An Overview on Vitamin D Deficiency Diagnosis and Management in Primary Health Care Settings: Simple Literature Review

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ABSTRACT

Background: Vitamin D is an important, fat-soluble, vitamin that is integral in the calcium metabolism as a whole and integral in the overall bone metabolism. Deficiency in this vitamin may lead to clinical diseases mainly osteoporosis, osteomalacia and rickets. Major concerns of this condition has grown higher and higher in the medical field, and locally, in the Middle East and North Africa; up to 81% of people, from various age groups, have this deficiency. Moreover, internationally, it is estimated that up to 1 billion people have clinical and subclinical deficiency. **Objectives:** WThe purpose of this study is to review the literature regarding the physiology of vitamin D and its deficiency consequences, risk factors, clinical features, diagnosis, and management. **Methodology:** PubMed database was used for articles selection, from where the papers were obtained and reviewed. **Conclusion:** Vitamin D deficiency has been established as a cause behind many diseases and been associated with many other issues. Raising the public awareness about this disease and the possible symptoms can be a huge factor to prevent complications. Treating this deficiency is possible by means of supplements and the clinician shall encourage people for adopting new lifestyles. Follow-ups by the family physicians are important because doses may change dependent on each case. New large- scale studies concerning the full scope of the effects of this disease, recommended dosage, and diagnosing values, are being done to fully understand this prevalent condition.

Key Words: *Vitamin D deficiency, Diagnosis, Clinical Features, Management*

eIJPPR 2020; 10(6):127-131

HOW TO CITE THIS ARTICLE: Eman Hamed A Albalawi, Abdulkarim Ibrahim Al Shadookhi, Adel Ahmed Bahumid, Abdulaziz Mohammed Hamdi, Mohannad Nasser Alqwayee, Ohoud Owayedh Almutairi and *et al.* (2020). "An Overview on Vitamin D Deficiency Diagnosis and Management in Primary Health Care Settings: Simple Literature Review", International Journal of Pharmaceutical and Phytopharmacological Research, 10(6), pp.127-131.

INTRODUCTION

Vitamin D is an important, fat-soluble, vitamin that is integral in the calcium metabolism as a whole and integral in the overall bone metabolism [1, 2]. Deficiency in this vitamin may lead to clinical diseases mainly osteoporosis, osteomalacia and rickets. Major concerns of this condition has grown higher and higher in the medical field, and

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
Received: 11 July 2020; **Revised:** 11 December 2020; **Accepted:** 12 December 2020

locally, in the Middle East and North Africa; up to 81% of people, from various age groups, have this deficiency [3, 4]. Moreover, internationally, it is estimated that up to 1 billion people have clinical and subclinical deficiency and some literature considered it a pandemic [5, 6]. Thus, some measures have been taken in order to help for limiting this issue. For example, milk is fortified with vitamin D in many countries, which results in eradicating rickets in children in almost all the world. Unfortunately, the general knowledge and awareness about this deficiency is lacking in many countries, including Saudi Arabia, and this can be crucial for early diagnosis and thus prognosis [7]. This paper is aimed to review the current knowledge on vitamin D deficiency, etiology behind it, clinical features, diagnosis, and management of such cases.

METHODOLOGY

PubMed database was used for articles selection, and the following key terms used in the mesh ((“Vitamin D deficiency"[Mesh]) AND (“Diagnosis"[Mesh] OR "Management"[Mesh])). In regards to the inclusion criteria, the articles were selected based on inclusion of one of the following topics; Vitamin D deficiency pathophysiology, evaluation, management and diagnosis. Exclusion criteria were all other articles, which did not have any of these topics as their primary endpoint.

Review

It has been proved that Vitamin D plays a critical role in bone and mineral metabolism. Moreover, it is effective in prevention and the treatment of rickets and osteomalacia. Furthermore, it has been associated with other diseases, such as osteoporosis, cancer, cardiovascular diseases, diabetes, autoimmune diseases, and depression. This can be related to the fact that vitamin D receptors (VDRs) are expressed in almost every cell which make the many extra skeletal effects of vitamin D deficiency a wide field of research.

Physiology:

Generally, vitamin D has 2 varieties including ergocalciferol (D2) and cholecalciferol (D3) that both can be acquired via dermal synthesis and dietary intake. The most common source of vitamin D production is the ultraviolet-B (UV-B)-induced production in the skin with around 80% of the supply, and with dietary intake (e.g. eggs, fish, and/or vitamin D fortified food) providing a lesser role. D2 and D3 are then converted into 25-hydroxyvitamin D2 (25-OH-D2), and/or 25-hydroxyvitamin D3 (25-OH-D3). This process is done by hepatic enzyme 25–hydroxylase, in the liver. The next step is converting these 2 hydroxyvitamin variety into 1, 25dihydroxyvitamin D (1,25[OH]2D-or calcitriol-) which is the most active form of the vitamin. This process is done in the kidney by 1-alpha-hydroxylase enzyme. The resulted 1,25 dihydroxyvitamin D is the most active form (and has the highest affinity to related receptors) which carry out the main functions related to human physiology including increasing the rate of intestinal absorption of calcium, increasing bone resorption rate, and decreasing renal excretion rate of phosphate and calcium. Vitamin D metabolites circulating in the body mainly bound to vitamin D-binding protein (DBP), and to albumin and lipoproteins. However, less than 1% is circulating the body in its unbound -free- form, and most cells are dependent on this form, which diffuses through cell membrane, reaching the intracellular vitamin D receptors (VDR). Nevertheless, some tissues can still take up the DBP bound vitamin D metabolite megalin–cubilin system [8, 9]. Regarding the definition of vitamin D deficiency, serum (or plasma) levels of 25 hydroxyvitamin D are the best markers to assess it. This is primarily because it reflects the free fractions of the vitamin D metabolites due to its much longer life (about 3 weeks in comparison to 1 day in vitamin D), and higher serum concentration; however, bioavailable fractions may be more clinically informative. 1,25 dihydroxyvitamin D does not reflect the supply because it depends on many regulators of mineral metabolism such as parathyroid hormone (PTH), phosphate and/or fibroblast growth factor-23 (FGF-23) levels, and/or kidney function [10].

Etiology and Risk Factors:

As many diseases, genes play a role in this disease and this can be noted with certain malabsorption syndromes like celiac disease and cystic fibrosis that may lead to vitamin D deficiency. In some cases, children may present with hereditary vitamin D resistant rickets where their end organs show resistance to vitamin D itself. Moreover, other causes of malabsorption such as inflammatory bowel disease, short bowel syndrome, gastric bypass, and chronic pancreatic insufficiency still cause the deficiency in many cases. In the elderly it is noted that the oral intake of vitamin D from its food sources is less. Another possible etiology behind the disease is inadequate sun exposure since it is the main source of vitamin D. Hence, twenty minutes of sun exposure daily with more than 40% of the skin exposed provides enough protection against vitamin D deficiency. Some risk factors that are involved are aging due to less cutaneous synthesis, race (e.g. African Americans & Hispanics), excessive sun-screen usage, people working in institutions, and/or prolonged hospitalizations. Defective enzymes that are needed in the physiology of vitamin D – mentioned earlier- can be seen in conditions like chronic liver diseases (e.g. cirrhosis), renal failure, hyperparathyroidism, and 1-alpha hydroxylase deficiency [11, 12]. Some medications have been associated with this deficiency including carbamazepine, dexamethasone,

phenobarbital, spironolactone, rifampin, clotrimazole, and nifedipine. These medications induce the hepatic p450 enzymes that result in degradation of vitamin D [13].

Pathophysiology:

All the aforementioned factors may lead to chronic and/or severe vitamin D deficiency, which result in less calcium and phosphorus absorption in intestines. Thus, hypocalcemia is a direct result of this deficiency, and a secondary hyperparathyroidism is noted in these patients as well. Moreover, the resulted secondary hyperparathyroidism causes phosphaturia in these patients and further accelerates the bone demineralization process. All these mechanisms may result in many complications such as osteomalacia (in adults & children), osteoporosis (in adults), and rickets (in children) [14].

Clinical Features:

Unfortunately, most vitamin D deficiency patients are asymptomatic. Nevertheless, patients with even mild deficiency may develop complications such as osteoporosis mainly in the elderly. So patients may present to the primary health care center with fall and history of fractures, which shall alarm the clinician for the possibility of vitamin D deficiency. Moreover, patients may present to the family clinician with symptoms of secondary hyperparathyroidism when the vitamin D deficiency is severe or prolonged. These symptoms include bone pain, myalgias, fatigue, weakness, arthralgias, and fasciculations (muscle twitching). Nevertheless, the clinician shall not forget that children may present with this disease as well and usually presenting with lethargy, irritability, bone changes, developmental delay, and/or fractures. The exact effect of vitamin D deficiency alone on falls and fractures risk is controversial. Some studies showed small to no benefit at all when treated; however, this can be attributed to the fact that only sensitive people showed benefit, like high fractures and fall risk patients (e.g. long time hospitalized individuals) [11, 15].

Diagnosis and Screening:

Clinical suspicion is pivotal in this disease especially in children, because the diagnosis is easily made by the measurement of serum 25-hydroxyvitamin D. The cut-off number for deficiency of vitamin D is a controversial matter between studies and guidelines. Nevertheless, most studies regard levels of –serum or plasma- 25-OH-D below 75 nmol/L (or 30 ng/ml) as vitamin D deficiency. Moreover, severe deficiency is defined as any level below 25 (or 30 in some guidelines) nmol/L (or 10-12 ng/ml). In these patients, the risk of complications such as osteomalacia and nutritional rickets increases dramatically [16]. Nevertheless, some clinical guidelines, such as the Endocrine Society Task Force on Vitamin D, defined 50 nmol/L as the cut-off level of vitamin D deficiency. Additionally, many studies and clinical societies, including The Institute of Medicine (IOM -USA-), have defined the dietary reference intake for normal healthy people as 50 nmol/L per day. Institute of Medicine (IOM) further advices that vitamin levels of below 30 nmol/L (or 12 ng/ml) should be prevented with a wide-public-health approach if discovered in a significant number in society [17, 18]. If the deficiency is diagnosed, the primary health care physician shall check levels of parathyroid hormone and serum calcium immediately to evaluate the presence of secondary hyperparathyroidism. Patients may require a referral to a specialist if they come presenting with one of the complications, or if the primary health care center is not fully equipped to do these tests [19].

Regarding screening, it is not recommended to do screening on all people if there are no risk factors. However, all patients with any vitamin D deficiency associated disease, taking medication, and/or condition (e.g. bariatric surgery) should be screened. High-risk patients shall be screened as well on their check up with family physician, including the elderly, cases with low sun exposure, and patients with high risk of fall. This screening is paramount in order for early diagnose of the disease and prevention of any future complication [20].

Management:

The clinician should encourage the patient to change her/his lifestyle, consume more food with vitamin D, and try to be more exposed to the sun. However, generally the clinician starts management with vitamin D supplements and re-evaluation of the patient in two months. Various vitamin D metabolites and supplements are available, with different efficacy, half-life, and risk of toxicity. However, vitamin D3 (cholecalciferol) supplements have shown better results achieving the targeted 25-hydroxyvitamin D levels when compared to vitamin D2 (ergocalciferol). As a result, vitamin D3 supplements are favored as a treatment of choice in these cases. Based on the degree of deficiency and the presence of all underlying risk factors, the clinician decides about the dosage given to these patients. Family physician can start vitamin D3 supplement with an initial dose of 6,000 international units (IU) daily or 50,000 IU once a week, for two months. If the patient had a level of serum 25(OH)D higher than 30 ng/mL upon follow up, clinician can start a maintenance dose of 1,000 to 2,000 IU per day. Moreover, in high-risk adult patients (e.g. obese, African Americans, Hispanics, malabsorption syndromes) it is recommended to start Vitamin D3 supplements with 10,000 IU per day. and upon follow up, if these patients' serum 25(OH)D level was higher than 30ng/mL, a maintenance dose of 3000 to 6000 IU per day can be initiated. Children with this condition generally advised to start vitamin D3 supplements on 50,000 IU once a week or

2000 IU per day for a month and half. If the serum 25(OH)D level is higher than 30 ng/mL was children, the maintenance dose is 1000 IU per day. If patients did not show any improvement after using D3 and D2 supplements, calcitriol shall be considered by the physician. Other cases to consider calcitriol are patients with fat malabsorption or severe liver disease.The clinician should tightly monitor the serum calcium levels, because there is a higher risk of secondary hypercalcemia in patients taking calcitriol. Clinician should be clear with the patient not to exceed the recommended dose that results in toxicity. Patients show toxicity with 25-hydroxyvitamin D level more than 88 ng/mL; acute toxicity may cause acute hypercalcemia, which presents with confusion, vomiting, anorexia, polyuria, polydipsia, and muscle weakness. Patients who have chronic vitamin D intoxication may present with bone pain and nephrocalcinosis [11, 21, 22].

In terms of prevention, the American Academy of Pediatrics, recommends a 400 IU dose of vitamin D supplements per day, if the child is being breastfed and/or consumes less than 1 L of vitamin D-fortified milk. Generally, adults younger than 65 years of age with limited sun exposure shall take between 600 and 800 IU of vitamin D3 supplements daily. Moreover, adults who are 65 years of age should consume between 800 and 1000 IU of vitamin D3 supplements daily. Some studies have reported that a daily consumption of vitamin D supplements has been associated with lower overall mortality. However, according to Women's Health Initiative, vitamin D supplementation (and calcium) results in lower risk of all cancers, (including breast & colorectal cancer) but does not affect mortality [23-25].

CONCLUSION

Vitamin D deficiency has been established as a cause behind many diseases like rickets and osteomalacia and is associated with many other problems. Thus, early detection, screening the high-risk population and prevention are paramount for society. Raising the community awareness about the sources of vitamin D, possible symptoms, and risk factors of this disease can be a huge factor to prevent complications. Furthermore, despite the differences among guidelines and recommendations, the clinician does not miss deficiency cases (especially if severe), investigates possible causes, and monitors calcium and parathyroid hormone levels. Treating this deficiency is possible by means of supplements, and the clinician should encourage adopting new lifestyles by all patients. Follow up by family physicians is important because doses and management may change dependent on each case. New large-scale studies concerning the full scope of the effects of this disease, recommended dosage, and diagnosing values, are being done to fully understand this prevalent condition.

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