

RESEARCH ARTICLE

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Vitamin D status among patients visiting a tertiary care center in Riyadh, Saudi Arabia: a retrospective review of 3475 cases

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Abstract

Background: Vitamin D deficiency has been implicated in several chronic, non-communicable diseases independent of its conventional role in bone and calcium homeostasis. In this retrospective study, we determined the prevalence of vitamin D deficiency and its association to several cardiometabolic indices among patients visiting King Abdulaziz Medical City (KAMC), a tertiary hospital in Riyadh, Saudi Arabia.

Methods: A total of 3475 charts of out-patient subjects who visited KAMC from September 2009 until December 2010 were reviewed and included. Variables of interest included measurements of vitamin D status, glycemetic and renal profile, as well as trace elements (calcium and phosphorous).

Results: The over-all prevalence of vitamin D deficiency in the cohort studied was 78.1% in females and 72.4% in males. 25(OH) vitamin D was significantly associated with increasing age and weight (p -values < 0.0001 and 0.005, respectively). It was also positively associated with albumin, calcium and phosphorous (p -values < 0.0001, < 0.0001 and 0.0007, respectively) and negatively associated with alkaline phosphatase as well as circulating levels of PTH (p -values 0.0002 and 0.0007, respectively).

Conclusion: In conclusion, vitamin D deficiency is overwhelmingly common among patients seen at KAMC regardless of the medical condition, and it is significantly associated with increasing age, weight and markers of calcium homeostasis. Findings of the present study further stress the spotlight on vitamin D deficiency epidemic in the country and region in general.

Keywords: Vitamin D, Vitamin D deficiency, Saudi

Background

Recent epidemiologic studies have found out an unpredictably high prevalence of vitamin D deficiency in apparently healthy adults living in different countries, which could be a major health problem in the future [1,2]. Adequate vitamin D status has important clinical advantages in decreasing risk of many diseases such as cancer [3-6], diabetes mellitus, cardiovascular [7] and autoimmune diseases [8]. Evidences from clinical and epidemiological studies support a possible relationship between low vitamin D status and chronic disease

progression such as obesity, hypertension and diabetes mellitus [9-11]. Studies in Saudi Arabia, the United Arab Emirates, Australia, Turkey, India, and Lebanon, reported that 30 to 50% of children and adults had 25-hydroxyvitamin D levels under 20 ng/ml [12-15]. Saudi Arabia belongs to one of the sunniest regions in the world, and while the Saudi population should have adequate sun exposure, vitamin D deficiency remains prevalent in the country [16]. Various reasons include protection from strong heat during daytime, genetic and diet. Vitamin D deficiency was found to be very common among Saudi males and females [16-20]. Ardawi *et al.* found that vitamin D deficiency was common among older and obese Saudi men [21]. Findings from Al-Daghri *et al.* indicated severe hypovitaminosis D as more common among non-diabetic than diabetic Saudis [22].

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Several studies have also reported conflicting findings on the relationship between vitamin D status and obesity. Results of Al-Elq *et al.* study found an inverse relationship between vitamin D and BMI in Saudi males but not in females which appears that obesity is protective against vitamin D deficiency [23]. While negative association was found in many studies [24-28], some observed no relationship [29,30]. The mechanism behind such an association is that elevated concentrations of 1-25-vit D stimulate lipogenesis and inhibit lipolysis in cultured human adipocytes, leading to accumulation of fat [31]. Additionally, 1, 25-vitamin D inhibits the expression of adipocyte uncoupling protein 2 (UCP2), which would cause a reduction in the adipocyte's metabolic efficiency [32]. Cumming *et al.* found that vitamin D and calcium were more effective in reducing systolic blood pressure than calcium alone [33]. Furthermore, many studies reported a positive association between 1, 25(OH) 2D and vitamin D inadequacy and hypertension [34-36]. Some studies nevertheless reported conflicting results on the link between vitamin D intake and blood pressure [37,38]. Low serum vitamin D levels elevate the risk for early-stage diabetes (Pre-DM), hypertension (Pre-HTN) [37] and DM [39-41]. On the other hand, many studies reported no association between vitamin D deficiency and type 2 diabetes mellitus [42,43]. In the present study, we examined the relationship between serum levels of 25-hydroxyvitamin D (25[OH] D), Parathyroid Hormone (PTH), obesity and selected cardiovascular disease risk factors in Saudi subjects.

Methods

In this single-center retrospective study done in the outpatient department of King Abdulaziz Medical City, Riyadh, Saudi Arabia, a total of 3475 subjects' charts were reviewed from September 2009 until December 2010. There were 2719 (78%) females and 756 (22%) males. Vitamin D (25[OH] D) was measured using High Performance Liquid Chromatography (HPLC). Data was collected from the laboratory master database of the Clinical Biochemistry section, Department of Pathology and Laboratory Medicine, in KAMC. In addition to vitamin D2, other laboratory tests such as fasting blood sugar (FBG), HbA1C, and PTH were also noted.

The corresponding medical record number of those patients were utilized to obtain the following information from Quadramed and/or medical files: Height, weight, blood pressure, HbA1c, albumin, creatinine, BUN, alkaline phosphatase, calcium, phosphorous and parathormone. All clinical parameters were measured at the same time or close to the date of vitamin D measurement. The study has been approved by the [Institutional Review Board (IRB)] Clinical Research Ethics Committee in KAMC.

Data analysis

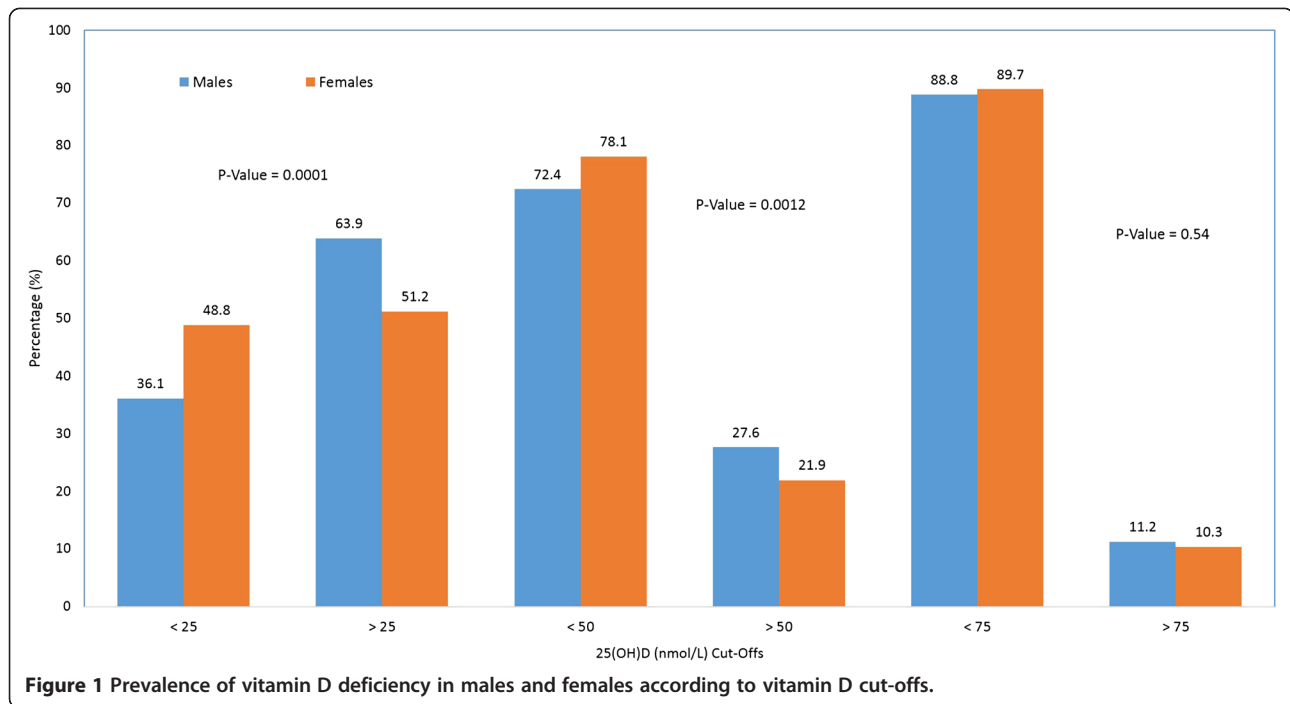
Data was analyzed using the Statistical Package for the Social Sciences (SPSS version 16.0, Chicago, IL, USA). Frequencies were expressed in percentages (%) and continuous variables were presented as mean \pm standard deviation. Variables that were not normally distributed (alkaline phosphatase, BUN, creatinine, 25(OH) vitamin D, and PTH) were transformed and normalized prior to parametric analysis (Pearson bivariate correlation). Student independent T-test was done to compare means of normally distributed variables and Mann-Whitney U-test for variables that are non-Gaussian. Chi-Square test was used to compare frequencies. Significance was set at $p < 0.05$.

Results

Figure 1 shows the differences in the prevalence vitamin D deficiency according to severity across genders using different cut-off values. Females had a significantly higher prevalence of 25(OH)D < 25 nmol/L than males (48.8% versus 36.1%; p -value 0.0001) as well as a higher prevalence of 25(OH) vitamin D < 50 nmol/L (78.1% versus 72.4%; p -value 0.0012). Using the same cut-off, it can be observed that the over-all prevalence of vitamin D deficiency in the cohort studied was 78.1% in females and 72.4% in males (Figure 1).

Table 1 describes the general characteristics of subjects and the associations of 25(OH) vitamin D to the different parameters measured. 25(OH) vitamin D was significantly associated with increasing age and weight (p -values < 0.0001 and 0.005, respectively). Furthermore, 25(OH) vitamin D was modestly, but significantly associated with increasing systolic blood pressure ($p = 0.03$). Among the biochemical parameters, 25(OH) vitamin D was positively associated with albumin, calcium and phosphorous (p -values < 0.0001, < 0.0001 and 0.0007, respectively) and negatively associated with alkaline phosphatase as well as circulating levels of PTH (p -values 0.0002 and 0.0007, respectively). It is worthy to note that the prevalence of obesity in the cohort studied is 21.9%, while the prevalence of morbid obesity was 44.2% (not shown in table).

Table 2 shows the comparison of the different variables using different cut-offs for 25(OH) vitamin D. Across all groups, subjects categorized to be in the upper half (≥ 25 , ≥ 50 and ≥ 75 nmol/L) were significantly older (p -values < 0.0001, < 0.0001 and 0.0003, respectively) and had significantly higher levels of serum albumin (p -values 0.0002, < 0.0001 and 0.0021, respectively) and calcium (p -values < 0.0001, < 0.0001 and 0.0029, respectively) than those in the lower half. In the first grouping (< 25 and ≥ 25 nmol/L), subjects whose 25(OH) vitamin D levels were ≥ 25 nmol/L had significantly higher systolic and diastolic blood pressure as well as BMI (p -values < 0.0001, 0.0017 and < 0.0001, respectively) than subjects with 25(OH) vitamin D < 25 nmol/L. Among the



biochemical parameters measured, those in the upper half (≥ 25 nmol/L) had a significantly higher blood fasting glucose, BUN and phosphorus (p -values < 0.0001 , 0.0002 and < 0.0001 , respectively) as well as a significantly lower alkaline phosphatase (p -value = 0.0001) than the lower half (< 25 nmol/L). In the second grouping, serum alkaline

phosphatase was also observed to be significantly lower in the upper half (≥ 50 nmol/L) as compared to the lower half (< 50 nmol/L) (p -value = 0.0082). Both the upper half of the 2nd and 3rd group (≥ 50 and ≥ 75 nmol/L) had significantly lower PTH levels (p -values = 0.034 and 0.039 , respectively) than their corresponding lower halves (< 50 and < 75 nmol/L). The rest of the comparisons done for other variables not mentioned in all groups were non-significant. Worthy of mention however is the mean HbA1c among subjects whose 25(OH) vitamin D is > 75 nmol which, while not significant, is considered the lowest as compared to the rest of the groups.

Table 1 General characteristic of subjects

Parameters	Mean \pm SD	R ²	P-value
N = 3475 (Males = 756; Females = 2719)			
Age (years)	46.9 \pm 16.3	0.15	< 0.0001
Weight (kg)	75.2 \pm 18.2	-0.06	0.005
Height (cm)	147.0 \pm 18.0	0.01	0.64
BMI (kg/ m ²)	36.4 \pm 13.8	-0.03	0.17
Systolic blood pressure (mmHg)	122.0 \pm 19.0	0.05	0.03
Diastolic blood pressure (mmHg)	71.0 \pm 11.0	0.04	0.09
Glucose (mmol/L)	6.4 \pm 3.0	0.02	0.24
HbA1c (%)	7.0 \pm 1.9	0.01	0.70
Albumin (g/L)	46.0 \pm 4.9	0.11	< 0.0001
Alkaline phosphatase (U/L)#	97.1 \pm 82.7	-0.09	0.0002
BUN (mmol/L)	5.1 \pm 3.4	0.03	0.12
Calcium (mmol/L)	2.34 \pm 0.15	0.14	< 0.0001
Creatinine (umol/L)#	79.4 \pm 70.2	-0.01	0.48
25OH Vitamin D (nmol/L)#	35.5 \pm 30.6	1.00	-
Phosphorus (mmol/L)	1.14 \pm 0.23	0.09	0.0007
PTH (mmol/L)#	34.2 \pm 58.3	-0.10	0.0007

Note: Data presented as mean \pm standard deviation; R² is the correlation coefficients compared to the concentration of 25OH Vitamin D; #denotes non-Gaussian variable.

Discussion

The major finding in the present one-year retrospective study is the overwhelming prevalence of vitamin D deficiency among Saudi patients seen at the outpatient clinics of KAMC. This confirms, and adds to the increasingly accumulating evidence that vitamin D deficiency in Saudi Arabia, specifically in urban areas such as the capital Riyadh, is alarmingly high [12-22]. Furthermore, the results of local epidemiologic findings on vitamin D deficiency, including the present study, are undeniably consistent, regardless of the methods used to quantify 25(OH)D, strengthening the premise that vitamin D deficiency is an epidemic in Saudi Arabia. What makes the present study unique is the arguably larger sample size as compared to previous studies, and that the type of cohort used can be considered representative of the general population, since patients referred to KAMC are not limited to the capital Riyadh, and that inclusion

Table 2 Comparison of variables using different vitamin d cut-off values (t-test)

Parameters	25 (OH) vitamin D cut-offs (nmol/L)					
	< 25	≥ 25	< 50	≥ 50	< 75	≥ 75
N	1601	1874	2672	803	3110	365
Age (years)	43.5 ± 16.3	49.9 ± 15.8**	45.7 ± 16.3	51.0 ± 15.8**	46.6 ± 16.3	49.8 ± 15.8**
BMI (kg/ m ²)	35.1 ± 12.6	37.9 ± 14.8**	37.1 ± 14.9	33.8 ± 11.5**	37.0 ± 14.0	30.3 ± 7.7**
Systolic blood pressure (mmHg)	120.0 ± 19.0	124.0 ± 19.0**	122.0 ± 19.0	123.0 ± 17.0	122.0 ± 19.0	121.0 ± 16.0
Diastolic blood pressure (mmHg)	70.0 ± 11.0	72.0 ± 11.0**	71.0 ± 11.0	71.0 ± 11.0	71.0 ± 11.0	70.0 ± 10.0
Glucose (mmol/L)	6.2 ± 2.6	6.5 ± 3.4**	6.4 ± 2.9	6.4 ± 3.4	6.4 ± 3.0	6.6 ± 2.8
HbA1c (%)	6.9 ± 1.8	7.1 ± 1.9	7.1 ± 1.9	6.9 ± 1.8	7.0 ± 1.9	6.8 ± 1.9
Albumin (g/L)	45.6 ± 5.1	46.3 ± 4.5**	45.7 ± 5.0	46.9 ± 3.9**	45.9 ± 4.9	46.9 ± 4.0**
Alkaline phosphatase (U/L)	106.0 ± 103.0	90.0 ± 60.0**	100.0 ± 88.0	88.0 ± 69.0**	98.0 ± 85.0	91.0 ± 58.0
BUN (mmol/L)	4.9 ± 3.5	5.3 ± 3.3**	5.0 ± 3.5	5.2 ± 2.8	5.1 ± 3.5	5.0 ± 2.2
Calcium (mmol/L)	2.3 ± 0.2	2.4 ± 0.2**	2.3 ± 0.2	2.4 ± 0.1**	2.33 ± 0.15	2.37 ± 0.15**
Creatinine (umol/L)	77.0 ± 65.0	82.0 ± 74.0	80.0 ± 75.0	77.0 ± 53.0	80.0 ± 74.0	73.0 ± 21.0
Phosphorus (mmol/L)	1.11 ± 0.24	1.16 ± 0.22**	1.13 ± 0.24	1.15 ± 0.21	1.13 ± 0.23	1.15 ± 0.22
PTH (pmol/L)	38.0 ± 67.0	31.0 ± 51.0	36.0 ± 62.0	28.0 ± 48.0**	36.0 ± 61.0	25.0 ± 35.0*

Note: Data presented as mean ± standard deviation; *denotes significance at < 0.05 level; **denotes significance at < 0.01 level.

of cases was not stringent, making the selection of cases devoid of bias.

Among the associations of 25(OH) vitamin D and cardiometabolic variables elicited, it is worthy to emphasize that vitamin D deficiency is less common among the elderly in the Saudi population. Looking back at the mean glucose and HBA1c levels of the cohort, it is apparent that majority of the subjects included had diabetes mellitus type 2 (DMT2), and age-related disease. Subjects who harbor this disease have been observed to have higher levels of 25(OH) D than their non-diabetic counterparts [22-45]. Part of the explanation lies in the almost mandatory multi-vitamin supplementation (multivitamins contain 400 IU vitamin D on average) given to Saudi elderly patients and those with DMT2 as well as other anti-DM medications that have been observed to augment circulating levels of 25(OH) vitamin D [45,46]. Another obvious risk factor from the present cohort is obesity. The mean BMI for the entire cohort fell within this category (36.4 ± 13.8). Obesity is a well-known cardiovascular risk factor associated with vitamin D deficiency, more so for the Arab population where vitamin D correction has modest, if not negligible effect on BMI [47-49].

With regards to other biochemical parameters measured, the association of 25(OH) vitamin D to albumin is expected in the study. It has been established that majority of circulating vitamin D is bound both to vitamin D binding protein and albumin [50,51]. The same expected significant association is true for vitamin D and calcium, in which the former is directly involved in calcium homeostasis. Lastly, the lack of significant difference in PTH levels of those below and above 25 nmol/L

is consistent with the findings of Al-Saleh *et al.*, where PTH levels remain normal despite having low to very low 25(OH) vitamin D levels, a unique feature among the Arabian cohort [52]. Nevertheless, the present study showed a significant and inverse association between PTH and vitamin D status, but differences in levels were only prominent if < 50 or < 75 nmol/L was used. Longitudinal studies are needed to confirm at what level of vitamin D status correction in the Arab cohort is needed to elicit a PTH response.

The study acknowledges several limitations. The retrospective and cross-sectional nature of the study as well as the population selected from the general outpatient clinics limit the findings to the information available at the database. The study was not able to consider confounding variables and other risk factors that can be used to adjust analysis such as presence of DMT2, skin color, sun exposure information and season where vitamin D was measured, the latter 2 factors being considered as very important predictors for vitamin D status in this geographical region [53]. Nevertheless, the study has several strengths and that includes the large sample size and the inclusion of all adult subjects whose vitamin D status was measured at a given time frame in one institution, which removed selection bias and increased the generalizability of present findings.

Conclusion

In conclusion, vitamin D deficiency is overwhelmingly common among patients seen at KAMC regardless of the medical condition, further stressing the spotlight on this epidemic in the country and region in general. Aggressive

measures should not be limited on the diagnosis, and multi-institutional involvement that includes policy makers, government and private companies should carry out public health campaigns to increase awareness and limit the spread of vitamin D deficiency engulfing the nation.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

HF designed study, collected and revised data, drafted the initial and the final version of the manuscript. HT carried out data analysis and interpretation. SJ, SH and WT revised data and manuscript. All authors provided intellectual contributions to the manuscript and has read and approved the final version.

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