

Serum 25-hydroxyvitamin D concentrations are inversely associated with body adiposity measurements but the association with bone mass is non-linear in postmenopausal women

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ABSTRACT

Vitamin D deficiency has been linked to increased adiposity and decreased bone density. It is not known if vitamin D is linked to adiposity measures and bone mass in postmenopausal Qatar women. We investigated an association between serum vitamin D [25-hydroxyvitamin D (25(OH)D)] and adiposity measurements in postmenopausal women using Qatar Biobank data (n = 935). The post-menopausal status was self-reported by participants. Multivariate adjusted regression was applied to determine the association between serum 25(OH)D and body adiposity markers and bone mass. Serum 25(OH)D was significantly, inversely associated with body mass index (p < 0.0005), waist circumference (0.044), fat mass (p < 0.003), gynoid fat (p < 0.001), and android fat (p < 0.009). Serum 25(OH)D appeared to have an inverse 'U' association with several adiposity measures. Overall, body adiposity markers were the lowest in the 4th quartile serum 25(OH)D and significantly lower compared to the 1st quartile serum 25(OH)D. In multivariable adjusted analysis, no association was found between serum 25(OH)D concentration and bone mass when serum 25(OH)D was categorized. In a continuous variable analysis, the association between 25(OH)D and bone mass was significant, non-linear, inverse 'U'. In conclusion, serum 25-hydroxyvitamin D was inversely associated with adiposity measures and non-linearly associated to bone mass in postmenopausal Qatari women.

1. Introduction

Vitamin D is a lipophilic vitamin needed for calcium and phosphorous homeostasis. Vitamin D is obtained from limited dietary sources such as fatty fish, egg yolk, and fortified cereals and dairy [1,2]. Also, vitamin D is synthesized endogenously in the skin from 7-dehydrocholesterol through thermal isomerization when exposed to ultraviolet-B light. Exogenously ingested and endogenously synthesized vitamins are converted to 25-hydroxyvitamin D [25(OH)D] in the liver [3]. 25(OH)D is a major circulatory form and is widely used as a biomarker of vitamin D nutritional status [4]. Further, 25(OH)D is converted to biologically active 1,25 dihydroxyvitamin D [1,25(OH)₂D] in the kidney through the action of 1 α -hydroxylase [5]. All metabolic functions associated to vitamin D are mediated through the action of 1,25(OH)₂D and vitamin D receptors (VDR) via gene modulation at target tissues [6].

In addition to maintaining calcium homeostasis, 25(OH)D has been linked to several non-calcemic diseases. Studies have shown that poor vitamin D status has been associated with the increased risk of many

ailments such as metabolic syndrome [7], cardiovascular disease (CVD), diabetes [8], depression [9], infectious diseases [10], and cancer [11]. Post-menopausal women are at a higher risk for several chronic diseases due to loss of estrogen [12]. The reduction of estrogen increases the risk of breast cancer and CVD due to changes in body composition (increased abdominal fat) and blood lipids [13]. The prevalence of vitamin D deficiency [<10 ng/mL of serum 25(OH)D] in post-menopausal women (17.5%) is higher than pre-menopausal women (13.2%) in Qatar [14]. Also, post-menopausal women have a higher prevalence of bone fractures and falls [15]. Among several reasons, vitamin D deficiency could also play a role because low vitamin D has been linked to bone demineralization [16].

In Qatar, serum 25(OH)D deficiency is highly prevalent among women due to less exposure to sunlight. The prevalence of 25(OH)D deficiency in general population is reported to be 90.4% in Qatar [17]. Several studies have linked serum 25(OH)D deficiency with increased adiposity measures such as BMI and waist circumference (WC) [18]. A few studies found an inverse association with BMI [19–24]. Given a role

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of 25(OH)D in muscles and adipose tissues [25], it has been hypothesized that 25(OH)D may play a role body adiposity. Also, the association between serum 25(OH)D concentrations and body composition measures and bone mass/density is not clear, especially in post-menopausal women. There are no studies conducted on the association of 25(OH)D concentrations with adiposity measurements and bone mass in post-menopausal women in Qatar. Therefore, the objective of this study was to investigate the association between serum 25(OH)D and adiposity measurements in post-menopausal women utilizing the data from the Qatar Biobank (QBB). The hypothesis is that circulating 25-hydroxyvitamin D concentrations will be inversely associated with the measurements of body adiposity such as BMI, fat mass, and WC and directly associated with bone mass and lean mass in post-menopausal women in Qatar.

2. Methods

2.1. Brief Description of Qatar Biobank Survey

QBB was established in 2012 in collaboration with the Ministry of Public Health and Hamad Medical Corporation. QBB collects the data from the participants' lifestyle and health of Qatari people and long-term residents of Qatar. Persons who are 18 years and older will be allowed to participate in this survey study. QBB study population consisted of 51% men and 49% women with the highest number of participants were in the age group of between 25 and 34 years. Participants are required to give urine, blood, and saliva samples for biochemical analysis. Part of the biological samples was cryogenically frozen for future use. Also, the data on physical measurements, health status indicators, lifestyle factors, grip strength, body composition, and lung and heart functions are collected as part of the overall health assessment of Qatari population. This study was approved by the Qatar Biobank Institutional Review Board. Detailed Qatar Biobank methods were explained elsewhere [26].

2.2. Biochemical measurement

Blood samples were obtained from each participant and serum was separated. Immediately, serum samples were stored frozen at -80°C . Later they were analyzed at Hamad Medical Centre Laboratories for various biochemical health markers. Participants were asked to fast overnight before blood collection. Quantitative measurements of serum 25(OH)D concentrations [$25(\text{OH})\text{D}_2$ and $25(\text{OH})\text{D}_3$] were measured using LIAISON assay, a Chemiluminescent immunoassay. The procedure consisted of 2 step process. During the first procedure, blood samples were centrifuged to collect serum. Then vitamin D was dissociated from its binding protein and a tracer was added. Then the unbound protein was removed by a washing. Starter reagents were added to initiate the chemiluminescent reaction. Then 25(OH)D concentrations were measured with a photomultiplier.

2.3. Description of study variables

The postmenopausal status was assessed with a self-administered questionnaire. Subjects answered to the question "are you currently in post-menopause status?" Subjects who answered "yes" to this question was identified as a person undergone menopause. Therefore, the postmenopausal status was self-reported. Only these subjects formed the initial study sample. Height and weight were measured with seca stadiometer. BMI was computed from height and weight measurements (height in m^2/weight in kg). Hip and WC were measured using a measuring tape. Body composition and bone mineral density were assessed using full body dual energy x-ray absorptiometry (GE Healthcare, Madison, WI, USA). We have used bone mass, lean body mass, fat mass, android fat, and gynoid fat as markers of body composition. Also, BMI and WC were used as surrogate markers of body adiposity.

Several confounding variables were considered in the data analysis. The data on these variables were extracted from the main questionnaire and nurse's interview. These variables were age, education, income level, smoking, alcohol intake, season of examination, physical activity, hormone replacement therapy, and vitamin D supplements use.

2.4. Data analysis

A random sample of 1000 post-menopausal women was obtained from the Qatar Biobank. After excluding data for several missing confounding variables the final sample for the data analysis was 935. All continuous variables were presented as mean and standard deviation (SD) of mean. In the analysis, serum 25(OH)D concentrations were categorized in to quartiles. For non-normal data, median and intern quartile ranges were used. As part of the primary analysis, multivariate-adjusted linear regression was used to determine the association between 25(OH)D concentrations (categorized into quartiles) and body adiposity markers (WC, BMI, body fat mass, lean body mass, gynoid fat, and android fat) and bone mass.

As part of the secondary priority, we have determined a multivariable adjusted continuous association between serum 25(OH)D concentrations and body composition measurements using these variables in a continuous form with restricted cubic spline procedure. Multiple confounding variables were taken into consideration in the data analysis. These were age, income, use of vitamin D supplements, hormone replacement therapy, physical activity, education, season of examination, and smoking. Only the continuous association between serum 25(OH)D and bone mass was presented for simplicity. Stata (Stata 15.1 version, College Station, TX, USA) was used for data analysis. Statistical significance was set at $p\text{-value} < 0.05$ for analyses.

3. Results

The age of the participants ranged from 45 y to 83 y old. The mean age across the quartiles ranged from 56 to 58 y old. The proportion of subjects in the highest serum 25(OH)D quartile category was highest (27%) for vitamin D supplement users ($P = 0.001$) compared to other categories. Individuals in the highest quartile for serum 25(OH)D were more educated (46%) compared to those in the lowest quartile ($\approx 38\%$). Prevalence of obesity ($\text{BMI} \geq 30 \text{ kg/m}^2$) was highest in the lowest serum 25(OH)D quartile (≈ 70). Detailed subjects' characteristics are presented in Table 1.

The association between serum 25(OH)D concentrations and body adiposity measures for Qatar post-menopausal women is presented in Table 2. Overall, in the multivariate adjusted analysis, we found serum 25(OH)D concentrations were significantly, inversely associated with the markers of adiposity such as BMI (P for trend, 0.005), WC (P for trend, 0.044), fat mass (P for trend, 0.003), gynoid fat mass (P for trend, 0.001), and android fat mass (P for trend, 0.009). The mean BMI, WC, and android fat were the highest in the 2nd quartile serum 25(OH)D category. Therefore, the body adiposity measurements appeared to rise slightly initially and then decline. Adiposity measures such as BMI, fat mass, gynoid fat, and android fat were significantly lower in the 4th quartile serum 25(OH)D compared to the 1st quartile serum 25(OH)D concentration ($P < 0.05$).

No association was observed between serum 25(OH)D concentrations and bone mass when serum 25(OH)D concentrations were categorized. However, in a continuous association between serum 25(OH)D and bone mass, we observed a non-linear, significant association ($P < 0.011$) (Fig. 1). This non-linear association between serum 25(OH)D and bone mass was inverse 'U'. Additionally, overall, the association between serum 25(OH)D and several body composition measurements in a continuous form is inverse 'U' (data not presented).

Table 1
Study sample characteristics by quartiles of serum 25(OH)D concentrations¹.

Characteristic	Serum 25(OH)D concentration ²				p-value
	Q1 (n = 232) (4-17 nmol/L)	Q2 (n = 267) (18-23 nmol/L)	Q3 (n = 221) (24-29 nmol/L)	Q4 (n = 215) (30-104 nmol/L)	
Age, y	57 (5.9)	56.9 (5.9)	58.4 (6)	58 (6.6)	0.022
Education					0.07
Low, %	123 (53)	137 (51.3)	134 (60.6)	100 (46.5)	
Medium, %	21 (9.1)	18 (6.7)	17 (7.7)	16 (7.4)	
High, %	88 (37.9)	112 (41.9)	70 (31.7)	99 (46)	
Smoking					0.42
No, %	229 (98.7)	261 (97.8)	217 (98.2)	209 (97.2)	
Yes, %	1 (0.4)	1 (0.4)	3 (1.4)	1 (0.5)	
Ex-smoker, %	2 (0.9)	5 (1.9)	1 (0.5)	5 (2.3)	
HRT, %	16 (6.9)	22 (8.2)	11 (5)	24 (11.2)	0.1
Supplement use, %	20 (8.6)	42 (15.7)	45 (20.4)	58 (27)	<0.001
BMI, kg/m ²					<0.001
Normal	9 (3.9)	9 (3.4)	8 (3.6)	17 (7.9)	
Overweight	61 (26.3)	61 (22.8)	53 (24)	82 (38.1)	
Obese	162 (69.8)	197 (73.8)	160 (72.4)	116 (54)	
Leisure time physical activity, MET h/wk	0 (0-12.2)	0 (0-48.8)	0 (0-48.8)	0 (0-48.8)	0.32

¹ n = 935. Date were obtained from the Qatar Biobank. Abbreviations: 25(OH)D, 25-hydroxyvitamin D; HRT, hormone replacement therapy; MET, metabolic equivalents; WC, waist circumference.

² Data are presented as mean (SD) or median (inter quartile range) for continuous measures and n (%) for categorical measures. Measures were reported according to the quartile serum 25(OH)D concentrations.

4. Discussion

In this study, we report an association between serum 25 (OH)D and body adiposity measures and bone mass in postmenopausal women in Qatar based on a recently updated serum 25(OH)D data that were released by the QBB in November 2018. The prevalence of vitamin D deficiency in our study sample was 77% based on the serum 25(OH)D concentration of <30 nmol/L. This prevalence rate is lower than general population of Qatar due to increased vitamin D supplement consumption in this population compared to general population. We report that serum 25(OH)D concentration is significantly, inversely associated with body adiposity markers such as BMI, WC, fat mass, gynoid fat, and android fat. The association of serum 25(OH)D with bone mass was significant, non-linear, inverse 'U'.

Studies on the association between serum 25(OH)D and body composition measures yielded equivocal results. In agreement with our findings, Chacko et al [27] found an inverse association between serum 25(OH)D and BMI and WC in postmenopausal women (n = 292). Another study also confirmed the inverse association between serum 25 (OH)D concentrations and body composition measurements such as WC in post-menopausal women [28]. In contrast to our findings, Simas et al [29] did not find an association between serum 25(OH)D and body composition measures in postmenopausal women. Similarly, very recently, in a prospective study on postmenopausal women, Elliot et al [30] also found no association between serum 25(OH)D and body adiposity measures. However, both studies were based on a small sample size (n = 106 and n = 112). Although we found an inverse association

Table 2
Association between serum 25(OH)D concentrations and body composition measurements in multivariate adjusted analysis in post-menopausal Qatari women¹.

Body composition measurement	Serum 25-hydroxyvitamin D concentrations ²				p for trend ⁴
	Q1 ³ (n = 232) (4-17 nmol/L)	Q2 (n = 267) (18-23 nmol/L)	Q3 (n = 221) (24-29 nmol/L)	Q4 (n = 215) (30-104 nmol/L)	
BMI, kg/m ²	33.2 (32.5, 33.9)	33.9 (33.3, 34.6)	33.4 (32.6, 34.1)	31.7 (30.9, 32.5) ⁵	0.005
WC, cm	94.5 (93.1, 96)	95.8 (94.4, 97.1)	94.4 (92.9, 95.9)	92.7 (91.1, 94.2)	0.044
Fat mass, kg	38.5 (37.2, 39.9)	39.5 (38.3, 40.7)	38.3 (36.9, 39.6)	35.8 (34.4, 37.2) ⁵	0.003
Gynoid fat, kg	6.2 (6, 6.4)	6.2 (6, 6.4)	6 (5.8, 6.2)	5.7 (5.4, 5.9) ⁵	0.001
Android fat, kg	3.3 (3.2, 3.5)	3.4 (3.3, 3.6)	3.3 (3.2, 3.4)	3.1 (2.9, 3.2) ⁵	0.009
Lean mass, kg	39.3 (38.5, 39.9)	39.8 (39.1, 40.4)	39.9 (39.1, 40.7)	38.3 (37.6, 39.1)	0.13
Bone mass, kg	2 (2, 2.1)	2.1 (2.1, 2.1)	2.1 (2.1, 2.2)	2.1 (2, 2.1)	0.21

¹ n = 935. Date were obtained from the Qatar Biobank. Abbreviations: 25(OH)D, 25-hydroxyvitamin D; WC, waist circumference.

² Data are presented as mean (95% CI). Measures were reported according to the quartile serum 25(OH)D concentrations.

³ Referent category.

⁴ Significance in the multivariate adjusted regression analysis. Adjusted for age, leisure time physical activity, education, smoking, estrogen hormone replacement therapy, and vitamin D supplement use.

⁵ Significantly different from the referent category (quartile 1).

between serum 25(OH)D and body adiposity measures in a categorized analysis, it is interesting to note, in a continuous analysis the association is more like an inverse 'U', non-linear. These results need further confirmation from large prospective cohort studies.

In a meta-analysis and systematic review based on 23 studies, prevalence of 25(OH)D deficiency among obese subjects was 35% higher than normal subjects and 24% higher in overweight subjects [31]. Previous studies reported similar results of our study that women who have optimum to mild 25(OH)D had the lowest percentage of body fat when compared to women who were deficient in 25(OH)D [18]. Further, low serum 25(OH)D has been identified as a risk factor for increased body adiposity which increases the risk of 25(OH)D deficiency [32]. The exact mechanism through which 25(OH)D reduces the body adiposity is not clearly known. However, several mechanism are proposed for low circulating 25(OH)D concentrations in obese persons. These include decreased sun exposure by obese persons and decreased bioavailability of vitamer from dermis and dietary sources compared to their lean counterparts. It is not known exactly to what extent obese persons avoid sunlight exposure. This crucial information is missing in several studies. Other mechanisms include, obese persons tend to have an increased 1,25(OH)₂D concentrations which negatively inhibits the circulating 25(OH)D concentrations. Serum 25(OH)D gets sequestered within the adipose tissue of obese persons leading to decreased serum 25 (OH)D. Lastly, low serum 25(OH)D in obese persons is due to volumetric dilution of vitamer in adipose tissue [33]. It is clearly not known whether increased adiposity drives the differences in serum 25(OH)D concentrations or the differences in serum 25(OH)D concentrations

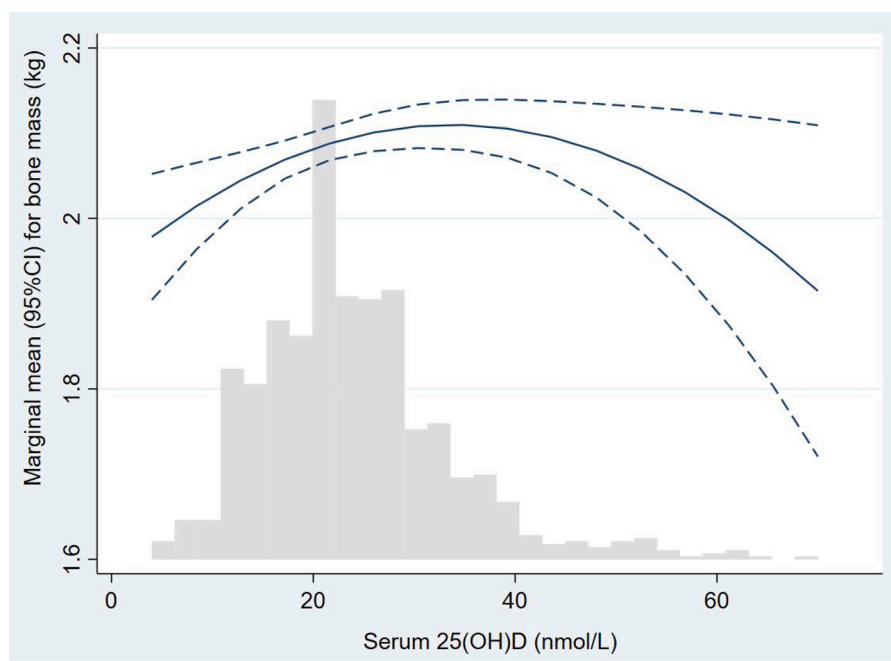


Fig. 1. Non-linear, significant association between serum 25-hydroxyvitamin D concentrations and bone mass in post-menopausal Qatari women ($P < 0.011$). Adjusted for age, leisure time physical activity, education, smoking, estrogen hormone replacement therapy, and vitamin D supplement use. Data were obtained from national Qatar Biobank.

drive the differences in adiposity/body composition measurements. It is likely the relationship is bi-directional.

Our results showed that the android fat was highest in the second quartile, lower in the first quartile, and lowest in the fourth quartile. According to previous studies in postmenopausal women, the drop in estrogen level will cause a drop in serum 25(OH)D concentrations and affect the distribution of fat where fat will accumulate mostly in the central area “android fat” [18]. Furthermore, Andreozzi et al [28] concluded that there was a significant inverse association between 25(OH)D and WC ($p < 0.0001$) which suggests persons with lower 25(OH)D had higher android fat. In a study conducted on Chinese population, increased visceral fat is significantly associated with 25(OH)D deficiency and insufficiency [34]. There is no clear evidence to explain why in the second quartile, android fat was highest compared to the rest of quartiles. It remains to be seen, if this association persists in a population with a large sample size.

The bone mass was highest in the third quartile serum 25(OH)D and lowest in the first quartile serum 25(OH)D. However, in the fourth quartile serum 25(OH)D, the bone mass decreased. This association in the categorized multivariable-adjusted analysis was not significant. This association is further illustrated when serum 25(OH)D concentrations and bone mass were used as continuous variables in which we observed a significant, non-linear inverse ‘U’ trend association. The association between serum 25(OH)D and bone health has yielded conflicting results. Based on the systematic review of 167 studies, there was a fair amount of evidence of direct association between serum 25-hydroxyvitamin D and bone mineral density [35]. A study by Bener et al [14] reported that in postmenopausal women with low serum 25(OH)D had low bone density. Low circulating 25(OH)D can lead to secondary hyperparathyroidism which in turn causes loss of bone minerals leading to lower bone density [36]. In contrast to our findings, Zhou et al [37] reported no association between serum 25(OH)D and bone mineral density in peri-menopausal women. Another study on European population also found no association between serum 25(OH)D and bone density, lumbar spine bone density, and T score ($n = 126$) [38]. Further, the effect of vitamin D supplementation on bone mass in a randomized control trial is also not encouraging. Hansen et al [39] reported no effect of vitamin D

supplementation at a dose level of 800 IU on bone mineral density in post-menopausal women. The finding of non-linear association in this study between serum 25(OH)D and bone mass needs further investigation in other populations.

One possible explanation for observed findings is that high 25(OH)D can act on bones as a demineralization agent leading to decalcification of bones. If calcium intake is not adequate then active $1,25(\text{OH})_2\text{D}$ can cause a decrease in bone mass in order to maintain calcium homeostasis [40]. Also, low levels of 25(OH)D can impair the absorption of dietary calcium which in turn can lead to bone loss [41]. Further, due to lack of estrogen hormone in post-menopausal women speeds up bone loss [42]. Conversely, estrogen suppresses bone resorption by upregulating osteoclast apoptosis [43]. Increased vitamin D in the absence of adequate dietary calcium makes things worse for post-menopausal women. Thus, post-menopausal women should consume adequate amounts of vitamin D and calcium to optimize bone mass and to reduce bone resorption.

Our study has several strengths. Because we used the data from the Qatar Biobank, these results can be applied to the general post-menopausal women of Qatar. The Qatar biobank collects data on several demographic characteristics and other health markers. Because of the richness of the data, we were able to adjust the analysis for several confounding variables. Results presented in this study should not be viewed in terms of cause and effect association. Because vitamin D contents of supplements were not available in QBB database, we were unable to adjust the analysis for vitamin D intake from supplements. However, we adjusted the data for vitamin D supplements use.

5. Conclusion

Our study confirmed an association between serum 25(OH)D concentration and body adiposity measures in Qatar population. However this association between serum 25(OH)D and bone mass is non-linear, inverse ‘U’. The strength of the inverse ‘U’ relationship is weaker because in the extreme quartile, there were only 215 subjects (23% of sample). A minority of the subjects had serum 25(OH)D concentrations above 50 nmol/L, a concentration that is considered adequate for bone health. If the sample size is larger, the inverse ‘U’ relationship only gets

stronger. Therefore, further research is needed to confirm the association between 25(OH)D and body composition especially bone mass in postmenopausal women.

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Authors contributions

HA, SA, SA, ZJ; data analysis, interpretation of data, initial drafting of manuscript. ZH; data analysis, interpretation of data, revision of manuscript. VG; conceptualization of study, interpretation of data, initial drafting and revision of manuscript, and supervision.

Declaration of Competing Interest

The authors report no declarations of interest.

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