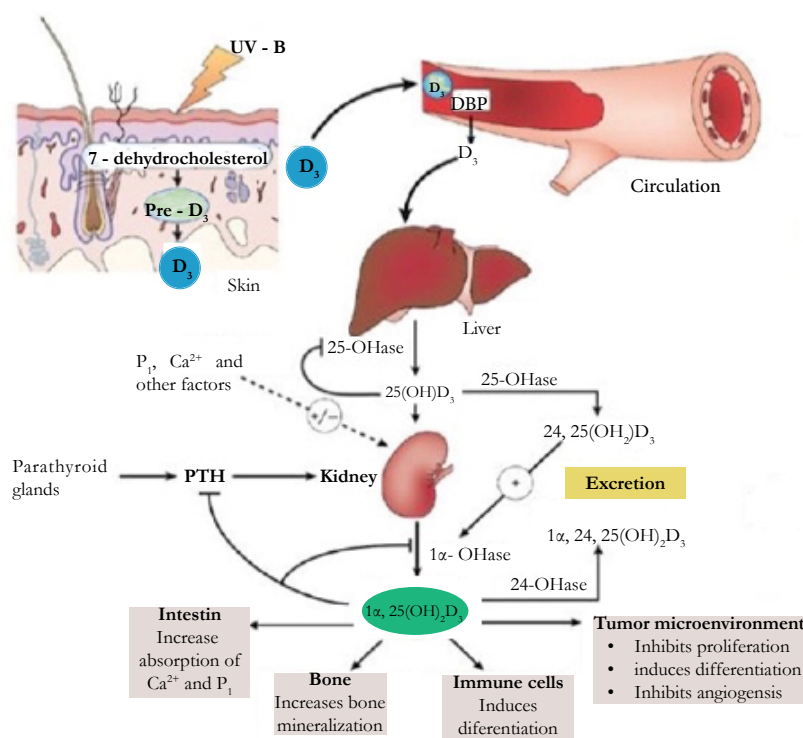
Vitamin D Deficiency in Saudi Arabia

AS early as 1982, Woodhouse and Norton [39] reported low vitamin D level in ethnic Saudi Arabian population. Later Sedrani et al., [40, 41] confirmed the earlier findings and also found that vitamin D levels were not related to one region, sex, age or season [42]. Recently, Al Dubayee et al., [43] in their national study on adolescents school based cross-sectional study through the country, showed that 95% had vitamin D deficiency. Kensarah and Azzeh [44], showed that the prevalence of vitamin D deficiency in school children in Makkah area was very high and the deficiency was higher in females by studying randomly a total of 148 health school children. Also, Siddiques and Kamfar [45] showed a similar results from the Western Saudi Arabia. Naeem et al., [46] found 28.3 % of 180 apparently healthy adults, were vitamin D deficient, 39.4% were vitamin D insufficient and only 32.2% had normal vitamin D levels. El-Idrissy et al., [47] and Al-Elig [48] from two different regions, North Western and eastern, Saudi Arabia showed a high prevalence of vitamin D deficiency. However, there was no significant change in prevalence since the report of Sedranil earlier [49-56]. Furthermore, several hospital based studies from different hospitals in different regions of Saudi Arabia indicated a very high prevalence of vitamin D deficiency [57-66].

Pathophysiology

The ossification of osteoid cells depends on adequate levels of ionized calcium and phosphate in the extracellular fluids which influenced by metabolites of vitamin D. As the vitamin D deficient,

Figure 3. Vitamin D metabolism.



ionized calcium depletion occurs, so does parathormone PTH – hypersecretion leading to increase bone resorption and poor mineralization, hence, serum alkaline phosphatase (ALP) activity is elevated [67-69], Figure 4, and the typical radiological findings [4, 70-73]. In rickets, anteroposterior radiography of the knees and posteroanterior radiography of the wrists show widening of growth plates, Typically the metaphysics are splayed, ragged, and concave, and the epiphyses appear as a cup. In osteomalacia, the changes are best seen in the subperiosteum, with pseudofractures as a characteristic, Figure 5. Bone scintigraphy is useful, but does not provide a diagnosis. Enhanced radiosotope uptake occurs when osteodesis is present hence; rickets and osteomalacia can produce a “superscan”, Figure 6.

Sunlight and Vitamin D

The exposure to ultraviolet radiation in the range of 290 to 315 nm from sunlight is the major source of vitamin D synthesis [74]. Saudi Arabia, being among the top concentrations of sunlight in the world, which lies between latitude 24-42° North and Longitude 46-43° East [57]. The weather is usually sunny throughout the year. However, Saudi ironically suffer from lack of vitamin D of which the sun is natural source [74].

The angle of which the sun reaches the earth has dramatic effect on the number of UVB photons that reach the earth’s surface. This is why when the Zenith angle is increasing during the winter time and in the early morning and late afternoon, little if any vitamin D3 synthesis occurs. Living at higher latitude is also associated with vitamin D3 deficiency. The best time for sun exposure to maximize vitamin D absorption and synthesis is between 9 AM and 3 PM during the winter, and between 8 AM and 10 AM and 2 PM and 4 PM during the summer. The recommended period of exposure to sun is 15 - 30 minutes two to three days a week.

People with dark skin require exposure 3 to 5 times longer [75-79].

Risk Factors

The physicians should be familiar with the important major risk factors associated with rickets and osteomalacia. With the realization of those, coupled with a high index of suspicion, the care taker should be able to diagnose rickets and osteomalacia. The major risk factors are: [3, 6, 7, 30, 66, 74].

- Dark skin ethnic population
- Exclusively breast – fed infants
- Children and those aged over 65 years
- Pregnancy
- Obesity
- Lactating mothers
- Malnutrition or low milk or dairy products intake
- Vegetarianism
- Cold environment
- Living in countries at high latitude or crowded high rise buildings
- Family history of vitamin D deficiency
- Routine covering of the face and body
- Housebound or institutional
- Prematurity or small for gestational age
- Medications such as steroids and anticonvulsant drugs

Causes of rickets and osteomalacia

The following are the major causes of rickets and osteomalacia.

- **Primary vitamin D deficiency**
 - o Classic vitamin D deficiency – infants and puberty

Figure 4. Pathophysiology of Vitamin D.

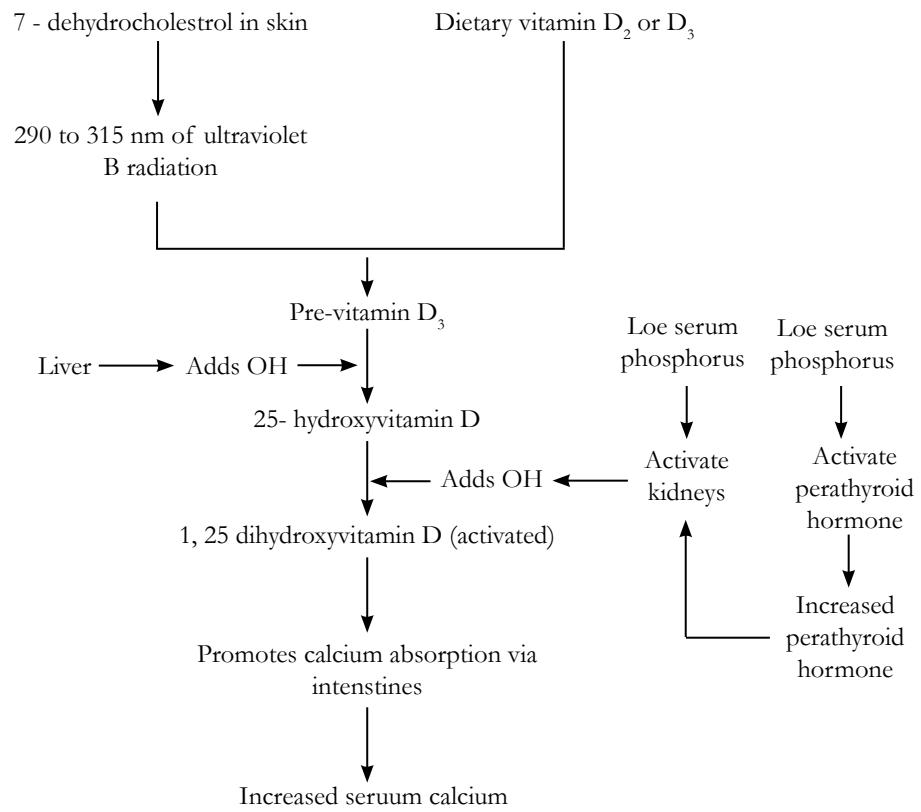
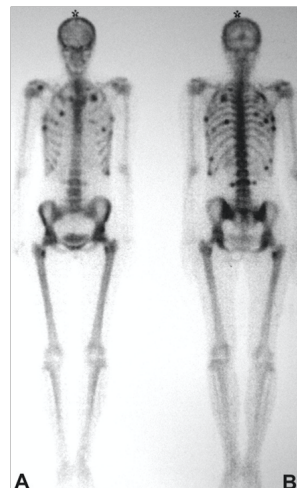


Figure 5. Anteroposterior view of the pelvis , showing Looser’s zone (pseudofracture) in the femur in a patient with osteomalacia.



Figure 6. A whole body Tc^{99m} scan (A) and (B), in a patient with osteomalacia. Note, the multiple hot spots ‘superscan’ i.e. multiple stress fractures in various areas of the body.



- o Exclusively breast fed
- o Immigrant adults in industrialized countries
- o Decreased exposure to sunlight
- o Use of sunscreen
- o Elderly, housebound and institutionalized groups
- o Pregnancy and lactation
- o Food faddist or reduced dietary intake.
- o Morbid obesity
- **Secondary vitamin D deficiency**
 - o Partial gastrectomy
 - o Small bowel malabsorption syndromes (e.g. coeliac disease)
 - o Hepatobiliary disease
 - o Pancreatic insufficiency
 - o Chronic renal failure
 - o Metabolic acidosis
 - o Drugs and toxins
 - Anticonvulsants
 - Phosphate – binding antacids (e.g. aluminum hydroxide)
 - Bisphosphonate (etidronate sodium)
 - Steroid
 - Flouride
- **Miscellaneous forms**
 - o Calcium depletion
 - o Magnesium depletion
 - o Primary hyperparathyroidism
 - o Oncogenic
- **Hereditary forms**
 - o Hypophosphataemia (X-linked, autosomal dominant and recessive forms)
 - o Vitamin D-dependent rickets Type 1 and Type 2
 - o Proximal renal tubular disorders (Fanconi’s dyndrome)
 - o Distal renal tubular disorders (renal rickets with nephrocalcinosis and dwarfism)
 - o Hypophosphatasia
 - o Osteopetrorickets

Clinical manifestation of rickets and osteomalacia

Rickets and osteomalacia may manifests with a constellation of symptoms and signs of which muscle weakness and bone pains and tenderness were among the commonest. Rickets manifests

during growth and the signs are most prominent in areas where bone growth is most rapid, such as swollen wrists and ankles or bow legs. Short stature, bow - legs deformities, craniotabes, and hypocalcemic tetany are important features. While in osteomalacia in adolescents and adults may cause non-specific symptoms.

A high index of suspicion in the right clinical context is necessary for diagnosis. An underlying etiology is often suggested by detailed medical history [1-3, 6, 80].

Treatment and Prevention

Once laboratory and radiologic tests confirmed the diagnosis of vitamin D deficiency rickets or osteomalacia. Vitamin D supplementation, (Table), Until serum alkaline phosphatase level and skeletal deformities return to normal. Calcium should also be supplemented. Additionally, recommending a diet rich in calcium are vitamin D is advisable.

Currently, no clear recommendation whether or how to screen for vitamin D deficiency rickets or osteomalacia. Both patients and physicians need to be aware of the problem and the known risk factors. Therefore, efforts to encourage exposure to sunlight in the appropriate time, and a diet rich in vitamin D and calcium can help to prevent vitamin D deficiency. Vitamin D is found in large amounts in fortified dairy products, such as milk and yogurt, cereals, bread, egg yolks and fish oils. Finally, patients on anticonvulsant medications or steroid should be screened periodically for ostemalacia and rickets and also if they are at a high risk should be started on vitamin D and calcium supplements as prophylaxis. Therefore, in summary education measures, appropriate vitamin D and calcium supplement, and appropriate sun exposure mandatory to prevent osteomalacia and rickets [7, 80-88].

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Table: Pharmaceutical preparations of vitamin D and active metabolites.

	Calciferol	Dihydrotachysterol	Calcifediol	Calcitriol	Alfacalcidiol
Drug	Vitamin D ₃ and D ₂	DHT	25-Hydroxyvitamin D ₃	1, 25 (OH) ₂ D ₃	1a(OH)D ₃
Form and preparation	Capsules, 0.25 mg & 0.25 mg	Liquid 0.25 mg/ml	Capsules, 20 & 50 µg	Capsules, 0.25 & 0.50 µg Injection, 1µg/ml liquid 1µg/ml	Capsules, 0.25, 0.50 & 1 µg liquid 2 µg/ml Injection, 2µg/ml in propylene glycol
Time to maximum effect	4-10 weeks	2-4 weeks	4-20 weeks	0.5-1 week	0.5 – 1 week
Persistence of effect after cessation	6-30 weeks	2-8 weeks	4-12 weeks	0.5-1 week	0.5-1 week

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