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Review Article

Vitamin D Deficiency in the Middle East, and it's Management in Primary Care

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Abstract

Introduction: Vitamin D deficiency is considered to be a medical concern that is prevalent worldwide. Despite that normal mean vitamin D (25(OH)D) concentrations in adult and elderly individuals are found in regions of North America, Asia Pacific, and Europe (which is about 20.4 to 28.9 ng per ml), the regions of Middle East and North Africa (MENA) are considered to have the lowest concentrations of vitamin D (which is about 13.6 to 15.2 ng/ml), for the same age groups, despite having relatively high sun exposure.

Aim of Work: In this review, we will discuss the most recent evidence regarding vitamin D deficiency in the Middle East, and its management in primary care.

Methodology: We did a systematic search for vitamin D deficiency in the Middle East, and its management in primary care using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com).

Conclusions: In the MENA region, the IOM RDA of 600 IU/day is not sufficient to bring 25(OH)D to the desirable level of 20 ng/ml; higher doses of 1750-2000 IU/day may be needed. In addition to the dose, the baseline 25(OH)D level significantly affects the response to vitamin D re- placement. These findings provide the needed information to formulate MENA specific vitamin D guidelines. Additional long-term safety and high-quality studies using intermediate to high vitamin D doses are required, and more solid evidence on the effect of vitamin D on various skeletal and extra-skeletal outcomes is still needed.

Keywords: *Vitamin D Deficiency; The Middle East; Management in Primary Care*

Introduction

Vitamin D deficiency is considered to be a medical concern that is prevalent worldwide. Despite that normal mean vitamin D (25(OH) D) concentrations in adult and elderly individuals are found in regions of North America, Asia Pacific, and Europe (which is about 20.4 to 28.9 ng per ml) [1], the regions of Middle East and North Africa (MENA) are considered to have the lowest concentrations of vitamin D (which is about 13.6 to 15.2 ng/ml), for the same age groups, despite having relatively high sun exposure [2].

Among adults, the typical predisposing factors for developing vitamin D deficiency are usually associated with older age, female sex, living in an area with a higher latitude, and having dark skin pigmentations [3]. Other predisposing factors, which are specific to the MENA region, have been demonstrated and studied, including multiparity status, concealing clothes style, seasons (winter in the Mediterranean region, summer in gulf countries), living in a relatively lower socioeconomic status, living in urban areas, and the absence of governmental regulation of food fortification with necessary vitamins [4]. In addition, several genetic factors could play an important role in the development of vitamin D deficiency in the MENA region [5].

Multiple scientific associations and societies have published different guidelines on the replacement of vitamin D in the general population. However, the IOF society was the only one to specifically assess the Middle East as an area that has a relatively high frequency of vitamin D deficiency, and therefore, needing increased doses of vitamin D replacement, of 2000 IU per day [6]. While the Institute of Medicine (IOM), on the other hand, defined the recommended dietary allowance (RDA) of vitamin D supplement among adults originating from North America to be a dose of 600 IU per day allowing more than ninety-seven percent of participants to achieve the wanted 25(OH)D concentration that is at least twenty ng/ml [7], the Endocrine Society (ES) guidelines, on the other hand, recommended the use of increase doses of 1500 - 2000 IU per day among the adults and the elderly, to achieve their target of vitamin D concentration that is thirty ng/ml [8].

In this review, we will discuss the most recent evidence regarding vitamin D deficiency in the Middle East, and its management in primary care.

Methodology

We did a systematic search for vitamin D deficiency in the Middle East, and its management in primary care using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). All relevant studies were retrieved and discussed. We only included full articles.

The terms used in the search were: vitamin D deficiency, the Middle East, management in primary care.

Vitamin D is a steroid hormone that modulates a wide range of molecular and cellular physiological functions, most importantly known are its beneficial effects on the musculoskeletal parameters. Rickets and osteomalacia are known to represent the short-term latency complications of vitamin D deficiency and osteoporosis is known to be the long-term complication of more chronic cases [9]. More solid evidence has also been supporting other atypical, extra-skeletal, beneficial effects of vitamin D on the immune system, the metabolism of fuel, cardiovascular disorders and neoplasms [9]. Additionally, correlation of vitamin D concentrations and decreased mortality rates have been described in literature [10].

Despite that rickets is considered to be almost eradicated in western regions, its frequency remains to be significantly high in regions of Asia, Africa and the Middle East and resurgence is also registered in ethnic minority groups in some Northern European countries [11]. On the other hand, vitamin D deficiency is generally prevalent around the world, but is again most usually seen in Asia and surprisingly the Middle East, despite its relatively high sunshine exposure [9]. Although these observations stem mostly from non-population-based analyses, they have in most cases, consistent across reviews over the last years [12]. these findings can be explained by the relatively high

frequency of certain predisposing factors for the development of vitamin D deficiency in this area. These predisposing factors include the typical risk factors, in addition to the concealed clothing style among females in general and in males from gulf countries specifically. The, absence of governmental regulation for food supplementation with vitamin D in this region has also been noted to be an important factor.

In later sections of this paper we will be systematically reviewing the frequency of rickets, osteomalacia and vitamin D deficiency, in the Middle East and North Africa (MENA) regions, evaluating important predictors and describing the effects of low concentrations of vitamin D status on relevant outcomes in studies from the region. Implications of the vitamin D guidelines published by the Institute of Medicine and the Endocrine Society in 2011 will be put in perspective taking into consideration the status of vitamin D in the MENA region [8].

Is there a genetic basis for low vitamin D levels and rickets in the MENA?

Lifestyle, specifically the exposure to sunlight, the diet and the use of different supplements, are considered to be important determinants of circulating vitamin D concentrations [13]. Recently, it has been determined that genetic factors might also play a role that can be up to fifty percent of inter-individual variability in vitamin D concentrations [14]. Several genetics factors related to vitamin D status were recently studied in a large genome wide association project of more than thirty thousand European individuals and using fifteen cohorts. Additionally, single nucleotide polymorphisms (SNPs) at or near six pre-specified vitamin D routes candidate genes were assessed. These include the vitamin D receptor (VDR), 1-α-hydroxylase (CYP27B1), 25-hydroxylase (CYP2R1), 24-hydroxylase (CYP24A1), vitamin D binding protein (GC, DBP) and 27- and 25-hydroxylse (CYP27A1) genes. The discovered genetic polymorphisms included variants near genes involved in the synthesis of cholesterol (DHCR7), hydroxylation (CYP2R1 and CYP24A1) and vitamin D transport (GC), and these might detect individuals who are at a higher risk of developing vitamin D deficiency. African Americans were found to be a subgroup at a relatively higher risk for low vitamin D concentrations. A recent study that investigated the associations between ninety-four three single nucleotide polymorphisms (SNPs) in five vitamin D pathway genes (GC, VDR, CYP2R1, CYP24A1, CYP27B1) and serum 25(OH)D in about four hundred African American and other four hundred Caucasian controls, found statistical associations for three SNPS, two in the vitamin D transport pathway and one in the hydroxylation pathway, only in African Americans [15].

As researchers expected, they detected a dose-dependent elevation in the MD and in the estimated WM 25(OH)D level achieved post-intervention. However, the increments per 100 IU per day of vitamin D were relatively lower as the total daily dose increased, indicating a plateau in the dose response at relatively higher doses. Intermediate and high doses of vitamin D increased 25-hydroxyvitamin D concentrations by 0.5 - 1 ng per ml for each 100 IU per day vitamin D. Studies from other Western countries have evaluated the elevation in 25(OH)D concentrations in response to increasing doses of vitamin D. Gallagher., *et al*. evaluated the impact of a wide range of vitamin D3 (400 - 4800 IU per day) in white post-menopausal females originating from Nebraska (baseline 25(OH)D concentrations fifteen ng per ml) [16]. The calculated increments per 100 IU per day vitamin D varied between 1.6 ng per ml for the lowest dose and 0.6 ng per ml for the highest dose. In addition, the vitamin D dose response curve demonstrated a plateau at forty-five ng per ml, at a dose that is higher than 3200 IU per day [16]. A previous meta-analysis published by Shabbidar., *et al*. comparing vitamin D doses to placebo, demonstrated in a subgroup analysis, that the MD in 25(OH)D concentrations achieved was lower with doses that were higher than 800 IU per day [MD 13.7 (28.1 - 37) ng/ml], when compared to those equivalent to 800 IU per day [MD 15.7(42.4-57.4) ng/ml] [17]. Previous meta- regression analyses conducted by the IOM and other groups from Europe demonstrated that following logarithmic transformation of the dose, the response to vitamin D supplementation was blunted at doses that were higher than 1200 IU per day, and reaches a plateau at a concentration of about thirty-two ng per ml [18]. These outcomes unequivocally prove that, among adults, the achieved 25(OH)D level elevations in parallel to the elevation in the vitamin D dose administered. On the other hand, the increments in 25(OH)D concentrations, per a hundred IU per day vitamin D, tend to reach a plateau at relatively higher doses.

Subgroup analyses by the supplementation duration demonstrated interesting outcomes, favoring a relatively shorter duration. Actually, some trials on vitamin D have demonstrated that 25(OH)D concentrations reaches a peak at three-to-six months, then it will drop by

the end of the intervention [16]. Compliance might be a contributory factor, but this variable was poorly reported in the included studies. moreover, studies that extended for three months administered a higher vitamin D dose (up to 7140 IU per day), than the dose in longer duration studies (400 - 3500 IU per day).

Based on these findings, an intermediate vitamin D dose of 800-to-2000 IU per day, that is two to three times the dose recommended by the IOM RDA for adults and elderly (600 - 800 IU per day), is required to allow for about two thirds of the population to reach a 25(OH) D level that is higher than 20 ng per ml. This dose remains to be below the upper limit of intake set by the IOM at four thousand IU per day, and it is not expected to be linked to any risk of vitamin D toxicity. Unfortunately, the documentation of adverse effects in the detected studies was sketchy, at best, with the exception of studies among the elderly, and most studies lasted for less than twelve months. Data on the effect of vitamin D supplementation on skeletal outcomes were limited. None of the included studies evaluated the risk of fracture and only a single study demonstrated improvements in whole-body subtotal BMD with a high vitamin D dose [19]. Several included studies assessed the impact of vitamin D on extra-skeletal outcomes; a high vitamin D dose caused a significant improvement in the systolic blood pressure and insulin resistance which is measured by HOMA-IR. Despite the plethora of observational studies linking vitamin D deficiency with various atypical outcomes, auto-immune and cardio-vascular diseases, infections, and neoplasms, intervention studies from Western and non-Western countries are still required to assess the ideal vitamin D dose and target concentrations to prevent the development of such medical conditions [20].

Our review confirmed that the dose and the baseline 25(OH)D concentration are significant predictors of the 25(OH)D concentration that is achieved post-interventional. The increase in 25(OH)D concentrations approximated 0.4 ng per ml per 100 IU per day vitamin D. This elevation is similar to increments estimated with high doses in the standard meta-analysis, and to the increments ranging between 0.2 and 0.5 ng per ml per 100 IU/day vitamin D shown in previous meta-regressions, using a linear model, and pooling the results of trials from Western regions [17]. Results on other predictors, including the age, body mass index, and concomitant calcium supplementation were also consistent with previously published results. nevertheless, we were not able to find statistically significant outcomes. These findings indicate that the vitamin D dose response curve in the MENA region might be similar to the one that is characterized in Western regions, but the higher need might be driven by several factors, most importantly the lower baseline 25(OH)D concentrations, latitude, concomitant calcium supplementation, and body mass index.

Our systematic review has several limitations that are mostly associated with the inherent limitations of the identified studies. A large number of the studies that we included in our review were from Iran. Therefore, the outcomes might not represent the whole MENA region. A high heterogeneity was identified in the meta-analysis. This was associated with differences in the baseline characteristics of the included participants and in the dose given (a high dose can vary between 3570 and 7140 IU per day). A high heterogeneity is one of the important factors that can result in decreasing the quality of evidence derived from a meta-analysis of trials [21]. Additionally, multiple factors that could have impacted the effect size of the intervention were poorly described. Dietary vitamin D in- take was usually not reported, season and clothing style were not mentioned, except in few studies, and none of these quantified sun exposure in an accurate method. Compliance to vitamin D supplementation was described only in four out of all included studies. In addition, only 2 studies were conducted among healthy non-obese subjects. The variability in vitamin D assays used in the included studies remains a significant limiting factor, in view of the high discrepancies in accuracy and precision between assays [19] and the effects this might have on the ultimate review. Finally, the quality of several included studies was relatively low, related to selection, reporting, and other bias.

We report here the first systematic review in the MENA region that assesses the dose response of vitamin D in this population specifically. It makes it possible to explore the applicability of the IOM guidelines in the region. The search methodology was very comprehensive, including five databases, and two others relevant to the region, in addition to clinical trials registries. This systematic review sheds light on the availability and on the quality of vitamin D trials in the MENA region. It detects several knowledge gaps relevant to this topic and allows one to make priorities for future research policies and plans.

Management of vitamin D deficiency in the MENA region

The majority of healthy adults who have serum 25-hydroxyvitamin D (25[OH]D) of 12 to 20 ng/mL (30 to 50 nmol/L) do not need any additional assessment. Patients who have serum 25(OH)D concentrations that are less than twelve ng per mL are at risk for developing osteomalacia later. Among these patients, physicians usually measure the concentrations of serum calcium, phosphorus, alkaline phosphatase, parathyroid hormone (PTH), electrolytes, blood urea nitrogen (BUN), creatinine, and tissue transglutaminase antibodies (to evaluate for the possible presence of celiac disease). Radiographs are also considered to be important in specific cases, like the presence of bone pain.

Vitamin D repletion

Vitamin D and its metabolites have an essential clinical role due to their interrelationship with calcium homeostasis and bone metabolism. Despite that rickets (among children) and osteomalacia (among both children and adults) due to severe vitamin D deficiency are now relatively uncommon (except in the MENA populations that have relatively lower sun exposure, absence of vitamin D in fortified foods, and malabsorptive syndromes), subclinical vitamin D deficiency, as measured by low serum 25-hydroxyvitamin D (25[OH]D) concentrations, is considered to be very common. Many patients who have subclinical vitamin D deficiency have relative hypocalcemia and high serum parathyroid hormone (PTH) levels, which might contribute to the development of osteoporosis and to an elevated risk of fractures and falls in older adults.

Dosing

The amount of vitamin D that is needed to effectively treat vitamin D deficiency depends, partly, on the baseline concentration of serum 25(OH)D and also on an individual's vitamin D absorptive capacity, capacity to convert vitamin D to 25(OH)D in the liver, and, to some extent, unknown genetic factors.

In patients with normal absorptive capacity, for every 100 units (2.5 mcg) of added vitamin D3, serum 25(OH)D levels elevation by approximately 0.7 to 1.0 ng per mL (1.75 to 2.5 nmol per L), with the larger increments observed among patients with lower baseline 25(OH)D concentrations. The increment declines as the 25(OH)D concentration increases more than forty ng per mL (100 nmol per L) [22].

Multiple dosing regimens have been demonstrated to treat vitamin D deficiency effectively. Dosing frequency at intervals up to once per month seems to be less important than cumulative amount. As an example, in a two-month trial of using oral vitamin D3 repletion for older females who have hip fractures, the same cumulative dose given per day (1500 international units), per week (10,500 international units), or per month (45,000 international units) resulted in similar increments in serum 25(OH)D concentrations [23]. Despite that large, intermittent doses of vitamin D3 increase serum 25(OH)D concentrations, we do not use them in patients with normal absorptive capacity. In one trial, a large, annual oral dose of 500,000 international units of vitamin D3 had the undesirable effect of increasing falls and fractures among older individuals. In addition, monthly dosing with 60,000 international units [16] and 100,000 international units has had the undesirable effect of increasing risk of falling in older adults and nursing home residents, respectively.

Conclusion

In the MENA region, the IOM RDA of 600 IU/day is not sufficient to bring 25(OH)D to the desirable level of 20 ng/ml; higher doses of 1750 - 2000 IU/day may be needed. In addition to the dose, the baseline 25(OH)D level significantly affects the response to vitamin D replacement. These findings provide the needed information to formulate MENA specific vitamin D guidelines. Additional long-term safety and high-quality studies using intermediate to high vitamin D doses are required and more solid evidence on the effect of vitamin D on various skeletal and extra-skeletal outcomes is still needed.

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