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ORIGINAL ARTICLE

Vitamin D cutoff point in relation to parathyroid hormone: a population based study in Riyadh city, Saudi Arabia

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Abstract

Summary The current recommended cutoff value for low vitamin D may result in overestimation of hypovitaminosis D. Vitamin D levels at 30.0 nmol/L can diagnose the hyperparathyroid cases leading to bone loss, with moderate accuracy, in the Saudi population. The new cutoff may help in identifying true cases that need clinical treatment and can reduce the burden on healthcare system.

Purpose Different regions of the world have reported varying cutoff points as optimal values for vitamin D status to maintain bone health.

Methods A cross-sectional study comprising of interviews, anthropometrics, and blood samples was conducted in primary healthcare centers in Riyadh, Saudi Arabia. Standardized serum 25-hydroxyvitamin D [25(OH)D] and parathyroid hormone (PTH) were measured using electrochemiluminescence immunoassays. Independent sample and paired sample *t* test were conducted to compare the true means. Pearson correlation co-efficient was calculated to measure the association between original and standardized 25(OH)D. Software program, MedCalc, was utilized to measure the receiver operating curve (ROC) for determining the optimal threshold value for vitamin D.

Results The mean standardized 25(OH)D levels for 846 males and 1285 females were (32.0 ± 14.4 nmol/L vs 31.6 ± 16.7 nmol/L) respectively. Using the gold standard PTH cutoff > 6.9 pmol/L, the ROC had an optimal criterion value for males and females at 30.0 and 24.0 nmol/L, respectively. In the males, the sensitivity and specificity were 72% and 51%, whereas in females, it was 58.2% and 66.7%, respectively. The area under the curve (AUC) was at 0.62 and 0.65 ($p < 0.001$), respectively.

Conclusion The recommended cutoff value for 25(OH)D for determining bone health in the Saudi population is at 30.0 nmol/L. The comparatively low cutoff point can significantly decrease the number of people diagnosed and treated with low vitamin D, which can also reduce the burden on the health care system.

Keywords Vitamin D · Optimal level · Parathyroid hormone · Bone health

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Introduction

Vitamin D deficiency has emerged as a major public health concern in recent years, with important health consequences among children and adults all over the world [1, 2]. Sub-optimal serum levels of vitamin D have been implicated in low bone mineral density and increased bone loss by interfering with the vitamin D, calcium, and parathyroid axis [3, 4].

The proposed mechanism for bone loss is by the steady increase in parathyroid hormone as a consequence of hypovitaminosis D-induced hypocalcemia, resulting in calcium release from bones to maintain normal calcium levels in blood [5]. The existence of an inverse correlation between hypovitaminosis D and serum levels of parathyroid hormone (PTH) [6] points to the close association between these two markers. Other hypovitaminosis D-related comorbidities, such as rickets, osteomalacia, skeletal myopathy, and dilated cardiomyopathy, are potentially reversible and preventable conditions. Therefore, maintenance of optimal serum concentrations of vitamin D, especially in context to bones, appears to be of paramount importance both in healthy and diseased states [7]. Serum concentration of 1,25-dihydroxyvitamin(OH)D is often normal in individuals with hypovitaminosis D because of increased renal production of 1,25-(OH)D due to secondary hyperparathyroidism [8]. In contrast, 25-hydroxyvitamin D [25(OH)D] is considered to be the best marker for monitoring vitamin D status as it represents vitamin D intake from dietary sources and that synthesized in the skin [9]. However, opinions differ regarding the optimal blood levels of 25(OH)D [10, 11].

A regional large-scale study conducted in the Middle East defined deficiency as a level of 25(OH)D of < 50 nmol/L, at which PTH starts to increase in patients with normal renal function [12]. A few studies have used 25(OH)D < 37.5 nmol/L (15 ng/mL) as the cutoff value for vitamin D deficiency for the Middle East and North Africa (MENA) region [12], whereas others have used < 70 nmol (28 ng/mL) as the cutoff value for the Saudi population [13].

Application of later cutoff points in the Kingdom of Saudi Arabia has resulted in significantly higher prevalence rates for hypovitaminosis D, ranging between 83.6% and 95.3% [14, 15], emphasizing the need to determine a local cutoff point for low vitamin D that affects the bone health. The present study was performed to estimate PTH and serum 25(OH)D values and define the best cutoff values for adequate serum levels of vitamin D (for maintaining bone health) to avoid the increase in parathyroid hormone levels (> 6.9 pmol/L).

Methodology

Study design, setting and participants

Data in this study were collected from a large cross-sectional survey (Women in Saudi Arabia Health Examination Survey, WISHES). The study was conducted from December 2014 to August 2015. Eighteen primary healthcare centers (PHCCs) were randomly selected (https://www.random.org/) from the five different administrative regions of Riyadh City (north, east, west, south, and center). In addition to PHCCs, we approached five government institutions (technical institutes, college/university, and social organizations) to enroll eligible participants. Initially, 2997 Saudi adults (968 males and 2029 females) aged 30–75 years were enrolled in the "WISHES" study. In this particular study, we excluded participants who had past history of osteoporosis and/or renal disease, high creatinine levels ($n = 169$), epileptic ($n = 7$), and were on osteoporosis treatment ($n = 165$) or taking supplements ($n = 525$). A total of 2131 (846 males and 1285 females) were included in the final analyses. All participants provided a written, signed informed consent prior to the interviews. The study protocol was approved by the Institutional Review Board, King Saud University (E-12-658) and the Institutional Review Board of the Ministry of Health, Dammam (IRB ID MOH0151).

Research instrument

A detailed interview was conducted by trained data collectors with each of the participants and included socio-demographic information, sun-exposure habits, physical activity, dietary habits, medical history, and reproductive history (from females only). This information was used for another manuscript on vitamin D deficiency and its correlates [16].

Anthropometric measurements

Anthropometric indices included weight, which was measured with an electronic scale (Secca 220—Hamburg, Germany, 2009) and height, which was measured using the stadiometer following standard protocols [17]. Body mass index (BMI) was calculated as weight in kg divided by height in meters squared. Waist circumference (WC) was measured at the mid-point between the lowest rib and top of the hip bone (iliac crest) [18].

Laboratory measurement of vitamin D, parathyroid hormone, calcium, phosphorus, and alkaline phosphatase

Blood samples were collected in two different vials (a yellow cap and a purple cap). Five cubic centimeters of venous blood were collected in the yellow cap tube for basic biochemistry (cholesterol, lipids and triglycerides, alkaline phosphatase, calcium, phosphorus, creatinine and albumin), and another 5 cm^3 was collected in the purple cap for endocrinology (25(OH)D and parathyroid hormone). Needles of 22 or 23 gauges were used along with a sample adaptor to fill the vials. Both vials were placed in a labeled plastic bag and then refrigerated at a temperature of − 2 to 8 °Celsius. The samples were transferred into the storage box (under maintained temperature) and then transported to King Khalid University hospital laboratory.

Serum 25(OH)D was measured in a laboratory that participates in DEQAS with the automated Roche Elecsys Cobas e411 analyzer (Roche Diagnostics, GmbH, Mannheim, Germany) by means of electrochemiluminescence immunoassay. The intra-assay coefficient of variation (CV) was 6.8%, and the inter-assay CV was 13.1%. The total 25(OH)D values were corrected using the linear regression equation derived from the analysis of relationship between our measured total 25(OH)D values and the DEQAS total target values for five of the DEQAS samples [19]. Figure 1 shows the relation between serum total 25(OH)D in samples of 486 to 490 of the January 2016 Vitamin D External Quality Assessment Scheme (DEQAS) survey measured using Roche Elecsys Cobas e411 analyzer electrochemiluminescence immunoassay (CLIA) and the DEQAS National Institute of Standards and Technology (NIST) "total" target values [19].

After that, 200 specific stored serum samples were selected to be re measured from the sorted original 25(OH)D values of the complete dataset. The results were correlated with the old 25(OH)D values to develop a mathematical model that

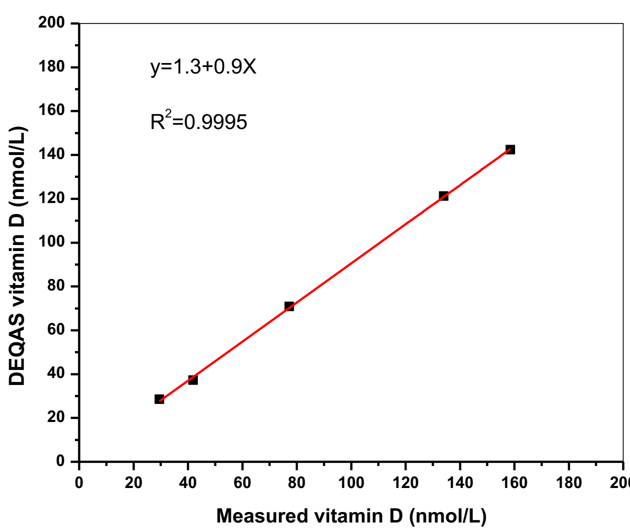


Fig. 1 Relation between serum total 25-hydroxyvitamin D (25OHD) in samples of 486 to 490 of the January 2016 Vitamin D External Quality Assessment Scheme (DEQAS) survey measured using Roche Elecsys Cobas e411 analyzer electrochemiluminescence immunoassay (CLIA) and the DEQAS National Institute of Standards and Technology (NIST) 'total' target values

enabled us to calibrate old vitamin D values to the true ones [19]. Figure 2 shows the relation between serum total 25(OH)D in 200 samples measured by Roche Elecsys Cobas e411 analyzer electrochemiluminescence immunoassay standardized method and the original results.

PTH assays were also performed using an electrochemiluminescence assay (ECLIA immunoassay, Modular Analytics E170, Roche Diagnostics GmbH, Mannheim, Germany) with a hospital standard laboratory reference range of (1.6–6.9 pmol/L). The intra-assay CV was 2.0%, and the inter-assay CV was 3.4%. Serum calcium (corrected for albumin binding) and phosphorous levels were measured in millimoles per liter, and serum alkaline phosphatase (ALP) was measured in units per liter (U/L) using routine chemical analyzers (Siemens StreamLab RxL Max, Erlangen, Germany).

Statistical analysis

Data were analyzed using IBM SPSS statistics version 21.0 and MedCalc software. Means and standard deviations were computed for continuous variables, and proportions were calculated for categorical variables. Student's *T* test for independent samples was used to compare mean values of blood markers (calcium, phosphorus, ALP, PTH) and continuous variables (age, body mass index) in relation to optimal vitamin D cutoff value (for males ≤ or > 30 nmol/L and for females ≤ or > 24 nmol/L. A paired *t* test was conducted to determine the *r* value and the statistically significant difference between the original and the standardized vitamin D levels. Pearson correlation coefficient value *r* was computed between 25(OH)D and PTH levels. MedCalc software was used to develop the receiver operating curve (ROC). PTH cutoff 6.9 pmol/L was taken as gold standard to identify the point at which the bones start getting affected [20]. Using the Youden index formula, the optimal cutoff value that yielded maximum value of sensitivity and specificity was determined for 25(OH)D to identify compromised bone health (corresponding to PTH value > 6.9 pmol/L). The 95% confidence intervals and *p* value < 0.05 were used to report the precision and statistical significance, respectively, of the estimate.

Availability of data and material The datasets generated and/or analyzed during the current study are not publicly available because it includes personal information of the participants but are available from the corresponding author on reasonable request.

Results

A total of 2131 Saudi adults (846 males, 1285 females) were included in the study. The mean ages of the male and female

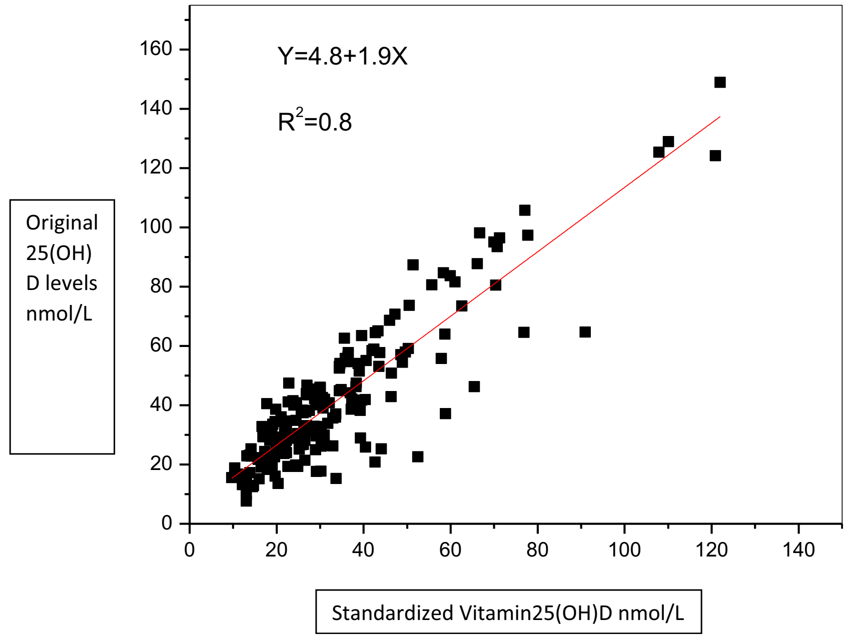


Fig. 2 Relation between serum total 25-hydroxyvitamin D (25OHD) in 200 samples measured by Roche Elecsys Cobas e411 analyzer electrochemiluminescence immunoassay standardized method and the original values

participants were 42.7 (11.5) and 42.1 (10.1) ($p = 0.22$) years, respectively. Majority (> 90%) of the participants were married, and > 50% of the females were housewives. About 75% males had university or higher level of education (Table 1). More than 90% males and around 57% females reported low physical activity (females reported moderate physical activity which included house work) (Table 1). A significant difference was observed in the mean waist circumference between males and females (96.25 ± 14.26 vs 92.73 ± 14.08, $p < 0.001$). More than 60% of the participants were not getting sun exposure at all, and only 10% said they were getting sun exposure on daily basis. The average number of children reported by married females was 5.0 (± 2.9). About 28% males and 2.0% females were current smokers (results not shown).

Strong correlation was observed between original and standardized vitamin D levels, with $r = 1.00$ ($p < 0.0001$) for both the males and the females. The paired t test in the males found that the mean values for the standardized vitamin D (32.0 ± 14.4) were significantly less than the original values (39.4 ± 19.7); a statistically significant difference of 7.2 (95% CI 6.8, 7.5) nmol/L, t (846) = 38.6, $p < 0.001$, was observed between the two readings. Similar results were observed in the females as well. The mean values for the standardized vitamin D (31.6 ± 16.7) were significantly less than the original values (38.6 ± 22.8), a statistically significant difference of 7.1 (95% CI 6.6, 7.3) nmol/L, t (1285) = 40.2, $p < 0.001$, was detected between the two readings. A significant difference was found in the mean values of vitamin 25(OH)D (nmol/L) between males and females (31.2 ± 18.4 vs 34.9 ± 18.6; $p < 0.001$, respectively). In both genders, linear association was observed between 25(OH)D and the PTH (Figs. 3 and 4). In the males, the correlation coefficient (r) value between standardized 25(OH)D and PTH was − 0.20 ($p < 0.001$) and 0.09 for calcium, whereas no significant correlation was observed with ALP and phosphorus. In females, a significant correlation was observed between standardized 25(OH)D and PTH (− 0.21), calcium (0.12), and phosphorus (0.07) ($p < 0.001$). Almost similar percentage of males and females (5.5% vs 5.6%) was showing hyperphosphatemia (> 1.45 mol/L), whereas a significant high percentage of males (12.5% vs 8.6%) were having high alkaline phosphatase as compared to females (results not shown).

The ROC analysis determined an optimal criterion value for 25(OH)D of 30.0 nmol/L and 24.0 nmol/L for the males and females, respectively. Using the cutoff of 30.0 nmol/L, sensitivity and specificity for discriminating participants with high PTH were 72% and 51%, respectively. The area under the curve (AUC) was 0.62 (Fig. 5). In females, the criterion value of 24.0 nmol/L yielded a sensitivity and specificity of 58.2% and 66.7%, respectively. The AUC was 0.65 (Fig. 6). The log likelihood ratio (+ LLR and − LLR) for males was 1.4 (1.3, 1.7) and 0.5 (0.4, 0.7), and for the females, it was 1.7 (1.5, 2.0) and 0.6 (0.5, 0.7). A total of 503 participants (151/846 [17.8%] males and 352/1285 [27.4%] females) had hyperparathyroidism (PTH > 6.9 pmol/L). A significant difference was observed between the age categories ranging from 30 to 75 years, with majority of males and females (71 males and 255 females) with increased PTH in the age category of 30–40 years (Fig. 7).

Comparison of blood markers in Saudi male and female participants in relation to vitamin D status is shown in Table 2. Male participants with 25(OH)D < 30.0 nmol/L tended to be younger (mean age = 40 ±

Table 1 Socio-demographic characteristics of Saudi males and females in Riyadh, Saudi Arabia ($N = 2131$)

Socio-demographic characteristics	Males $N = 846$ (%)	Females $N = 1285$ (%)
Age groups (in years)		
30–44	516 (61.0)	795 (61.9)
45–60	243 (28.7)	391 (30.4)
61–75	87 (10.3)	99 (7.7)
Marital status*		
Single	91 (10.8)	99 (7.7)
Married (including divorced/widowed)	755 (89.2)	11.86 (92.3)
Educational level of participant*		
University level or post-graduation	631 (74.6)	597 (46.5)
Intermediate and secondary	174 (20.6)	358 (27.9)
Illiterate and primary	41 (4.8)	330 (25.7)
Participant's occupation*		
Doctors/engineers/business/lawyer	97 (11.5)	25 (1.9)
Military/home maker	102 (12.1)	645 (50.2)
Teacher/secretary/health staff	547 (64.7)	517 (40.2)
Unskilled workers	23 (2.7)	68 (5.3)
Retired	77 (9.1)	30 (2.3)
Household monthly income*[1] (in US dollars) (M = 825, F = 1089)		
≥ 5000	127 (15.4)	104 (9.6)
> 2600–< 5000	420 (50.9)	367 (33.7)
≤ 2600	278 (33.7)	618 (56.7)
Type of housing*		
Villa	496 (58.6)	764 (59.5)
Apartment	302 (35.7)	330 (25.7)
Arabic style house	48 (5.7)	191 (14.9)
Waist circumference*[2]		
Normal (M ≤ 90 cm; F ≤ 80 cm)	377 (44.6)	239 (18.6)
Central obesity (M > 90 < 102 cm; F > 80 < 88 cm)	221 (26.1)	291 (22.6)
High central obesity (M ≥ 102 cm; F ≥ 88 cm)	248 (29.3)	755 (58.8)
Physical activity*[3]		
Low	767 (90.7)	738 (57.4)
Moderate/high	79 (9.3)	547 (42.6)

*$p < 0.001$

[1] Numbers are less because participants said do not know/do not want to tell

[2] Waist circumference: normal males ≤ 90 cm and females ≤ 80 cm; central obesity: M > 90 < 102 cm F > 80 < 88 cm; high central obesity: M ≥ 102 cm and F ≥ 88 cm

[3] High physical activity defined as "at least 3 days of activity achieving a minimum total physical activity of at least 1500 MET-minutes/week and moderate as five or more days of moderate-intensity activity and/or walking of at least 30 min per day"

[4] Low activity those not included in high or moderate activity

10.3 years) and more obese (mean BMI 30 ± 6.7) than male who were not deficient. Mean values of serum calcium, phosphorus, ALP, and PTH were significantly different between groups based on the cutoff. Mean serum calcium levels were lower in the vitamin D ≤ 30 group as compared to > 30 nmol/L (2.28 ± 0.08 vs 2.29 ± 0.08 nmol/L, $p < 0.003$), whereas mean ALP was higher in the decreased vitamin D group (< 30 nmol/L) (Table 2). The mean PTH levels were also significantly higher (5.77 ± 2.07 vs 4.67 ± 1.74) in the 25(OH)D < 30.0 nmol group (Table 2). Similar differences were observed for the female participants when comparing those with more vs less than 24.0 nmol/L of 25(OH)D. The mean phosphorus levels were significantly different, with higher levels (1.17 ± 0.15) in the > 24.0 nmol/L group, whereas ALP did not differ significantly. The mean PTH level in the deficient vs normal group was also significantly different (6.62 ± 2.47 vs 5.34 ± 1.90 pmol/L, $p < 0.001$) (Table 2).

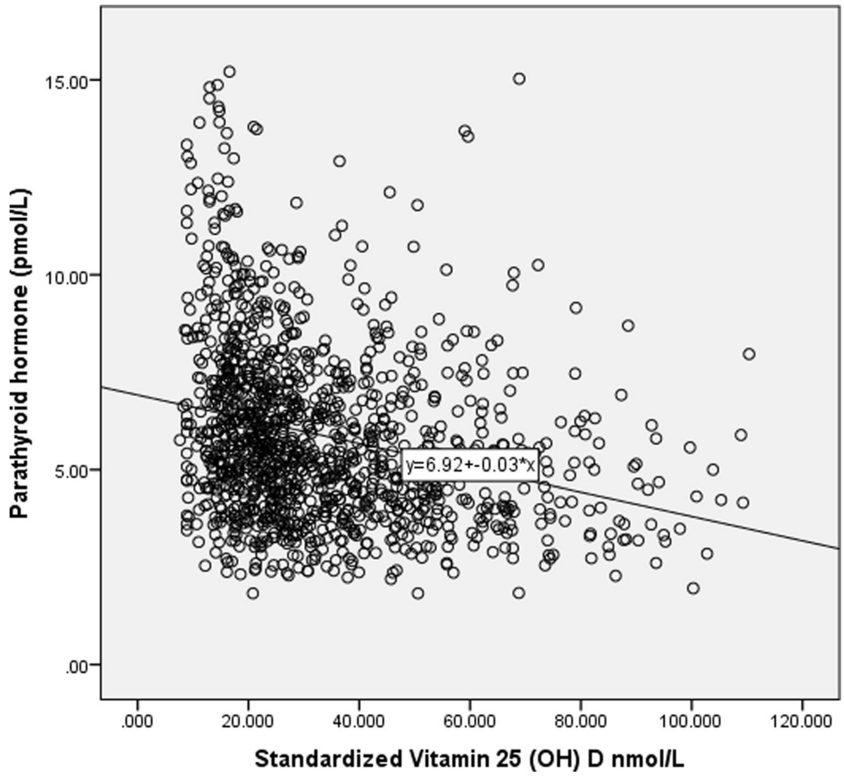


Fig. 3 Scatter plot between standardized vitamin 25(OH)D and parathyroid hormone in the females in Riyadh, Saudi Arabia ($n = 1285$)

Discussion

Vitamin D and PTH play major roles in bone health. Many studies have shown a significant association between 25(OH)D and serum PTH levels [21–23]. Moreover, hypovitaminosis D causes steady increase in parathyroid hormone levels, which results in bone loss [3–5, 24]. Ardawi et al. found a significant inverse correlation between PTH

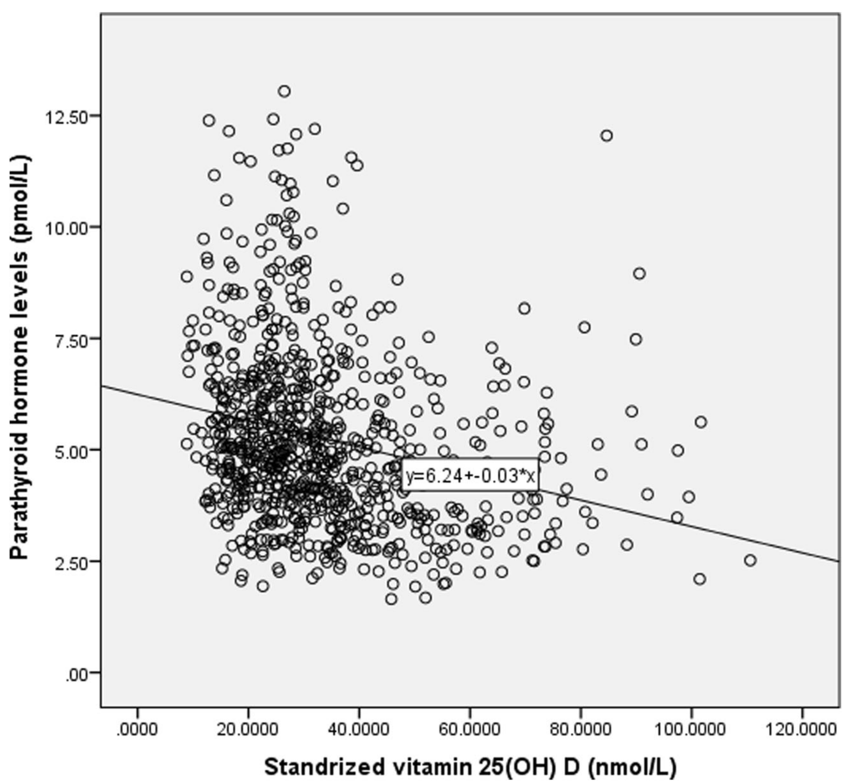
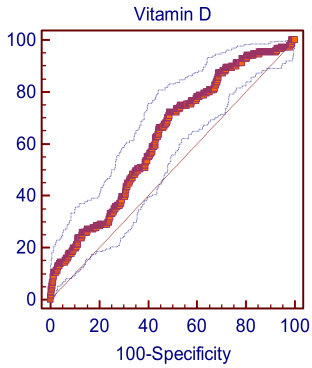


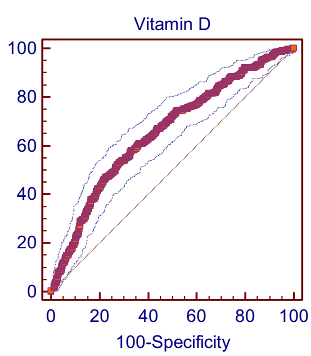
Fig. 4 Scatter plot between standardized vitamin 25(OH)D and parathyroid hormone in the males in Riyadh, Saudi Arabia ($n = 846$)



Area under the curve	0.62 (p<0.001)
Optimal criterion value for Vitamin 25(OH) D	30.0 nmol/L
Sensitivity	72.2 (64.3, 79.2)
Specificity	51.0 (47.1, 54.7)
Positive log likelihood ratio	1.4(1.3, 1.7)
Negative log likelihood ratio	0.5 (0.4, 0.7)

Fig. 5 ROC curve for determining optimal vitamin 25(OH)D for Saudi males (30.0 nmol/L cutoff point)

and bone mineral density (BMD), so that BMD values were interpreted according to PTH levels [25]. Hence, selecting cutoff values for serum 25(OH)D levels in relation to PTH is



Area under the curve	0.65 (p<0.001)
Optimal criterion value for Vitamin 25(OH) D	24.0 nmol/L
Sensitivity	58.2 (52.9, 63.4)
Specificity	66.7 (63.5, 69.7)
Positive log likelihood ratio	1.7 (1.5, 2.0)
Negative log likelihood ratio	0.6 (0.5, 0.7)

Fig. 6 ROC curve for determining optimal vitamin 25(OH)D level for Saudi females (24.0 nmol/L cutoff point)

fundamental for diagnosis and treatment of hypovitaminosis D to avoid hyperparathyroidism, which eventually would affect bone health.

In the present study, hypovitaminosis D, as defined by international cutoff values (< 50 nmol/L) for serum 25(OH)D levels [10], was very prevalent among otherwise healthy Saudi males (85.1%) and females (82.1%). Previously, Ardawi et al. found that 97.5% and 88.2% of Saudi males and females, respectively, had hypovitaminosis D [11, 25]. However, a recent meta-analysis study conducted by Al-Daghri gathered all epidemiologic local studies on vitamin D from 2011 to 2016 and found that overall prevalence was 81% at < 50 nmol/L in the Saudi population [26]. The majority of the Saudi population has hypovitaminosis D for reasons that are only partially understood. One of the reasons that could explain such high rates is the lack of sufficient sun exposure, specifically when considering countries like Saudi Arabia with sunny climates and hot seasons most of the year [11, 25]. Because the majority of the Saudi population were labeled as hypovitaminosis D with the current cutoff value, which is often questioned in daily practice, we propose that the lower limit of normal for 25(OH)D might differ from one population to another. With the current cutoff values in use in clinical practice, we are obliged to treat and follow many patients defined as deficient by the current standard [27]. Furthermore, many expensive unnecessary clinical investigations, such as DXA scans, will be overused while the diagnosis of hypovitaminosis D is still uncertain. Moreover, the defined level of 25(OH)D resulted from the regional large-scale study performed in the Middle East [11], but other few studies have used 25(OH)D < 37.5 nmol/L (15 ng/mL) as the cut cut-off for diagnosing vitamin D deficiency for the MENA region [12]. Others have used < 70 nmol/L (28 ng/mL) as the cutoff for the Saudi population [13]. Some countries with highly prevalent hypovitaminosis D have tried to decrease the cutoff level for defining 25(OH)D as deficient. For example, in Lebanon, only 72.8% of the population was deficient when 37 nmol/L was used as a cutoff of hypovitaminosis D [12].

This study was performed to determine the optimal cut-off points for the lower limit of normal for 25(OH)D levels to prevent hyperparathyroidism (PTH > 6.9 pmol/L). With this approach, we found that 30.0 nmol/L and 24.0 nmol/L for males and females, respectively, were the optimal cut-off points for the lower limits of normal 25(OH)D concentrations to prevent hyperparathyroidism and bone loss. However, similar observations have been documented before. Local and international studies conducted among adolescents and premenopausal females recommend that serum 25(OH)D levels of around 40 nmol/L should be sufficient to suppress PTH [23, 28, 29]. Our results are more in support of Lips et al., who found a level of 30 nmol/L was enough to suppress PTH level but in elderly individuals [30]. By using the new 25(OH)D cutoff values, only

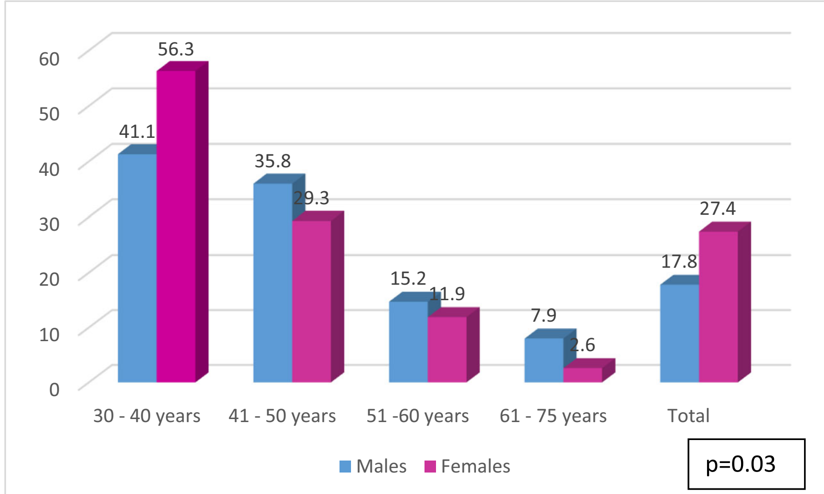


Fig. 7 Percentage of participants with serum parathyroid levels > 6.9 pmol/L, by age and gender ($n = 503$)

52.0% and 40.6% of Saudi males and females, respectively, would be diagnosed with low vitamin 25(OH)D levels. Thus, more than 22.1% and 30.8% males and females, respectively, who were previously diagnosed as suffering from low vitamin D (based on high cutoff point of 50 nmol/L), would be considered as normal.

Our data demonstrate that the optimal concentration of 25(OH)D differed by gender. This could be explained by gender differences in sun exposure, physical activity, and clothing habits [29] and more importantly by the effect of estrogen in females that increases the synthesis of 25(OH)D binding protein, which in turn affects overall 25(OH)D concentrations [30].

In the present study, cutoff levels for hypovitaminosis D (30.0 nmol/L and 24.0 nmol/L for males and females, respectively) were associated with significantly lower levels of calcium and ALP levels in Saudi males and calcium and phosphate levels in Saudi females.

These results emphasize that the lower levels of normal for 25(OH)D used in practice in Saudi differ from other international cutoff levels. Although according to our findings, more than 24 nmol/L is considered normal for females; for the sake of practicality and to make it easier to standardize, we propose that using 30.0 nmol/L as the cutoff for both genders will result in significantly less cases being diagnosed with hypovitaminosis D, as shown in our study. This in turn will

Table 2 Mean differences in blood markers in males and females with and without vitamin 25(OH)D cutoff in Riyadh, Saudi Arabia

Characteristics	Minimum, maximum value	Vitamin 25(OH)D Mean (± SD) (nmol/L) Male $n = 846$; female $n = 1285$		Mean difference (95% CI)	*P* value
		Males > 30.0 ($n = 406$) Female > 24.0 ($n = 763$)	Male ≤ 30.0 ($n = 440$) Female ≤ 24.0 ($n = 522$)		
Calcium (mmol/L) Normal 2.1–2.5					
Male	2.02, 2.77	2.29 (± 0.07)	2.28 (± 0.08)	0.01 (0.005, 0.02)	0.005
Female	1.23, 2.88	2.32 (± 0.10)	2.29 (± 0.08)	0.02 (0.01, 0.04)	< 0.001
Phosphorus(mmol/L) Normal 0.7–1.3					
Male	0.53, 3.06	1.15 (± 0.18)	1.15 (± 0.23)	0.004 (− 0.03, 0.02)	0.79
Female	0.4, 1.95	1.21 (± 0.16)	1.17 (± 0.15)	0.03 (0.01, 0.05)	0.001
Alkaline phosphatase(IU/L) Normal 50–136					
Male	35, 211	101.32 (± 26.08)	106.94 (± 26.31)	− 5.62 (− 9.18, − 2.06)	0.002
Female	20, 196	97.59 (± 26.14)	98.74 (± 27.82)	− 1.14 (− 4.15, 1.84)	0.45
Parathyroid hormone(pmol/L) Normal 1.6–6.9					
Male	1.65, 13.0	4.67 (± 1.74)	5.77 (± 2.07)	− 1.09 (− 1.36,-0.83)	< 0.001
Female	1.83,14.87	5.34 (± 1.90)	6.62 (± 2.47)	− 1.27 (− 1.51, − 1.03)	< 0.001

have a huge impact in health economics and the cost-effectiveness of this test.

The main strengths of this study is that we conducted and utilized the standardized vitamin 25(OH)D levels. The study included relatively large sample size and we used a population-based design, with participants belonging to all social classes. Further, the inclusion and exclusion criteria were comprehensive. The major limitation of this study was that it was a cross-sectional design, whereas the best study design for such question would be a prospective cohort in which 25(OH)D, PTH, and DXA scans were serially measured. 25(OH)D and PTH levels were measured only once for each patient, which is a limitation because the two tests undergo seasonal changes.

Conclusion

In summary, the prevalence of hypovitaminosis D was very high in our cohort and given the ambiguity of the clinical implications and the need to treat, we propose new cutoff points so as to improve the clinical value of the measures significantly in terms of more accurate and cost-efficient diagnosis and treatment. A good percentage of this healthy cohort would have been labeled as having abnormal hypovitaminosis D using the current screening cutoff points, whereas in fact, many were completely normal. With the current data, we recommend against treating or following patients in clinical practice with 25(OH)D levels > 30 nmol/L, unless other convincing clinical or biological parameters are present. The abovementioned cutoff point (30.0 nmol/L) however cannot be generalized as local guidelines until they are reproduced in more than one study in different regions in the country or in a national study. Adding DXA scans in future studies as confirmatory tests would make those studies very valuable and potentially change clinical practice.

Further studies are required nationally, regionally, and internationally that compare the cutoff points for 25(OH)D for bone health among different countries and factors affecting them.

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Authors' contribution JAQ conceptualized the study, supervised the data collection, and participated in write-up and critical review of the manuscript; MM supervised the data collection, wrote the discussion, and reviewed the manuscript; AK supervised the training and data collection, conducted the analysis, and participated in the write-up and review; RH facilitated the laboratory work and contributed towards manuscript writing and review of the manuscript; AA contributed towards manuscript writing and critical review; SS supervised the data collection, conducted the analysis, and critical review of the whole manuscript. NAD supervised the laboratory work related to the retrospective standardization of the vitamin D and the critical review of the manuscript.

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Compliance with ethical standards

Ethical approval and consent to participate The study protocol was approved by the Institutional Review Board, King Saud University (E-12-658) and the Institutional Review Board of the Ministry of Health, Dammam (IRB ID MOH0151). Participants were enrolled in the study after they read, understood, and signed the consent form.

Consent for publication The consent form included statement related to processing and publication of data for a scientific research paper.

Conflicts of interest None.

References

1. Ganji V, Zhang X, Tangpricha V (2012) Serum 25-hydroxyvitamin D concentrations and prevalence estimates of hypovitaminosis D in the U.S. population based on assay-adjusted data. J Nutr 142:498–507
2. González-Gross M, Valtueña J, Breidenassel C, Moreno LA, Ferrari M, Kersting M, HELENA Study Group et al (2012) Vitamin D status among adolescents in Europe: the healthy lifestyle in Europe by nutrition in adolescence study. Br J Nutr 107:755–764
3. Harinarayan CV, Sachan A, Reddy PA, Satish KM, Prasad UV, Srivani P (2011) Vitamin D status and bone mineral density in women of reproductive and postmenopausal age groups: a cross-sectional study from South India. J Assoc Physicians India 59:698–704
4. Sadat-Ali M, Al Elq AH, Al-Turki HA, Al-Mulhim FA, Al-Ali AK (2011) Influence of vitamin D levels on bone mineral density and osteoporosis. Ann Saudi Med 31:602–608
5. Sadat-Ali M, Al-Omran AS, Al-Turki HA (2015) Parathyroid glands response to low vitamin D levels in healthy adults: a cross-sectional study. Ulster Med J 84:26–29
6. Prince RL (2006) Secondary and tertiary hyperparathyroidism. In: Favus MJ (ed) Primer on the metabolic diseases and disorders of mineral metabolism. American Society for Bone and Mineral Research, Washington, DC, pp 190–195
7. Institute of Medicine (1997) Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride. National Academy Press, Washington, DC, pp 1–432
8. Papapoulos SE, Clemens TL, Fraher LJ, Gleed J, O'Riordan JL (1980) Metabolites of vitamin D in human vitamin-D deficiency: effect of vitamin D3 or 1,25-dihydroxycholecalciferol. Lancet 2(8195 pt 1):612–615
9. Grant WB, Holick MF (2005) Benefits and requirements of vitamin D for optimal health: a review. Altern Med Rev 10:94–111
10. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM, Endocrine Society (2011) Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 96:1911–1930

11. Ardawi MSM, Qari MH, Rouzi AA, Maimani AA, Raddadi RM (2010) Vitamin D status in relation to obesity, bone mineral density, bone turnover markers and vitamin D receptor genotypes in healthy Saudi pre- and postmenopausal women. Osteoporos Int 22:463–475
12. Maalouf G, Gannagé-Yared MH, Ezzedine J, Larijani B, Badawi S, Rached A, Zakroui L, Masri B, Azar E, Saba E, Nammari R, Adib G, Abou Samra H, Alrawi Z, Salman S, el Muntasser K, Tarseen R, el Kharousi W, al-Lamki M, Alothman AN, Almarzook N, el Dessouki M, Sulaimani R, Saleh J, Suhaili AR, Khan A, Delmas P, Seeman E (2007) Middle East and North Africa consensus on osteoporosis. J Musculoskelet Neuronal Interact 7:131–143
13. Raef H, Al Bugami M, Balharith S, Moawad M, El-Shaker M, Hassan A, , King Faisal Specialist Hospital Osteoporosis Working group et al (2011) Updated recommendations for the diagnosis and management of osteoporosis: a local perspective. Ann Saudi Med 31:111–128
14. Hussain AN, Alkhenizan AH, El Shaker M, Raef H, Gabr A (2014) Increasing trends and significance of hypovitaminosis D: a population-based study in the Kingdom of Saudi Arabia. Arch Osteoporos 9:190. https://doi.org/10.1007/s11657-014-0190-3
15. Al Shaikh AM, Abaalkhail B, Soliman A, Kaddam I, Aseri K, Al Saleh Y et al (2016) Prevalence of vitamin D deficiency and calcium homeostasis in Saudi children. J Clin Res Pediatr Endocrinol 8: 461–467. https://doi.org/10.4274/jcrpe.3301
16. AlQuaiz MJ, Kazi A, Fouda M, Alyousefi N (2018) Age and gender differences in the prevalence and correlates of vitamin D deficiency. Arch Osteoporos 13:49. https://doi.org/10.1007/s11657-018-0461-5
17. National Health and Nutrition Examination Survey (NHANES). Anthropometry procedure manual. Accessed on January 2014 at https://www.cdc.gov/nchs/data/nhanes/nhanes_07_08/manual_an.pdf
18. World Health Organization. Obesity: preventing and managing the global epidemic. Report on a WHO Consultation on Obesity, Geneva, 3–5 June, 1997. WHO/NUT/NCD/98.1.2000. Technical Report Series Number 894. Geneva: World Health Organization. Accessed August 2016
19. Jakab E, Kalina E, Petho Z, Pap Z, Balogh A, Grant WB, Bhattoa HP (2017) Standardizing 25-hydroxyvitamin D data from the HunMen cohort. Osteoporos Int 28:1653–1657
20. Parathyroid hormone. Mayo Clinic Laboratories. https://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/28379
21. Peppe J, Romagnoli E, Nofroni I, Pacitti MT, De Geronimo D, Letizia C et al (2005) Vitamin D status as the major factor determining circulating levels of parathyroid hormone: a study in normal subjects. Osteoporos Int 16:805–812
22. Souberbielle JC, Cormier C, Kindermans C, Gao P, Cantor T, Forette F et al (2001) Vitamin D status and redefining serum parathyroid hormone reference range in the elderly. J Clin Endocrinol Metab 86:3086–3090
23. Sulimani RA, Mohammed AG, Alfadda AA, Alshehri SN, Al-Othman AM, Al-Daghri NM et al (2016) Vitamin D deficiency and biochemical variations among urban Saudi adolescent girls according to season. Saudi Med J 37:1002–1008. https://doi.org/10.15537/smj.2016.9.15248
24. Bolland MJ, Grey AB, Ames RW, Horne AM, Mason BH, Wattie DJ, Gamble GD, Bouillon R, Reid IR (2007) Age-, gender-, and weight-related effects on levels of 25-hydroxyvitamin D are not mediated by vitamin D binding protein. Clin Endocrinol 67:259–264
25. Ardawi MS, Sibiany AM, Bakhsh TM, Qari MH, Maimani AA (2012) High prevalence of vitamin D deficiency among healthy Saudi Arabian men: relationship to bone mineral density, parathyroid hormone, bone turnover markers, and lifestyle factors. Osteoporos Int 23:675–686. https://doi.org/10.1007/s00198-011-1606-1
26. Al-Daghri NM (2018) Vitamin D in Saudi Arabia: prevalence, distribution and disease associations. J Steroid Biochem Mol Biol 175: 102–107
27. Al-Daghri NM, Al-Saleh Y, Aljohani N, Sulimani R, Al-Othman AM, Alfawaz H, Fouda M, Al-Amri F, Shahrani A, Alharbi M, Alshahrani F, Tamimi W, Sabico S, Rizzoli R, Reginster JY (2017) Vitamin D status correction in Saudi Arabia: an experts' consensus under the auspices of the European Society of Clinical and Economic Aspects of Osteoporosis, Osteoarthritis, and Musculoskeletal Diseases (ESCEO). Arch Osteoporos 12(1):1
28. Bacon CJ, Woo J, Lau EM, Lam CW, Gamble GD, Reid IR (2010) Effects of 25-hydroxyvitamin D level and its change on parathyroid hormone in premenopausal Chinese women. Osteoporos Int 21: 1935–1941
29. Outila TA, Kärkkäinen MU, Lamberg-Allardt CJ (2001) Vitamin D status affects serum parathyroid hormone concentrations during winter in female adolescents: associations with forearm bone mineral density. Am J Clin Nutr 74:206–210
30. Lips P, Wiersinga A, van Ginkel FC, Jongen MJ, Netelenbos JC, Hackeng WH et al (1988) The effect of vitamin D supplementation on vitamin D status and parathyroid function in elderly subjects. J Clin Endocrinol Metab 67:644–650