VITAMIN D DEFICIENCY STATUS, MEASUREMENT AND ITS TREATMENT IN THE UNITED ARAB EMIRATES

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ABSTRACT

Objectives: The present study will begin with a brief recap of the physiological roles of vitamin D, and the issue of defining vitamin D status in the United Arab Emirates. Deficiency of vitamin D has already been known a problem all over the world. Hypovitaminosis D is a widespread disorder across all age groups in the United Arab Emirates, particularly in teenagers. The high prevalence of hypovitaminosis D exists in a number of middle eastern countries despite having sufficient sunlight all round the year for vitamin D synthesis. Methods: The Roche Cobas electrochemiluminescence (ECL) competitive protein binding assay was used for total 25 hydroxyvitamin D [25(OH)D] is useful and comparable with the High Performance Liquid Chromatography (HPLC) and Liquid Chromatography Mass Spectroscopy (LCMS/MS) techniques which are known as gold standard in detecting vitamin D deficiency, insufficiency and sufficiency. Results: In a retrospective study carried out in more than 60,000 patients of 136 nationalities we showed that 82.5% of patients have vitamin D deficiency especially the teenagers (13–19 years) with the lowest levels of serum 25(OH)D. That is the reason to pay more attention to this group of patients and focus on level of vitamin D of juveniles till 18 years old (included). 59.2% of females and 44.5% of males from 1-18 years of age were found deficient of serum 25(OH)D (≤30 nmol/L). According to the coefficient of variation females have significantly higher variability among juveniles (63.82%) than males (49.97%). 58.2% of United Arab Emirates (UAE) nationals were vitamin D deficient in comparison with patients of other nationalities (45%). Among the juveniles group of patients age seems to be an important factor as the percentage of deficiency of serum 25(OH)D is increasing with age till they are 15 years old, for instance, 9.5% of patients in age between 1-3 years have a deficiency of vitamin D, then 56.4% of kids between 7-9 years and 79.9% of teenagers between 13-15 years. In all analysed age groups females were found with lower levels of 25(OH)D than males. The need for nutritional public health-awareness campaigns about the importance of vitamin D is pressing, specifically in the UAE and other middle eastern countries where the prevalence of hypovitaminosis D is very high. Conclusion: We need to have global recognition to improve the overall health and well-being of children and adults as it relates to their vitamin D status. Recommendations for vitamin D fortification programs and sensible sun exposure should be embraced by Governmental agencies, health care providers and regulators.

KEYWORDS: Vitamin D deficiency, 25(OH)D, measurement, electrochemiluminescence, treatment, toxicity, United Arab Emirates.

INTRODUCTION

Vitamin D is essential for intestinal calcium absorption and plays a central role in maintaining calcium homeostasis and skeletal integrity.[1] It is well-established that prolonged and severe vitamin D deficiency leads to rickets in children and osteomalacia in adults.[2] In addition, while the etiology of osteoporosis is multifactorial, it is believed that secondary hyperparathyroidism as a result of a more marginal vitamin D deficiency is a significant

Abbreviations used: 25 hydroxyvitamin D- 25(OH)D; electrochemiluminescence -ECL, High Performance Liquid Chromatography-HPLC, Liquid Chromatography Mass Spectroscopy- LC-MS/MS, Vitamin D binding protein-DBP, 1,25-dihydroxyvitamin D- 1,25(OH)2D, Food and Drug Administration- FDA, Institute of Medicine - IOM, College of American Pathologists-CAP
Vitamin D from all sources is not biologically active and must undergo hydroxylation in the liver by 25-hydroxylase (CYP27A1) enzyme to produce 25(OH)D, the storage form of vitamin D.[18] 25(OH)D circulates after binding to vitamin D binding protein (DBP). Limited evidence suggests that 25(OH)D3 has a higher binding affinity for DBP than vitamin 25(OH)D2.[8] A second hydroxylation is necessary to produce the biologically active form of vitamin D i.e., 1,25-dihydroxyvitamin D [1,25(OH)2D]. More recently, it has been identified that many other cells and tissues in the body can also express the 1-alpha-hydroxylase enzyme and locally produce 1,25(OH)2D from 25(OH)D.[10] Research for the last 20 years is mostly concentrated on non-skeletal role of vitamin D.

Our previous research showed that 82.5% of patients have a vitamin D deficiency to insufficiency. 26.4% of females and 18.4% of males have an extreme deficiency of 25(OH)D.[12] Especially teenagers (13–19 years) have shown the lowest levels of serum 25(OH)D.[12] It has been reported that extreme deficiency causes rickets or osteomalacia.[13] The deficiency of serum 25(OH)D between 25-50 nmol/L is associated with bone disease increasing risk of cancers, autoimmune diseases, hypertension, and infectious diseases.[13-16] Low level of vitamin D is associated with all-cause mortality and cardiovascular mortality, but it remains unclear whether serum 25(OH)D deficiency is a cause or a consequence of a poor health status.[17,18]

The present study will begin with a brief recap of the physiological roles of vitamin D, and then briefly consider the issue of defining vitamin D status in the United Arab Emirates. The data on prevalence of poor vitamin D status among children and adolescents, use of vitamin D supplements for treating vitamin D deficiency will be discussed.

MATERIALS AND METHODS

Measurement of D2 and D3 metabolites as total vitamin D

Individuals of all ages were eligible for study if they resided in Abu Dhabi anytime during the 2-year period from October 2012 to September 2014 had not refused research authorization. We reviewed the medical records and laboratory data of patients who had both 25(OH)D values to determine the levels of vitamin D or another health related cause. Information abstracted from the medical record included age, sex, race, duration, and dosage of vitamin D, seasonal variation in 25(OH)D and calcium supplement, other medical diagnoses, medications, laboratory values, and reported symptoms.

Vitamin D status is commonly assessed by serum levels of the metabolite 25(OH)D3 and 25(OH)D2, which reflects storage better than 1,25(OH)2D3. Vitamin D total assay is a competitive electrochemiluminescence (ECL) protein binding assay intended for the quantitative determination of total 25(OH)D in human serum and plasma. The patented ECL method by F. Hoffman-La Roche AG (Basel, Switzerland) for the Cobas platform offers a 25-hydroxy vitamin D assay. The test is available for use on all of the Roche cobas modular analyzer platforms; it received Food and Drug Administration (FDA) clearance in July 2012.[19] The assay was validated in our laboratory following clinical laboratory standards.[20] Between day precision was CV = 4.9% and 1.9% at mean concentrations of 43.3 and 105 nmol/L respectively using quality control material provided by Roche Diagnostics. External quality controls from College of American Pathologists (CAP) were used periodically to maintain the quality and precision of 25(OH)D testing.

Reference ranges used in this study are based upon the recommendations of the Endocrine Society.[21] and the Institute of Medicine (IOM).[22,23] The US Endocrine Society guidelines defines vitamin D deficiency as 25(OH)D less than 20 ng/mL (50nmol/L), vitamin D insufficiency as 25(OH)D between 21 and 29 ng/mL and the safety margin to minimize the risk of hypercalcemia as 25(OH)D equal to 100 ng/mL (250 nmol/L). Evidence from multiple observational studies and meta-analysis, suggested additional health benefit with serum 25(OH)D above 20 ng/mL up to 30 ng/mL. Optimal levels are not unanimously defined, but most experts agree that values ≤20 ng/mL indicate deficiency, values between 21 and 29 ng/mL indicate relative insufficiency and levels ≥30 ng/mL sufficiency.[24] Ethical approval for the study was obtained from the Institutional Review.

Board/Ethics Committee of VPS Healthcare/Burjeel Hospital, and was in accordance with the Helsinki Declaration. Consent from the patients was taken during their 1st visit to the hospital which states” I grant permission for my medical data to be used for clinical research, if needed, with the understanding that my identity shall remain confidential and privacy respected.
Treating vitamin D deficiency

Incrasing awareness of vitamin D deficiency in recent years and use of vitamin D supplements by the population has increased and the prescription of high-dose vitamin D supplements has gained attraction in the treatment of vitamin D deficiency. The increasing use of vitamin D supplementation may be associated with increasing risk of vitamin D toxicity, particularly when high dose (600,000 IU injection) is used for several weeks. The 25(OH)D concentrations at which toxicity is evident have proven to be difficult to determine. Most reports on acute vitamin D toxicity involve serum 25(OH)D values above 140 ng/mL (to convert to nmol/L, multiply values by 2.496), with the primary clinical manifestation being hypercalcemia and its associated symptoms. In a vitamin D risk assessment, Hathcock et al. concluded that a reasonable and safe tolerable upper intake level (UL) should be 10,000 IU of vitamin D per day, which corresponds to a serum 25(OH)D concentration of approximately 100 ng/mL.

In the UAE now more than 2 dozen brands of vitamin D are available as supplements(personal survey conducted by Prof. Afrozul Haq in February 2016). These supplements are from various manufacturers of Europe, USA, Switzerland and UAE in the form of injections, tablets and capsules with varying potency. Recently, there is introduction of an exciting supplemental vitamin D in the solution form (Colemed 50,000 IU/mL) which is already in use at the National Health Services (NHS), UK. This product is currently launched in the UAE with the name Colemed from MYMED Pharma Ltd, Birmingham Science Park, England, UK. Colemed 50,000 IU/mL is the only solution form of high potency to treat vitamin D deficiency and healthcare professionals around UAE and Saudi Arabia have shown great interest in this product. In a preliminary study, Colemed 50,000 IU/mL formulation was given to patients suffering from joints pain, muscles pain, body ache and found effective in alleviating these symptoms after 6-8 weeks of supplementation (Prof. Haq’s personal observation).

DATA ANALYSIS

Statistical software SPSS IBM Statistics 22 and SAS 9.4 have been used for the analysis of data for the vitamin D. There were 60,979 cases of patients considered from October 2012 to September 2014. Normality was tested by Anderson-Darling test, where is confirmed that there is not normal distribution in the data on significance level of alpha 0.05. In the data of vitamin D, skewness was found, therefore the median was used to describe the data and non-parametric tests, for instance two-tailed Mann-Whitney, multidimensional Kruskal-Wallis non-parametric test and Chi-Square test. The power analysis was used to reduce sample size before testing of hypothesis.

RESULTS

In our studied population (n = 60,979), analyzed cases consists of 35,066 females (57.5%) and 25,913 males (42.5%). When the levels of vitamin D sorted by gender, the maximum number falls under the category of 21–30.99 nmol/L of vitamin D with 16.4% of female and 17.4% of male. The next category for male was 31–40.99 nmol/L (16.4%) and for female was 11–20.99 nmol/L (15.4%). These results are shown in Tables 1 and 2.

Table: 1 Age and gender distribution of 60,979 patients included in the study.

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>Female</th>
<th>Male</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–14</td>
<td>3173</td>
<td>3039</td>
<td>6212</td>
</tr>
<tr>
<td>15–29</td>
<td>9720</td>
<td>5167</td>
<td>14,887</td>
</tr>
<tr>
<td>30–44</td>
<td>13,958</td>
<td>9678</td>
<td>23,636</td>
</tr>
<tr>
<td>45–59</td>
<td>6153</td>
<td>5652</td>
<td>11,805</td>
</tr>
<tr>
<td>60–114</td>
<td>2062</td>
<td>2377</td>
<td>4439</td>
</tr>
<tr>
<td>Total</td>
<td>35,066</td>
<td>25,913</td>
<td>60,979</td>
</tr>
</tbody>
</table>

Table: 2 Patients (%) with extreme deficient, mild deficient, insufficient or optimal concentration of 25(OH)D(nmol/L) according to gender.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Extreme deficiency (24.99) (%)</th>
<th>Mild deficiency (25–49.99) (%)</th>
<th>Insufficiency (50–74.99) (%)</th>
<th>Optimal levels (75–250) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>26.4</td>
<td>35.0</td>
<td>21.6</td>
<td>17.0</td>
</tr>
<tr>
<td>Male</td>
<td>18.4</td>
<td>39.9</td>
<td>23.6</td>
<td>18.1</td>
</tr>
<tr>
<td>Total</td>
<td>23.0</td>
<td>37.0</td>
<td>22.5</td>
<td>17.5</td>
</tr>
</tbody>
</table>
Figure: 1. 25(OH) D levels (mean ±SE) of patients from Middle Eastern countries. Green stars over Lebanon and Turkey show higher levels of 25(OH)D in females than males.

Figure: 2 25(OH) D levels (mean ± SE) in different age groups

Figure: 3 Vitamin D levels of juvenile group aged from 1 to 18 years
Age and result value of vitamin D were tested by Kruskal-Wallis non-parametric test. By p-value (Sig.=0.000) is confirmed at a significance level of 0.05, the alternative hypothesis. That means with probability 95% there is a statistically significant difference between age groups in vitamin D, so age can affect the result value of vitamin D. The age with the result value of vitamin D are correlated with Spearman correlation coefficient -0.615 at a significance level 0.01 which is negative and therefore, serum 25O (HD) is decreasing with age.

**DISCUSSION**

Based upon our published report shown above [12] that 82.5% of patients have vitamin D deficiency especially the teenagers (13–19 years) with the lowest levels of serum 25(OH)D. That’s the reason to pay more attention to this group of patients and focus on level of vitamin D of juveniles till 18 years old (included). 59.2% of females and 44.5% of males from 1-18 years of age were found deficient of serum 25(OH)D (≤30 nmol/L).

According to the coefficient of variation females have significantly higher variability among juveniles (63.82%) than males (49.97%). 58.2% of UAE nationals were vitamin D deficient in comparison with patients of other nationalities (45%). Among the juveniles group of patients age seems to be an important factor as the percentage of deficiency of serum 25(OH)D is increasing with age till they are 15 years old, for instance, 9.5% of patients in age between 1-3 years have a deficiency of vitamin D, then 56.4% of kids between 7-9 years and 79.9% of teenagers between 13-15 years. The reasons for the high prevalence of vitamin D insufficiency in juveniles are unclear. Future research will be focused on kids and teens that were found with the lowest levels of vitamin D in our studied cohort.

In all analyzed age groups females were found with lower levels of 25(OH)D than males. Most experts agree that 25(OH)D of < 20 ng/ml is considered to be vitamin D deficiency whereas a 25(OH)D of 21-29 ng/ml is considered to be insufficient. The goal should be to maintain both children and adults at a level > 30 ng/ml to take full advantage of all the health benefits that vitamin D provides. The total 25(OH)D, i.e., [25(OH)D2 + 25(OH)D3] is what physicians need to be aware of for their patients. A level > 30 ng/ml is now considered to be the preferred healthful level that all children and adults should maintain throughout the year. [37]

Vitamin D toxicity has been of great concern especially for children. However, it is now recognized even by the IOM that vitamin D is not as toxic as once thought. [38] They recommended that up to 4,000 IUs of vitamin D daily for most children and adults was safe. A study in healthy adult males receiving 10,000 IUs of oral vitamin D3 daily for 5 months did not cause any untoward toxicity. [39] The IOM and the Endocrine Society also recognize that patients with kidney stones or with primary hyperparathyroidism can receive vitamin D supplementation without concern for increased risk for developing kidney stones or increased blood calcium respectively. [38,40] In a recent study of 11 patients who were treated with high dose of vitamin D (600,000 IU injectable) for back pains, osteoarthritis, osteoporosis, diabetes suffered with hypervitaminosis D. All these patients developed symptoms of hypercalcemia, recurrent vomiting, abdominal pain, polyuria, polydipsia, constipation, anorexia and weakness. [41] Before prescribing vitamin D supplements, we should properly look into the background history of the patient along with biochemical parameters to know the status of vitamin D so that toxicity is prevented. Recently we developed the clinical practice guidelines for the treatment of vitamin D deficiency for the people living in the United Arab Emirates. [42] These guidelines are based on both the recent clinical practice guidelines published by The Endocrine Society [21] and The Institute of Medicine guidelines. [38] It is intended to be used as guidelines for physicians in the UAE and the Gulf Cooperation Council (GCC) member states.

**CONCLUSION**

Vitamin D deficiency is highly prevalent, even in countries with abundant sunshine, when skin exposure to UVB sunlight is limited by lifestyle and other factors. Low vitamin D levels in the Middle East, may reflect cultural dress customs that limit skin exposure. Our results from a relatively large cohort suggest that an effective strategy to prevent vitamin D deficiency and insufficiency is necessary. We need to have global recognition that to improve the overall health and well-being of children and adults as it relates to their vitamin D status. Vitamin D guidelines for the Middle Eastern and Asian countries should be developed. In addition, recommendations for vitamin D fortification programs and sensible sun exposure should also be embraced by Governmental agencies, health care providers and regulators. It has been estimated that there could be as much as a 25% reduction in all health care costs just by improving the vitamin D status of children and adults worldwide.

**Financial disclosure**

The authors declare no financial interest.

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