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THE EPIDEMIC OF HYPOVITAMINOSIS D IN SAUDI ARABIA. IS IT REAL OR OVERINFLATED?

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Abstract:

Background: *Over the last decade, there was significant interest in the role of vitamin D in general health, which led to a dramatic increase in vitamin D testing and supplementation.*

Objective: *To evaluate the status of vitamin D among Saudi female students at the Health Sciences Colleges and compare the levels of 25-OHD between two generations.*

Materials and methods: *A cross sectional study was carried out at Health Sciences Colleges, Taibah University, Medina, Saudi Arabia. Serum 25-OHD levels were measured in 270 students during the academic years of 2011 and 2018; 135 students from each year, using electrochemiluminescence method. Vitamin D status was classified according to the recent consensus agreement in the optimal level of 25-OHD concentrations (≥75 nmol/L is the optimal level and <50 nmol/L is a deficiency) [referred to as the high cutoff value] versus the Institute of Medicine (IOM) criteria (≥50 nmol/L is the optimal level, and <25 nmol/L is a deficiency) [referred to as the low cutoff value]. Parathyroid hormone (PTH) levels were measured for the 2011 group only.*

Results: *The mean age of the subjects was 22.0±2.134 and the mean level of 25-OHD was 21.5±8.375 nmol/L with no differences between the two groups. The prevalence of vitamin D deficiency was 99.3% when the high cutoff value was applied versus 69.1% when the low cutoff value was applied, with no significant differences between the two groups. The mean PTH level was 3.81±2.1 pmol/L, and only 5.1% of the studied group had PTH levels above the normal range.*

Conclusion: *Despite the recent trends in vitamin D testing and supplementation, vitamin D deficiency remains highly prevalent among the Saudi population, affecting even healthy active young students from the Health Sciences Colleges with no differences between generations. This overestimation is most likely caused by applying the current recommended cutoff levels for defining the adequacy of 25-OHD. Future studies are needed to define the optimal level of 25-OHD concentrations in the Saudi/Gulf population.*

Key words: *Vitamin D deficiency, 25-hydroxyvitamin D, Saudi Arabia, Hypovitaminosis D, Calcitriol.*

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INTRODUCTION:

Vitamin D, the sunshine vitamin, plays an important physiological role in bone homeostasis. In the last decade, attention has turned to the possible non-skeletal effects of vitamin D, mainly in relation to cancer, cardiovascular disease, diabetes mellitus, and immune dysfunction. (1) However, evidence regarding the role of vitamin D in health and disease beyond bone is conflicting. (2)

Vitamin D_3 (cholecalciferol) is produced primarily in the skin under the influence of sunlight and can also be obtained from food, such as fish, egg yolks, or liver. In addition, vitamin D_2 (ergocalciferol) may be ingested from plant sources. Few foods naturally have considerable vitamin D content, and dietary vitamin D is obtained mainly through fortified foods or supplements. Both forms of vitamin D are converted in the liver to 25-hydroxyvitamin D (calcidiol, 25-OHD), which is the major circulating form of vitamin D. In the kidney, 25-OHD is hydroxylated to 1,25-dihydroxyvitamin D (calcitriol), which is the biologically active form of vitamin D. (3)

Measurement of the 25-hydroxyvitamin D (25-OHD) level in serum or plasma is the best index of vitamin D status. However, thresholds of serum 25-OHD concentration to define the optimal level of vitamin D are highly debated. The Institute of Medicine (IOM) considers 50 nmol/L to be the optimal level and 25-OHD levels below 25 nmol/L to be deficiency. (4) The recent consensus agreement is that the optimal level of 25-OHD level is 75 nmol/L and levels below 50 nmol/L are considered deficient. (5)

Vitamin D testing and supplementation have received significant media and research attention in recent years, and both physicians and patients seem to believe that screening and correcting vitamin D deficiency improves health outcomes. (6) However, vitamin D screening and supplementation have virtually no established health benefits. (2) Furthermore, a recent meta-analysis found that vitamin D supplementation does not prevent fractures or falls and has no clinically meaningful effects on bone mineral density, with no differences between the effects of higher and lower doses of vitamin D. (7) Costs associated with clinical management of low vitamin D have increased exponentially and resulted in wasting billions of dollars. (6) For these reasons, professional societies and authoritative bodies do not recommend screening for vitamin D in adults who are asymptomatic or at low risk of vitamin D deficiency. (8,9)

In recent years, numerous clinical studies have concluded that vitamin D deficiency is very prevalent worldwide, even in countries with abundant sunshine throughout the year. (10,11,12) The reported prevalence of vitamin D insufficiency and deficiency is even higher in Saudi Arabia, reaching 90% and 99%, respectively, in some studies. (13,14,15,16,17,18)

Students from the Health Sciences College are expected to have higher levels of vitamin D than the general population, and the current generation is expected to have higher levels of vitamin D than their peers from a decade ago. The present study was conducted to evaluate the status of vitamin D among Saudi female students at the Health Sciences College of Taibah University, Medina, and to compare the levels of 25-OHD between the two generations, seven years apart. The secondary objective was to compare the rate of vitamin D deficiency when applying the high cutoff value that defines the optimal level of 25-OHD concentrations (75 nmol/L) versus the low cutoff value (50 nmol/L).

MATERIAL AND METHODS:

The current study was a cross-sectional study involving 270 apparently healthy females $\geq$ 18 years of age who were randomly selected from Health Sciences College of Taibah University, Medina, Saudi Arabia, during the academic year of 2011 and the academic year of 2018.

The exclusion criteria included concurrent pregnancy and lactation, malabsorption, liver or kidney diseases and malignancy. Students on medications that affect vitamin D metabolism, e.g., phenytoin, were also excluded. Male students were not involved because the study was conducted in the women's section of the university. The study was approved by the research and human ethics committee of Taibah University, Medina, Saudi Arabia.

After the participants provided informed consent, demographic data were obtained, and the following information was assessed using a self-administered questionnaire: dietary intake of vitamin D, sun exposure, physical activity, and previous treatment for vitamin D deficiency. Measurements of weight and height were obtained for all participants, and BMIs were calculated.

Peripheral nonfasting blood samples were collected from the first group in the month of March during 2011 (2011 group) and 2018 (2018 group) for 25-OHD and calcium levels for all participants. Parathyroid hormone (PTH) levels were collected from the 2011 group only. Serum 25-OHD was determined by electrochemiluminescence immunoassay using a Cobas autoanalyzer (Roche Diagnostics, West Sussex, UK). The calcium level was measured using the clinical chemistry automated machine Dimension XP and Siemens (Healthcare Diagnostics Ltd. Frimley, Camberley). Serum PTH levels were determined by electrochemiluminescence immunoassay.

Vitamin D status was classified according to the recent consensus agreement in the optimal level of 25-OHD concentrations (≥75 nmol/L is the optimal level and <50 nmol/L is a deficiency) [referred to as the high cutoff value] versus the IOM criteria (≥50 nmol/L is the optimal level, and <25 nmol/L is a deficiency) [referred to as the low cutoff value].
Statistical analyses were performed using SPSS software (version 20.0; SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as the mean ± standard deviation (SD), and categorical variables were expressed as numbers (percentages). An independent Student's t-test was used to test for differences in the continuous variables, and chi-square analysis was used to test for differences in the categorical variables. $P < 0.05$ was used as the cutoff value for significance.

RESULTS:

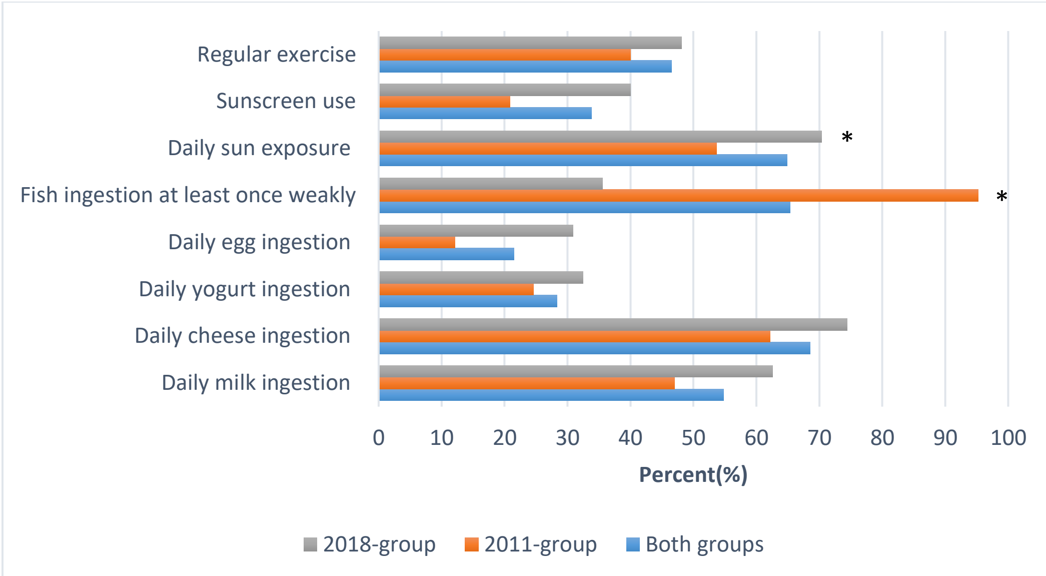
A total of 270 healthy young female students, including 135 students from each academic year, with a mean age of 22.0±2.13 years, were involved in the study. The baseline and biochemical characteristics of the participants are presented in table 1. Dairy products and fish intake, outdoor physical activity, sun exposure, and use of sunscreen among the participants are presented in figure 1.

Table 1: Baseline and biochemical characteristics of the participants.

		Both groups	2011 group	2018 group	P-value
Age (year)*		22.0±2.134	23.3±2.3	21.4±1.8	0.000
Height (cm)*		157.35±6.567	158.03±7.3	157.03±6.2	0.319
Weight (kg)*		56.01±12.460	58.6±13.8	54.81±11.6	0.046
BMI (kg/m^2)*		22.58±4.557	23.4±4.9	22.2±4.3	0.079
25-OHD level (12.5 nmol/L)*		21.5±8.375	22.525±7.7500	20.8±8.5	0.056
Calcium level (mmol/L)*		2.31±0.12	2.30±0.1	2.32±0.1	0.137
Marital status (%)	**Single**	89.7	86.8	91.1	0.338
	Married	10.3	13.2	8.9	
Skin color (%)	**White**	47.1	58.0	41.5	0.032
	Brown	52.0	40.6	57.8	
	Black	1.0	1.4	0.7	

***Mean ± SD**

Figure 1: Intake of foods that contain vitamin D and sun exposure among the study participants, with a comparison between the two groups.



* P-value <0.05

The mean level of 25-OHD was 21.5±8.375 nmol/L, with no differences between the two groups. The prevalence of vitamin D deficiency was 99.3% when the high cutoff value was applied versus 69.1% when the low cutoff value was applied, with no significant differences between the two groups. Very low vitamin D levels (25-OHD level < 12.5 nmol/L) were observed in 10.3% of the participants; however, the 2018 group had a significantly higher rate of very low vitamin D levels than the 2011 group (17% versus 3.1%, respectively, P= 0.000), despite 22.2% of the current group reported receiving treatment for vitamin D deficiency at some stage. The mean PTH level was 3.81±2.1 pmol/L (normal range= 1.6 - 6.89 pmol/L). In addition, only 5.1% of the studied group had PTH levels above the normal range. The mean calcium level was 2.31±0.12 mmol/L, and only 5.2% of the participants had calcium levels below the normal range.

DISCUSSION:

Despite the recent trends in vitamin D testing and supplementation, vitamin D deficiency remains extremely prevalent among Saudi female students at the Health Sciences College, with no differences between the two generations almost a decade apart. The results of this study were similar to the results of a study with 118 female medical and paramedical students from King Abdulaziz University in Jeddah, where 99.2% of the study group had vitamin D levels less than 50 nmol/L, 72% had levels less than 25 nmol/L, and 19% had severe deficiency with levels <12.5 nmol/L. (19) Our results are also consistent with the results for medical students from King Faisal University in Dammam, as 99.0% of the female and 92.6% of the male students were vitamin D deficient. (20) Similarly, 92.0% of male medical students from King Saud University in Riyadh had a vitamin D deficiency. (21) Vitamin D deficiency is also very prevalent among the general population of Saudi Arabia, affecting both sexes and all ages and was reported as high as 90%- 99%. (13,14,15,16,17,18) These conclusions about the epidemic of hypovitaminosis D in Saudi Arabia raise a question regarding the reality of these conclusions, as they can adversely affect patient care, including unnecessary screening and treatment, and cause an exponential increase in health costs.

Several factors are implicated in the apparent high prevalence of vitamin D deficiency in a sunny country such as Saudi Arabia with abundant sunshine throughout the year. The first factor is the use of high cutoff points for defining the optimal level of 25-OHD concentrations (75 nmol/L). This was clearly demonstrated by the present study, in which the estimated prevalence of vitamin D deficiency was 99.3% when the higher cutoff value was used (75 nmol/L) and 69.1% when the lower cutoff value was used (50 nmol/L), indicating a 1.44-fold rise in vitamin D deficiency with the higher cutoff value. Similarly, most of the global population will be vitamin D deficient if the higher cutoff value is used; hence, many experts are questioning this level and

calling against using inappropriate cutoff points because they inflate the estimated prevalence of deficiency and overestimate the needed intake. (22)
Second, vitamin D metabolism and levels vary according to ethnicity due to variation in skin pigmentation and genetic factors. Skin-derived synthesis of vitamin D reduces with increased pigmentation, and levels of 25-OHD are considerably lower among blacks than among whites. In a study from the US, low serum 25-OHD levels <50 nmol/L was reported in 41.6% of white adults, 69.2% of Hispanic adults, and 82.1% of black adults. (10) As most of the data that defines the "optimal" 25-OHD concentrations are derived from the white-skin population, using these laboratory reference ranges in all ethnicities seems inappropriate. The fact that PTH levels were not elevated, as the mean level was 3.81±2.1 pmol/L (normal range 1.6 - 6.89) despite the low levels of 25-OHD concentrations, suggests that the Saudi population has a lower level of vitamin D than the white population. Furthermore, although nearly one-quarter of the current group had received treatment for vitamin D deficiency at some stage, they still have low levels of vitamin D, and their levels are not better than those of the 2011 group, which indicates that vitamin D levels returned to their baselines. Future studies are needed to establish the optimal level of 25-OHD concentrations in the Saudi population to avoid routine supplementation in generally healthy people with adequate vitamin D levels.

Third, the use of the chemiluminescence immunoassay (CLIA) method for the measurement of 25-OHD levels might be another factor contributing to the apparent high prevalence of vitamin D deficiency in Saudi Arabia. CLIA is the most commonly used technique among commercial laboratories and is widely used among laboratories in Saudi Arabia; however, the CLIA method was shown to underestimate the levels for 25-OHD. (23,24) In a recent study that compared the performance of the CLIA method with the radioimmunoassay (RIA) and the liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay methods in a group of Saudi individuals, a significant difference between the results of the assays was found. The mean 25-OHD levels were the highest for the LC-MS/MS method (54.125 nmol/L), followed by the RIA method (41.525 nmol/L), and they were the lowest for the CLIA method (34.6500 nmol/L). Using 75 nmol/L as a cutoff value, the number of subjects diagnosed with vitamin D deficiency by the CLIA method was higher than the number of subjects diagnosed by the LC-MS/MS method (80.8% versus 57.3%, respectively), which indicates that the CLIA method overestimates vitamin D deficiency. (25) High-performance liquid chromatography (HPLC) and LC-MS/MS are better methods for measuring 25-OHD levels; however, both require more expensive equipment and expert staff. (26)

Other contributors to vitamin D deficiency in the study groups and other Saudi populations include avoidance of sun exposure, use of sunscreen, conservative clothing, and low intake of foods that contain vitamin D or foods fortified with vitamin D.

Seasonal variations are known to influence vitamin D levels, which tend to be lower during winter than during summer. The current study was conducted in March, when lower levels of vitamin D are expected; however, year-round vitamin D deficiency was reported among Saudi women with no significant difference between seasons. (14)

Obesity also influences vitamin D levels, and obese individuals tend to have lower levels than do normal-weight individuals. The reasons for this difference are not understood, but greater deposition of vitamin D into adipose tissue is a possible explanation. (27) The participants of the current study were mostly of average weight with a mean BMI of 22.58 kg/m^2, which eliminated the possibility that obesity could explain the high prevalence of vitamin D deficiency in this cohort of young Saudi women.

One of the study limitations is the inclusion of only females; nevertheless, previous studies indicated that vitamin D deficiency is prevalent throughout the Saudi population, affecting both sexes and all ages. The study was conducted in March, when a lower level of vitamin D is expected, though a year-round vitamin D deficiency was reported among Saudi women. (14) Finally, we used the CLIA assay method for vitamin D measurement, which is known to underestimate the levels of 25-OHD. Liquid chromatography-tandem mass spectrometry assay is a more accurate and reliable method than CLIA assay (26); however, the instrument is unavailable in our laboratories and in most Saudi Arabia laboratories.

Despite the recent trends in vitamin D testing and supplementation, hypovitaminosis D remains highly prevalent among the Saudi population, affecting even healthy active young students from the Health Sciences College with no differences between generations. This overestimation is most likely caused by applying the current recommended cutoff levels for defining the adequacy of 25-OHD derived mainly from the white population. Given this reason and given the conflicting evidence concerning the role of vitamin D in health and disease beyond bone (2), wide screening for vitamin D in asymptomatic individuals or those at low risk of vitamin D deficiency should be avoided to minimize unnecessary treatment and reduce extra healthcare costs. Implementing strategies that reduce clinicians' and patients' interest in vitamin D screening and supplementation is essential. Future studies are needed to define the optimal level of 25-OHD concentrations in the Saudi/Gulf population.

List of abbreviations

25-OHD: 25-hydroxyvitamin D
IOM: Institute of Medicine
PTH: Parathyroid hormone
CLIA: Chemiluminescence immunoassay
RIA: Radioimmunoassay
LC-MS/MS: Liquid chromatography-tandem mass spectrometry
HPLC: High-performance liquid chromatography

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