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Research Article

Evaluation of the Relationship Between Body Mass Index and Vitamin D in Women Admitted to the Obesity School

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Abstract: Although the vitamin D is classically known for its role in bone metabolism, it plays an extensive role for overall body beyond the musculoskeletal system. In this study, we aimed to evaluate vitamin D status in obese women and to investigate the relationship between vitamin D and severity of obesity which classifed according to body mass index (BMI). The study involved 259 women. The study population were divided into two groups as obesity and non-obesity group according to their BMI values (kg/m^2). The obesity group consisted of 127 women and non-obesity group consisted of 132 women. Subjects in obesity group were selected from women who admitted to "The Obesity School Program". Serum 25-hydroxyvitamin D [25(OH)D], intact parathormon (iPTH), insulin, calcium, phosphorus, and glucose concentrations were measured and HOMA IR values were calculated. Mean values for all variables were compared between obese and non-obese group using *t* test. The relationship between measured parameters was evaluated by Pearson's correlation coefficient. For all statistical tests, $P < 0.05$ was considered statistically significant. Serum iPTH and HOMA IR values were higher in obese group, and serum 25(OH)D values were lower in obese group. Vitamin D deficiency was higher in obese group. Negative correlation was found between serum 25(OH)D levels, age, and BMI. According to our results, we observed a negative correlation between BMI and 25(OH)D. These results should be supported by further experimental studies.
Keywords: 25-hydroxyvitamin D, body mass index, insulin resistance, obesity, parathyroid hormone.

INTRODUCTION

Vitamin D is a lipid-soluble nutrient that is obtained from dietary sources as ergosterol (D_2) or cholecalciferol (D_3). D_3 can be produced in the skin when exposed to sufficient ultraviolet B rays in sunlight [1]. Vitamin D is hydroxylated to 25-hydroxyvitamin D [25(OH)D] (calcidiol) by 25-hydroxylase in the liver, subsequently 25(OH)D is converted to its biologically active metabolite, 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] (calcitriol), by 1-α-hydroxylase in the kidneys. Since 1-α-hydroxylase is also found to be active in extra-renal tissues, vitamin D plays a widespread role for overall body beyond the musculoskeletal system. The expression of vitamin D metabolizing enzymes has been also demonstrated in human adipose tissue [2]. Active vitamin D needs to be bind to vitamin D receptors (VDR) before biological actions occur. It demonstrated that VDR is almost present every tissue in the human body. This discovery suggests an involvement of vitamin D mediated effects in several other system apart from musculoskeletal tissues. The VDR is also exist in adipose tissue and may contribute to the action of vitamin D in adipocytes [3].

The 25(OH)D has a half-life of several weeks, therefore, the most accurate way to determine vitamin D status is to measure serum 25(OH)D levels [4]. Serum 25(OH)D levels represents endogenous vitamin D synthesis from the skin and also dietary intake. Measures of 1,25$(OH)_2$D are not good indicators of vitamin D status, since it has a very short half-life, approximately four hours, and its blood levels are closely regulated by serum levels of PTH, calcium, and phosphate. It also does not reflect the vitamin D reserves, as it is frequently elevated in individuals presenting with hypovitaminosis D due to secondary hyperparathyroidism [5,6].

Obesity is an important public health problem because of the associated increased risk of hypertension, coronary heart disease, type II diabetes, stroke, gall bladder disease, certain type of cancer, osteoarthritis, sleep apnea and, other disorders. Definition of obesity is abnormal or excessive fat accumulation as a result of an imbalance between calorie intake and burn off that may impair health. World Health Organization (WHO) described obesity as a chronic disease that is so prevalent in developed and developing countries. Body mass index (BMI) is widely recognized as a weight for height index that has a high correlation with adiposity [7-9].

Purposes of this study; to investigate whether there was any correlation between serum 25(OH)D levels and severity of obesity which classifed according to BMI and to examine vitamin D status in the obese women who admitted to obesity school.

MATERIALS & METHODS

Study design

This observational cross-sectional study was performed in Dumlupinar University Evliya Celebi Research and Education Hospital, Kutahya city, Turkey between December 2014 and February 2015. Kutahya city located at 29:59 latitude and 39:25 longitude in North hemisphere, and it located in northwest of Turkey. This study was carried out in winter season period by assuming that the exposure to the sunlight was nearly similar in the all participants. The study involved 259 women and all volunteers were living in Kutahya. The study population were divided into two groups as obesity and non-obesity (control) group according to their body mass index (BMI) values (kg/m^2). This classification system was developed by WHO Obesity Task Force and adopted by Expert Panel on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults, a group was assembled by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institute of Health (NHI). Classification of obesity according to WHO is as follows; BMI is 18.8 to 24.9 kg/m2, normal; 25.0 to 29.9 kg/m2, overweight; 30.0 to 34.9 kg/m2, obesity class I; 35.0 to 39.9 kg/m2, obesity class II; ≥ 40.0kg/m2, obesity class III (morbid obesity) [10,11]. None of the women were taking any vitamin D, calcium, vitamin D plus calcium or multivitamin supplement. The obesity group consisted of 127 women who have BMI above 30 kg/m^2 and non-obesity group consisted of 132 women who have BMI under 25 kg/m^2. Subjects in obesity group were selected from women who admitted to "The Obesity School Program". Women in non-obesity group were selected from volunteer hospital workers. "The Obesity School Program" was carried out by Kutahya Directorate of Public Health of Ministry of Health of Turkish Republic. Aim of this program was to support to individuals who suffered from obesity or overweight problems and to provide education about healthy weight loss and prevention of obesity.

Ethics

The study was carried out in accordance with Declaration of Helsinki. Ethical committe approval was received from the local Human Research Ethics Committee (no: 2013/14-122). Written informed consent was obtained from the all volunteers.

Anthropometric measurements:

Anthropometric measurements including weight in kilogram (kg), height in centimetres (cm), and BMI for each participant were performed by the trained nurses using standart devices according to international guidelines [12]. Weight and height were measured in participants wearing light clothing but no shoes, then BMI was calculated by dividing the weight by the square of the height (kg/m^2). Three serial measurements were made and the average of the measurements was used in the analysis. Weight of each participant was measured by the mobile digital scale (Seca, Hamburg, Germany) (sensitive to 0.1 kg) in the morning after a starvation of 12 hours. For height measurements, a wall-mounted stadiometer was used (sensitive to 0.1 cm). BMI was calculated and the participants were classified according to their BMI values. A BMI ≥ 30.0 kg/m^2 was used as the cut-off point for determining global obesity.

For participants, exclusion criteria were as follows; pregnancy, a history of diabetes mellitus, polycystic ovary syndrome, malabsorption, kidney disease, parathyroid disorders, high calcium intake and vitamin D supplement, any medications or disease that can affect blood levels of measured biochemical parameters or can interfere with the study. Additionally, the other associated diseases which cannot affect the study were also recorded in the database. These diseases most commonly associated with obesity were cardiovascular complications such as hypertension, coronary artery diseases.

Sample collection and measurement of biochemical parameters:

After overnight fasting, venous blood samples were collected into an evacuated serum seperator clot activator tube (Vacuette® Z Serum Sep Clot Activator, GreinerBio-One, Kremsmunster, Austria) between 9 and 10 a.m. All samples were drawn by the same expert phlebotomists. All blood samples were centrifuged at 1500 × *g* for 10 min in room temperature within 1 h and serum aliquots were stored at -80ºC until biochemical analysis. Serum total 25(OH)D, intact parathormon (iPTH), and insulin levels were measured by electrochemiluminescence immunoassay (ECLIA) on Roche Cobas e 601 analyzer (Roche Diagnostics GmbH, Mannheim, Germany). Serum calcium (Ca), phosphorus (P), and glucose levels were measured on Roche Cobas c501 analyzer (Roche Diagnostics GmbH,

Mannheim, Germany). Serum Ca measurements were performed by 5-nitro-5-metil-BAPTA/EDTA method, serum P measurements were performed by UV molibdat method and serum glucose measurements were performed by hexokinase method. Insulin resistance was obtained by calculating the homeostasis model assessment index (HOMA-IR) from measured glucose and insulin levels.

Statistical analysis

Statistical analyses were performed using SPSS software (version 13.0 for Windows; SPSS, Inc, Chicago, IL, USA). All data were tested for normality using Kolmogorov-Smirnov test. All data were presented as mean ± SD. Categorical variables were compared using Chi-squared test. Continious variables were compared using unpaired *t* test. The relationships between variables were analyzed by *Pearson's* correlation coefficient. A *P* value of less than 0.05 was considered statistically significant.

RESULTS

All data were demonstrated a normal distribution in all groups. The mean age of study population was 39.42 ± 11.13 in obese group and 36.81 ± 12.31 in non-obese group. There was not found a difference between mean age of two groups (Table 1). The obese group were classified as first degree obesity (class I, 39.4%, N = 50), second degree obesity (class II, 23.6%, N = 30), and morbid obesity (class III, 37%, N = 47) according to BMI values.

When Ca and P levels were compared, there was not found a difference between two groups (Table 1). However, serum iPTH and HOMA IR levels were higher in obese group than non-obese group and serum 25(OH)D levels were lower in obese group than non-obese group and statistically significant ($P < 0.001$, Table 1).

Vitamin D status of participants was classified according to serum 25(OH)D levels as follows; vitamin D deficiency was ≤ 50 nmol/L, insufficiency was 51 to 75 nmol/L, and sufficiency was ≥ 75 nmol/L. In this classification, we used reference ranges recommended by The Endocrine Society's Clinical Practice Guideline on Vitamin D [13].

When distribution of biochemical parameters were evaluated, we observed that serum Ca and P levels were between normal reference ranges in both group. However, 64.9% of serum 25(OH)D levels were deficient, 30.9% of serum 25(OH)D levels were insufficient, and 4.2% of serum 25(OH)D levels were sufficient ranges in total study population. Furthermore, vitamin D deficiency was higher in obese group (78.7%, N = 100) than non-obese group (51.5%, N = 68) (Table 2). Serum iPTH levels were below reference range in 6.9% of subjects, between reference range in 64.9% of subjects and upper reference range in 38.2% of subjects in total study population. However, serum iPTH levels which upper reference range were higher in obese group (37%, N = 47) than non-obese group (%19.7, N = 26) (Table 2). We found a negative correlation between serum 25(OH)D levels and BMI values (r = -0.295, $P < 0.001$, Fig 1A). In addition, we found a positive correlation between iPTH, HOMA IR levels and BMI values (r = 0.336, $P < 0.001$ and r = 0.348, $P < 0.001$, respectively, Fig 1B,1C). We found a negative correlation between serum 25(OH)D levels and age (r = -0.681, $P < 0.001$, Fig 1D).

Table-1: The comparison of demographic, anthropometric, and biochemical parameters in obese and non-obese groups.

Parameters (Mean ± SD)	Obese Group (N = 127)	Non-obese Group (N = 132)	Statistical Analysis (*P*)
Age (years)	39.4 ± 11.1	36.8 ± 12.3	0.149
Height (cm)	159.7 ± 6.5	163.9 ± 8.9	< 0.001
Weight (kg)	98.7 ± 15.5	64.2 ± 10.3	< 0.001
BMI (kg/m^2)	38.5 ± 6.1	23.7 ± 3.1	< 0.001
25(OH)D (nmol/L)	17.8 ± 14.6	27.2 ± 19.8	< 0.001
Ca (mmol/L)	2.3 ± 0.0	2.3 ± 0.3	0.267
P (mmol/L)	1.1 ± 0.1	1.1 ± 0.1	0.332
iPTH (pmol/L)	7.0 ± 3.3	5.4 ± 2.2	< 0.001
HOMA-IR	4.2 ± 2.9	2.5 ± 2.6	< 0.001

*SD: Standard deviation, BMI: Body mass index, Ca: Calcium, P: Phosphorus, iPTH: Intact parathormon, 25(OH)D: 25-hydroxy vitamin D, HOMA IR: Homeostatic model assessment insulin resistance.

Table-2: The comparisons of serum 25(OH)D and iPTH levels in obese and non- obese groups.

	ObeseGroup (N = 127)	Non-obeseGroup (N = 132)	Total (N = 259)
Serum 25 (OH)D (nmol/L)			
Deficieny (≤ 50)	100 (78.7)	68 (51.5)	168 (64.9)
Insufficiency (51 - 74)	25 (19.7)	55 (41.7)	80 (30.9)
Sufficiency (≥ 75)	2 (1.6)	9 (6.8)	11 (4.2)
Statistical analysis	$X^2 = 21.711$, $P = 0.001$		
Serum iPTH (pmol/L)			
Lowlevel (< 15)	10 (7.9)	8 (6.1)	18 (6.9)
Normal level (15 - 65)	70 (55.1)	98 (74.2)	168 (64.9)
High level (> 65)	47 (37.0)	26 (19.7)	73 (38.2)
Statistical analysis	$X^2 = 10.837$, $P = 0.004$		

* iPTH: Intact parathormon, 25(OH)D: 25-hydroxyvitamin D.

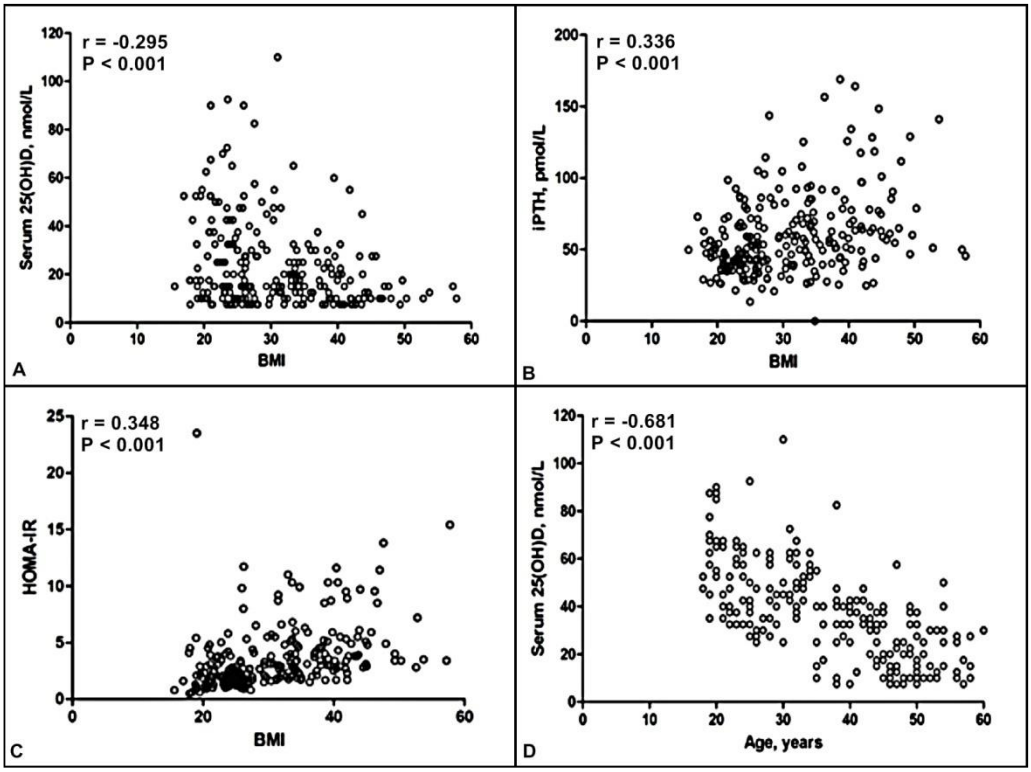

Fig-1A: Distribution of serum 25(OH)D levels according to BMI values
Fig-1B: Distribution of iPTH levels according to BMI values
Fig-1C: Distribution of HOMA-IR levels according to BMI values
Fig-1D: Distribution of serum 25(OH)D levels according to age

DISCUSSION

Obesity has been gradually increasing in worldwide population. It is presumed that a relationship may be between vitamin D deficiency and obesity, therefore, vitamin D status should be evaluated in obese subjects. The mechanism for how low serum 25(OH)D levels can increase the obesity incidence is not clearly understood. In the other words, the mechanism that whether low 25(OH)D concentrations are solely a consequence of obesity or whether vitamin D deficiency plays any casual role in the development of obesity is still not clearly revealed. May obese subjects have vitamin D deficiency or may low levels of vitamin D lead to obesity? Can vitamin D supplementation prevent obesity or improve obesity and it be used to treatment of obesity? These questions are not yet exactly answered.

In this study, we found that serum 25(OH)D levels were lower in obese group than non-obese group and serum 25(OH)D levels were inversely associated with BMI values and degree of obesity. These findings are compatible with previous studies [14,15]. Arunabh et al. [14] showed that 25(OH)D levels were negatively

correlated with BMI and they found stronger association between total body fat and low levels of vitamin D [14]. Mai et al. [15] found that 25(OH)D levels were inversely associated with BMI and body weight and they suggested that lower 25(OH)D levels were a risk factor for obesity [15]. However, some studies demonstrated a weaker inverse or even no correlation between 25(OH)D levels and percent body fat [16-18]. Khashayar et al. [19] found no correlation between the serum 25(OH)D levels and BMI values [19].

Some researchers hypothesized that vitamin D deficiency may be cause of obesity [20,21]. Foss [22] suggested that vitamin D is the cause of common obesity through a survival strategy developed by the organism during the evolutionary pathway to protect the organism from a cold climate [22]. The body would respond to lower UV radiation with reduced skin production of vitamin D that would signal the increase of fat tissue accumulation, enhancing organism protection from the cold weather by reducing heat conduction, and increasing its thermogenic capacity. A higher production of vitamin D3 by the skin, induced by increased presence of sunlight in summer, would inhibit this response and promote a reduction in fat deposits [22]. Conversely, some researchers hypothesized that vitamin D deficiency is not responsible for the development of obesity, but also obesity leads to vitamin D deficiency or insufficiency [23]. Vimaleswaran et al. [24] evaluated the relationship between vitamin D status and BMI by using genetic variants in bi-directional Mendelian randomization analysis [24]. They asserted that if lower vitamin D status causes to obesity, a genetic variant associated with lower 25(OH)D levels should be associated with higher BMI. Conversely, if obesity leads to lower vitamin D status, genetic variants associated with higher BMI should be related to lower 25(OH)D levels. They found that genetically determined BMI values were significantly related to 25(OH)D levels, however, genetically determined 25(OH)D levels were not significantly related to BMI. Consequently, they revealed that higher BMI leads to lower vitamin D status and vitamin D is not have a causal role in development of obesity [24]. An other theory to explain this relationship has been suggested by Wortsman et al. [25]. They demonstrated that there was no difference in endogenous synthesis of vitamin D_3 in the dermis between obese and non-obese subjects when exposed to sunlight; however, the release of vitamin D_3 from the dermis into the circulation was reduced in obese subjects. Consequently, they suggested that vitamin D deposition in adipose tissue may cause to lower circulating 25(OH)D levels in obese subjects [25]. Wong et al. [26] found that activation of the VDR in adipocytes negatively affected energy consumption and induced obesity. Therefore, according to these findings, increased vitamin D in the fat may induced obesity by decreasing energy consumption and by activating VDR, consequently, vitamin D may lead to obesity [26].

In our study, we found that serum iPTH levels were higher in obese group than non-obese group. In addition, serum iPTH levels which were upper reference range were higher in obese group than non-obese group. We found positive correlation between iPTH levels and BMI. However, we did not found differences in serum Ca and P levels between two groups and serum Ca and P levels were between normal reference ranges in both groups. Our results were similar with previous studies [27,28]. The increases of serum PTH levels in obese subjects may be explained by a compensatory mechanism in response to low circulating levels of serum 25(OH)D. Guasch et al. found that subjects with lower BMI had higher serum 25(OH)D and Ca levels than subjects with higher BMI. Serum PTH levels were increasing as BMI was increasing and higher serum PTH and lower 25(OH)D levels were associated with obesity [27]. Grethen et al. [28] demonstrated that in subjects who underwent bariatric surgey, PTH levels were negatively correlated with 25(OH)D and positively correlated with body weight. They suggested that the inverse relationship between PTH and 25(OH)D in obesity is not causative and both biochemical abnormalities are a direct effect of obesity [28].

In our study, HOMA-IR index values were higher in obese group than non-obese group. This association between low 25(OH)D level and impaired glucose metabolism in obese subjects may be direct effects of active vitamin D3 on pancreatic β-cell insulin secretion. VDR and vitamin D binding proteins are known to exist in pancreatic tissue, and calcium plays a role in β-cell insulin secretion. Some studies in vivo and in vitro demonstrated that $1,25(OH)_2D$ stimulates transcription and protein expression of the insulin receptors in peripheral tissues and facilitates insulin-mediated glucose transport [29,30]. Muscogiuri et al. [31] investigated that whether low 25(OH)D levels has a direct relationship with the pathogenesis of insulin resistance or whether this association is dependent on body size [31]. They performed multivarite regression analysis in a model including 25(OH)D, BMI, insulin sensitivity. They divided the obese subjects into two subgroups as low and high insulin sensitivity. The BMI values and 25(OH)D levels were similar in both two subgroup and they could not found any difference for BMI values and 25(OH)D levels between two subgroups. Consequently, they suggested that obesity is responsible for both insulin resistance and low 25(OH)D levels [31].

In this study, we also observed a negative correlation between age and serum 25(OH)D levels. It is likely that results from the elderly people with sedantery life-styles, and those who regularly wear clothes that cover most of the body [32]. Additonally, this finding may be caused by poor production of

vitamin D in the skin, decreased intestinal absorption, and impaired renal function [33-35].

In our study, low serum 25(OH)D levels were also observed in non-obese group. 51.5% of serum 25(OH)D levels were deficient, 41.7% of serum 25(OH)D levels were insufficient and 6.8% of serum 25(OH)D levels were sufficient in non-obese group. It is likely that results from impaired dermal production of vitamin D because of insufficient sunlight exposure. Additionally, vitamin D deficiency and insufficiency are highly prevalent; this is very well reflected by the fact that more than half of the population worlwide have 25(OH)D level less than 30 ng/ml [36]. Vitamin D deficiency is most common in regions such as South Asia and the Middle East. Older age, female sex, higher latitude, fewer hours of sun exposure during the winter season, darker skin pigmentation, less sunlight exposure, dietary habits, air pollution, and absence of vitamin D supplementation are the main factors that are significantly associated with lower 25(OH)D levels [37,38].

Because of the relationship between obesity and vitamin D, serum 25(OH)D levels should be measured and vitamin D status should be monitored in obese or overweight as well as elderly subjects, so that, the adverse effects of obesity on human health can be precluded. Serum 25(OH)D levels may be an important indicator of obesity and obesity related clinic outcomes. Our results are consistent with previous reports and demonstrate that obesity and BMI are significantly associated with lower serum 25(OH)D levels, higher serum iPTH levels and HOMA-IR index values. Despite these findings, vitamin D deficiency has not been clearly identified as the cause or the outcome of obesity. The questions the whether these changes of these hormones are a consequence or cause of obesity or whether treatment with vitamin D can improve obesity and insulin resistance cannot yet revealed. These results should be supported by further experimental studies.

CONCLUSION

The relation between obesity and vitamin D is complex. Although there is a lot of evidence available about its actions in obesity, there are still no consensus regarding preventive actions of supplementation and possible therapeutic roles of vitamin D. According to results of this study, we may suggest that there is a negative correlation between BMI and 25(OH)D as well as PTH and 25(OH)D, but there is still not enough evidence to confirm whether this relation is causal or no causal. We need to more evidence to explaine the mechanism of this relationship.

Finally, this relationship between obesity and vitamin D is similar to this idiom; " which came first the chicken or the egg?"

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