Original Article

Role of Parathyroid Hormone in Determination of Fat Mass in Patients with Vitamin D Deficiency

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Abstract

Background: Obesity has become a global epidemic and it is rising is Asia. Vitamin D deficiency (VDD) is widely prevalent in the Indian subcontinent. Studies have linked VDD to obesity and shown correlation between parathyroid hormone (PTH), 25-hydroxy Vitamin D (25(OH)D), and fat mass (FM). However, studies on the role of PTH among subjects with VDD are lacking. **Objective:** The objective of this study is to study the role of PTH in the determination of FM in participants with VDD. **Subjects:** Five hundred and fifty-one adults (m:247, f:304) were included in this study. **Materials and Methods:** Total and regional (trunk, arm, and leg) FM was assessed by dual X-ray absorptometry. Biochemical and hormonal parameters such as calcium, phosphorus, alkaline phosphatase, ionic calcium, 25(OH)D, and PTH were also analyzed. **Results:** The mean age of the study population was 58.8 ± 15.8 years (Male: [63.3 ± 13.1], Female: [55.2 ± 16.9]). FM and body mass index were significantly lower in females with higher levels of serum 25(OH)D. Total FM was negatively correlated with serum 25(OH)D ($r = -0.363$, $P < 0.0001$) and positively correlated with serum PTH (r: 0.262, $P < 0.0001$) in females only. Females with VDD and secondary hyperparathyroidism had higher FM than those with normal PTH. **Conclusions:** Females with VDD had higher total and regional FM. However, this correlation was evident only in those with high serum PTH levels, suggesting a potential role of PTH in the accumulation of FM.

Keywords: 25-hydroxy Vitamin D, fat mass, parathyroid hormone, Vitamin D deficiency

Introduction

In recent years, Vitamin D deficiency (VDD) has become a global epidemic, and Asian countries are no exception.[1,2] VDD prevails in epidemic proportions all over the Indian subcontinent, with the prevalence of 70%–100% in the general population.[3] Vitamin D has been associated with both classical skeletal and nonskeletal effects.[1] Several epidemiological studies have linked VDD to obesity and fat mass (FM).[4] The inverse correlation between FM and serum 25-hydroxy Vitamin D (25(OH)D) has also been reported in several studies.[5-12]

Vitamin D has a role in maintaining calcium homeostasis, bone metabolism and also linked to various noncommunicable diseases.[1,2] It has been reported that Vitamin D affects calcium absorption and bone health far below the levels currently used for the diagnosis of VDD.[13] However, there are no data on the serum levels of 25(OH)D which affect the body FM. We had earlier reported that bone mineral density is affected only in those Vitamin D deficient participants where serum parathyroid hormone (PTH) are raised.[14] Whether such phenomenon does exist for FM, is largely unknown. There are data suggesting that VDD could promote greater adiposity, leading to elevated PTH.[15] The role of 1,25-dihydroxy-Vitamin D ($1,25(OH)_2D$) in the modulation of adipogenesis through Vitamin D receptor (VDR)-dependent inhibition of critical molecular components of adipogenesis has also been reported.[16]

The association of high serum PTH with obesity,[17-19] body mass index (BMI),[20] and FM[7,21] has been reported by several researchers. However, some studies have failed to show any association between serum PTH and FM.[22,23] Since fat accumulates 25(OH)D, there always remains a controversy with

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regard to the relationship between fat and serum 25(OH)D.[13] Several studies have shown relationship of serum PTH and Vitamin D individually with FM, but there are only a few studies evaluating the combined effect of PTH and Vitamin D on FM.[5,6,8,12,19] In view of the above, this study was undertaken with the objective to evaluate the relationship of serum PTH and/or Vitamin D with FM. We hypothesized that FM will be significantly more among participants with VDD who has associated high serum PTH compared to those with normal serum PTH. This would indicate whether serum PTH is an important determinant of FM in participants with VDD or not.

Materials and Methods

A total of 551 apparently healthy adult participants with sedentary lifestyle from our earlier study[14] were included in this study. The participants belonged to Delhi, India (latitude 28 35°N). Those with hepatic, renal, dermatological disorders, alcoholism, or receiving medication which may adversely affect Vitamin D status were excluded from the study. Demographic, anthropometric, and clinical data were ascertained, and a detailed physical examination was conducted.

During their institutional visit for body composition assessment, fasting blood samples were collected, cold centrifuged, and serum kept immediately at −20°C till the assays were performed. All assays were carried out within a period of 15 days from the time sample collection. The study was approved by the Ethics Committee of the Institute of Nuclear Medicine and Allied Sciences, and written informed consent was obtained.

Biochemical estimations were carried out using automated analyzer (Hitachi 902) and commercial kits (Roche, Manheim, Germany). The normal ranges for serum total calcium (8.8–10.2 mg/dl, analytical sensitivity 0.2 mg/dl), ionic calcium (1.12–1.32 mM), inorganic phosphorus (2.7–4.5 mg/dl, analytical sensitivity 0.3 mg/dl), and alkaline phosphatase were (females: <240 U/L; males: <270 U/L, analytical sensitivity 5 IU/L). The serum concentrations of 25(OH)D (reference range: 9.0–37.6 ng/ml, analytical sensitivity 1.5 mg/dl) and PTH (reference range: 10–65 pg/ml, analytical sensitivity 0.7 pg/ml) were measured by RIA (Diasorin, Stillwater, MN, USA) and electrochemiluminescence assay (Roche Diagnostics, GMDM-Mannheim, Germany), respectively. Intra- and inter-assay coefficient of variation was 3.5% and 5% for serum 25(OH)D and 2.4% and 3.6% for serum PTH. Serum 25(OH)D level of <20 ng/ml was defined as VDD. VDD was further classified as severe (25(OH)D <5 ng/ml), moderate (25(OH)D <10 ng/ml), and mild (25(OH)D <20 ng/ml).[24] Secondary hyperparathyroidism (SHPT) was defined with serum PTH levels >65 pg/ml.

The participants (m:247, f:304) were grouped according to the quartiles of serum PTH. The quartiles for males and females were (≤40.2, 40.2–55.2, >55.2–73.5, and >73.5 pg/ml) and (≤34.8, >34.8–52.3, >52.3–74.7, and >74.7 ng/ml) and interquartile ranges were 33.3 pg/ml and 39.9 pg/ml, respectively.

Total and regional (arm, trunk, and leg) FM was measured using the Prodigy Oracle (GE Lunar Corp., Madison, WI) according to standard protocol. Quality control procedures were carried out in accordance with the manufacturer's recommendations. Instrument variation was determined regularly using a phantom supplied by the manufacturer, and mean coefficient of variation was <0.5%. For *in vivo* measurements, mean coefficients of variation for all sites were <1%.

Statistical analysis was carried out using software SPSS 20 (Chicago, IL, USA). Data were presented as mean ± standard deviation (95% confidence interval) or number (%) unless specified. *P* for trend was applied to detect differences in fat among the quartiles of PTH. Comparison of various parameters (FM) between individual quartiles was done with *post hoc* analysis in one-way ANOVA test. Pearson's correlation coefficient was calculated to assess the strength of relationship between total fat and 25(OH)D and PTH. $P < 0.05$ was considered statistically significant.

Results

The mean age, BMI, total and regional body FM, biochemical and hormonal parameters of study participants are shown in Table 1. The mean age of male participants was significantly higher than female participants. VDD was present in 472 (85.7%) subjects and SHPT in 188 (34.1%) subjects.

The total and regional FM was significantly lower in females with serum 25(OH)D levels of >10 ng/ml as compared to those with serum 25(OH)D levels of <10 ng/ml. However, significant lowering of arm fat became obvious only at serum 25(OH)D levels of >20 ng/ml. Although a similar trend of inverse relation was noted in men, it did not reach statistical significance. Similarly, BMI was also significantly lower only in females with higher serum 25(OH)D levels [Table 2]. No significant difference was observed in BMI, total and regional FM between participants with severe (<5 ng/ml),

Table 1: Baseline mean age, body mass index, biochemical, hormonal and body fat mass parameters of study population

Parameters	Males (*n*=247)	Females (*n*=304)	*P*
Age	63.3±13.1	55.2±16.9	<0.0001
Calcium (mg/dl)	9.6±0.4	9.7±0.4	0.033
Phosphorus	3.4±0.5	3.7±0.4	<0.0001
Alkaline phosphatase (IU/L)	202±62	227±73	<0.0001
Vitamin D (ng/ml)	11.2±6.8	12.2±8.2	0.126
PTH (pg/ml)	60.7±32.7	58.3±42.4	0.468
Ionic calcium	1.17±0.05	1.17±0.05	0.186
Trunk fat (kg)	14.12±5.66	15.55±5.55	0.003
Arm fat (kg)	1.77±0.77	2.65±1.46	<0.0001
Leg fat (kg)	6.26±2.52	9.96±3.53	<0.0001
Total fat (kg)	22.90±8.74	29.04±9.54	<0.0001
BMI (kg/m^2)	25.50±4.67	27.42±5.34	<0.0001

PTH: Parathyroid hormone, BMI: Body mass index

and moderately severe (5–10 ng/ml) categories of VDD in both genders.

As regards, the relationship of serum PTH with total and regional FM, a direct correlation was observed in both genders. The trunk, arm, leg, and total FM which increased with the increasing quartiles of PTH in females became significant at serum PTH levels of >52 pg/ml (third quartile). The similar rising trend of total and regional FM with increasing serum levels of serum PTH was observed in males, but only leg FM could reach statistical significance. BMI also revealed a similar relationship with serum PTH as total FM in both genders [Table 3]. Furthermore, females with VDD and SHPT had higher total and regional FM than those with VDD and normal serum PTH. The Same pattern was not observed in males [Table 4].

Total FM was negatively correlated with serum 25(OH)D ($r = -0.363$, $P < 0.0001$) and positively correlated with serum PTH (r: 0.262, $P < 0.0001$) in females. However, no such correlation was observed in males [Figure 1].

Discussion

The present study evaluated the relationship of body FM with serum levels of 25(OH)D and PTH. The significant inverse correlation observed between serum 25(OH)D and total and regional FM in females, is consistent with earlier reports from different populations.[5-12] A randomized controlled trial suggested greater loss in FM for females receiving Vitamin D,[25] indirectly suggesting an inverse correlation of FM with Vitamin D in females. A weak but significant correlation between FM and baseline serum 25(OH)D was also observed in a mixed population of normal weight, overweight, and obese participants which became highly significant after cholecalciferol loading.[26] In contrast, Sneve *et al*.[22] did not find any significant change in weight, waist-to-hip ratio, or percentage body fat following cholecalciferol supplementation.

Inverse correlation between visceral FM and 25(OH)D in both genders from Asian and European adults has been reported in several studies.[10,27,28] Consistent with the above reports, the truncal FM, representing visceral mass in this study, was also significantly lower in both male and female participants with serum 25(OH)D levels of >20 ng/ml, suggesting inverse correlation. Age and physical activity have been reported to be important determinants of relationship between Vitamin D and FM.[12,29] Males being physically more active than females might alter the relationship between Vitamin D and fat.[30] We, in one of our earlier studies, also found stronger correlation coefficient between 25(OH)D and total FM in sedentary women ($r = -0.222$) as compared to physically active paramilitary women ($r = -0.207$), further supporting the role of exercise.[31] Significant inverse correlation between 25(OH)D and fat, observed only in women in the present study, could possibly be due to their sedentary lifestyle and being significantly younger than their male counterparts. Dietary and hormonal differences between the two genders, though not evaluated in this study, could also play a role.[5,23,30,32]

Table 2: Association of serum 25-hydroxy Vitamin D with regional and total body fat mass (kg)

Parameters	25OHD levels				*P*
Males	**<5.0 (*n*=48)**	**5-<10 (*n*=73)**	**10-<20 (*n*=94)**	**20 and above (*n*=32)**	
Trunk fat	15.65±5.27	13.69±6.26	14.19±5.56	12.56±4.58	0.095
P		0.062*	0.147**	0.017#	
Arm fat	1.88±0.76	1.76±0.88	1.78±0.73	1.60±0.59	0.468
P		0.409*	0.486**	0.115#	
Leg fat	6.68±2.38	6.26±2.74	6.21±2.60	5.73±1.82	0.424
P		0.368*	0.288**	0.099#	
Total fat	25.01±8.15	22.46±9.73	22.95±8.70	20.61±6.77	0.159
P		0.116*	0.183**	0.028#	
BMI	26.4±4.20	25.31±4.68	25.72±5.25	23.8±2.84	0.093
P		0.186*	0.375**	0.014#	
Females	**<5.0 (*n*=58)**	**5-<10 (*n*=88)**	**10-<20 (*n*=111)**	**20 and above (*n*=47)**	
Trunk fat	17.65±6.00	17.04±4.71	15.12±5.00	11.14±5.11	<0.0001
P		0.482*	0.003**	<0.0001#	
Arm fat	2.87±1.01	2.92±2.04	2.56±0.894	2.06±1.54	<0.0001
P		0.838*	0.184**	0.004#	
Leg fat	10.96±4.17	10.67±3.10	9.56±3.20	8.32±3.50	<0.0001
P		0.608*	0.012**	<0.0001#	
Total fat	32.43±10.48	31.60±7.80	27.61±8.69	22.26±9.83	<0.0001
P		0.586*	0.003**	<0.0001#	
BMI	29.50±6.15	28.57±4.33	26.83±4.8	24.07±5.43	<0.0001
P		0.282*	0.001**	<0.0001#	

*P-value between Groups 1 and 2, **Groups 1 and 3, #Groups 1 and 4. 25OHD: 25-hydroxy Vitamin D, BMI: Body mass index

Table 3: Association of serum parathormone (parathyroid hormone) with regional and total body fat mass (kg)

Parameters	PTH quartiles				*P*
Males	**≤40.2 (*n*=63)**	**>40.2-55.2 (*n*=62)**	**>55.2-73.5 (*n*=61)**	**>73.5 (*n*=61)**	
Trunk fat	13.47±6.33	13.16±4.94	14.79±5.63	15.09±5.53	0.152
P		0.754*	0.192**	0.111#	
Arm fat	1.76±0.81	1.58±0.63	1.84±0.75	1.91±0.85	0.098
P		0.204*	0.542**	0.261#	
Leg fat	5.79±2.29	5.89±2.10	6.44±2.63	6.85±2.86	0.044
P		0.840*	0.153**	0.012#	
Total fat	21.74±9.34	21.36±7.48	23.85±8.81	24.73±8.98	0.092
P		0.807*	0.177**	0.057#	
BMI	25.41±4.20	24.30±3.68	26.11±5.89	26.21±4.54	0.086
P		0.182*	0.399**	0.339#	
Females	**≤34.8 (*n*=77)**	**>34.8-52.3 (*n*=75)**	**>52.3-74.675 (*n*=76)**	**>74.675 (*n*=76)**	
Trunk fat	13.07±6.66	14.60±5.27	16.05±4.93	17.20±4.93	<0.0001
P		0.336*	0.007**	<0.0001#	
Arm fat	2.26±1.01	2.53±0.85	2.66±0.91	3.16±2.37	0.001
P		0.248*	0.085**	<0.0001#	
Leg fat	9.15±3.53	9.43±2.78	10.26±3.52	11.00±3.94	0.005
P		0.628*	0.049**	0.001#	
Total fat	26.09±10.81	27.51±7.76	30.06±8.77	32.50±9.39	<0.0001
P		0.342*	0.008**	<0.0001#	
BMI	26.05±6.08	26.53±4.35	27.72±4.84	29.38±5.39	<0.0001
P		0.567*	0.048**	<0.0001#	

**P*-value between Groups 1 and 2, **Groups 1 and 3, #Groups 1 and 4. BMI: Body mass index, PTH: Parathyroid hormone

Table 4: Effect of serum parathyroid hormone levels on total and regional body fat mass in participants with Vitamin D deficiency

Parameters	25OHD ≤20 ng/ml		*P*
	PTH (≤65 pg/ml)	PTH (>65 pg/ml)	
Male	***n*=132**	***n*=83**	
Trunk fat	14.26±5.88	14.49±5.62	0.771
Arm fat	1.75±0.75	1.87±0.85	0.278
Leg fat	6.14±2.39	6.65±2.89	0.141
Total fat	22.90±8.87	23.79±9.14	0.463
Females	***n*=158**	***n*=99**	
Trunk fat	15.89±5.56	17.10±4.63	0.068
Arm fat	2.26±0.92	2.99±1.96	0.040
Leg fat	9.81±3.22	10.96±3.71	0.009
Total fat	29.18±9.03	32.02±8.61	0.013

PTH: Parathyroid hormone, 25OHD: 25-hydroxy Vitamin D

In the present study, serum PTH levels which were positively associated with body FM concurred with the observation made in normal-weight participants in both cross-sectional as well as prospective analysis.[23,27] Similarly, other studies have also shown positive correlation of serum PTH with BMI and FM in nonobese and obese adults.[7,18,20,27] Kamycheva *et al*.[20] reported a higher risk of obesity in the highest quartile of PTH and several others observed higher serum PTH levels in obese than in nonobese young adults.[17,18] Bolland *et al*.[19] on the contrary reported FM to be a significant determinant of serum PTH levels independent of the inverse relationship between 25(OH)D and FM.

The link between obesity and low 25(OH)D is not well understood. Whether low 25(OH)D levels are due to greater FM,[33] or is it VDD causing increase in FM? The results of the present study favor the latter for the following reasons: (1) The FM was significantly greater in females with VDD and SHPT than those with normal serum PTH levels. (2) The FM did not differ appreciably between those with serum 25(OH)D levels of <5 ng/ml and 5–10 ng/ml, but decreased significantly thereafter suggesting that the effect of Vitamin D on FM is observed only when the serum 25(OH)D level is ≤10 ng/ml. This also suggests that VDD *per se* is responsible for increase in FM in the presence of SHPT.

Vitamin D is known to play an important role in the physiology of adipose tissue. A reduction in serum 25(OH)D concentration may lead to an increase in fasting serum PTH regulating body FM enhancing lipogenesis.[34] Vitamin D inhibits adipogenesis through a VDR-dependent inhibition of CCAAT-enhancer binding protein-alpha and peroxisome proliferator-activated receptor-gamma (PPAR gamma) expression and a decrease in PPAR gamma trans-activating activity in the preadipocyte.[35] There is also evidence that Vitamin D affects body FM by inhibiting adipogenic transcription factors and lipid accumulation during adipocyte differentiation.[15] Furthermore, $1,25(OH)_2D$ also binds to nuclear VDR downregulating uncoupling protein 2 expression and activity; this genomic effect inhibits adipocyte apoptosis and activates adipocyte proliferation. $1,25(OH)_2D$ also suppresses the activity of caspases one and three leading to the suppression of adipocyte apoptosis by enhancing Bcl2/Bax.[36,37]

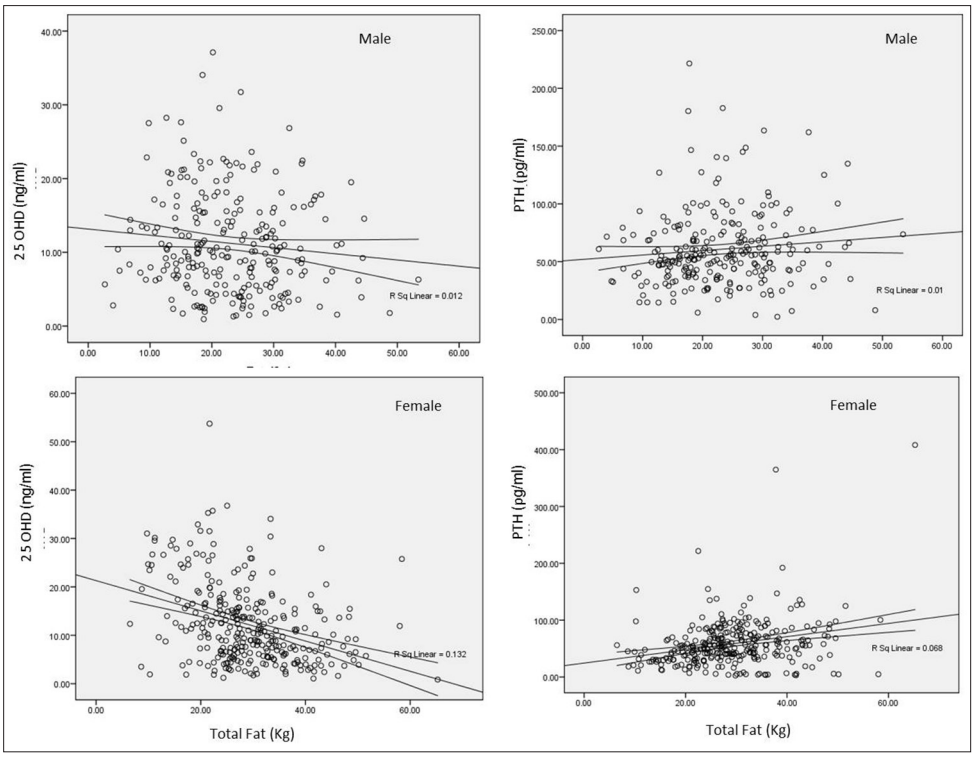

Figure 1: Scatter plot showing relationship of 25-hydroxy Vitamin D and parathyroid hormone with total body fat (Kg) in male and females

Serum PTH has also been known to play an important role in the accumulation of fat through several mechanisms such as decrease in lipoprotein lipase activity in dose-dependent manner in mature adipocytes,[38] increase in GLUT-4 phosphorylation which helps in triacylglycerol synthesis,[39] suppression of expression levels of beta-2 adrenergic receptor messenger RNA in mesenchymal cells, thus reducing lipolysis and increasing fat accumulation,[40] increase in $(1,25(OH)_2D)$ levels, which increases the levels of Ca^{2+} in adipocytes and decreases in lipolysis[41] and increase in fibroblast growth factor-23 which is associated with increase in FM in elderly individuals.[42,43]

The present study has the following limitations. (a) The cross-sectional design of the study prevented us from concluding the temporal nature of the observed association between FM and serum 25(OH)D levels. (b) Visceral FM was not quantified, and truncal FM measured in the study was not truly representative of visceral fat. (c) Dietary evaluation to assess calcium and Vitamin D intake should have been done as calcium intake is known to modify the effect of Vitamin D and PTH on FM.[18]

Conclusions

VDD with SHPT is associated with increased body FM in females when compared to those with VDD and normal PTH levels. Hence, PTH is an important determinant of FM in patients with VDD.

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Conflicts of interest

There are no conflicts of interest.

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