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Original Article

25-Hydroxy vitamin D3 in patients with morbid obesity of wait-listed bariatric surgery: it's association with adiposity and metabolic indices

Mahsa Hatami[1, 2], Abdolreza Pazouki[1, 3, 4], Ali Kabir[1]*

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Abstract

Background and aim: Vitamin D3 deficiency is associated with insulin resistance and metabolic syndrome. Although, the evidence was not conclusive. The aim of this study is to investigate the relationship between serum 25-hydroxy vitamin D3 (25(OH) D3) levels with some adiposity and metabolic indices related to metabolic syndrome.

Methods: In this cross-sectional study, the anthropometric, body composition information, the clinical laboratory tests including fasting blood sugar (FBS), insulin, lipid profile, liver enzymes, and serum 25(OH) D3 of 3750 patients with morbid obesity are extracted from Iran National Obesity Surgery Database. HOMA-IR and QUICKI were computed based on the standard formula. Associations were tested using analysis of variance and Kruskal–Wallis test.

Results: Approximately 69% of patients with morbid obesity had sub-optimal vitamin D3 levels (<20 ng/mL). An inverse significant relationship between serum 25(OH) D3 and body weight, body fat percentage, waist, and hip circumstance was observed ($p<0.05$ for all). Low serum 25(OH) D3 levels are significantly associated with higher FBS and A1C, dyslipidemia (higher LDL and TG), and also the elevated level of liver function enzymes ($p<0.05$ for all). Moreover, the patient with the higher serum 25(OH) D3 had a lower level of HOMA-IR and higher insulin sensitivity (QUICKI index); this association was not statistically significant, though.

Conclusion: Vitamin D3 deficiency has been associated with adiposity, impaired glucose metabolism, and metabolic disorders related to insulin resistance. Thus, vitamin D3 supplementation could be a potential approach in treatment or decrease of the metabolic complication of obesity before and after bariatric surgery.

Keywords: Vitamin D3, Morbid Obesity, Adiposity, Metabolic syndrome, Bariatric surgery

Introduction

Beyond the well-recognized osteo-muscular role of vitamin D3 through calcium-phosphorus homeostasis, vitamin D3 has multiple physiological functions as a steroid hormone (1). Sufficient vitamin D3 is vital for normal human metabolic hemostasis, however vitamin D3 deficiency compromises long-term health outcomes and play as a risk factor of chronic disorders (2). Vitamin D3 insufficiency is highly prevalent in the world; it is estimated that ≥1 billion people have 25-hydroxyvitamin D3 (25(OH) D3) insufficiency and deficiency (3). Vitamin D3 deficiency has been found to be related to several diseases, including diabetes, non-alcoholic fatty liver disease, and even obesity itself (4). Morbidly obese persons have an increased risk of vitamin D3 deficiency (5). Obesity is frequently characterized by reduced vitamin D3 bioavailability, insulin resistance, and a chronic inflammatory response. There is a relationship between serum concentrations of 25(OH) D3 and several circulating inflammatory markers in severely obese individuals (6). The exact mechanisms underlying the inverse relationship between obesity and vitamin D3 deficiency are largely unknown, but it might contribute to the storage of vitamin D3 in adipose tissue, the role of vitamin D3 in lipogenesis, and/or adipogenesis in the adipose tissue (7). Interestingly, recent studies also suggest that vitamin D3 modulate adipose tissue formation and function (8). Despite vitamin D3 deficiency has been reported in some studies to be associated with obesity, the exact relationship of serum vitamin D3 with anthropometric, adiposity indices, insulin resistance and metabolic syndrome indicators are not clear.

The objective of this study was to evaluate the associations between vitamin D3 status and some indicators of adiposity, including body weight, body fat percentage, waist, and hip circumstance and also, some metabolic syndrome indices including dyslipidemia, insulin resistance, insulin sensitivity, and liver function tests in morbidly obese patients of waiting-list of bariatric surgery.

Methods

Study Design, Setting, and Participants: This is a cross-sectional study conducted in the obesity clinic of Minimally Invasive Surgery Research Center of Iran University of Medical Sciences. The subjects who were bariatric surgery candidate patients with morbid obesity (BMI≥40 and/or BMI≥35 and at least one or more

1. Minimally Invasive Surgery Research Center; Iran University of Medical Sciences, Tehran, Iran
2. Department of Clinical Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran
3. Center of Excellence of European Branch of International Federation for Surgery of Obesity, Hazrat-e-Rasool Hospital, Tehran, Iran
4. Iranian National Center of Excellence for Minimally Invasive Surgery Education, Iran University of Medical Sciences, Tehran, Iran

Ali Kabir, kabir.a@iums.ac.ir

obesity-related co-morbidities (including type 2 diabetes mellitus (T2DM), hypertension, sleep apnea and other respiratory disorders, non-alcoholic fatty liver disease, osteoarthritis, lipid abnormalities, gastrointestinal disorders, or heart disease)) (9). The data used in this study has been obtained from the National Obesity Surgery Database (http://obesitysurgery.ir/) from December 2015 to May 2020. We excluded cases who have chronic autoimmune and/or inflammatory disease which affected the vitamin D3 levels. The present project was approved by the ethics committee of Iran University of Medical Sciences with the ID number of IR.IUMS.REC 1395.95-04-140-29239.

Variables, Data Sources/Measurement: The weight, height, hip, and waist circumference, were measured by a trained expert. For measuring the weight and height (with the SECA 711 scale, Medical Measuring Systems and Scales Factory, USA), it has been requested from participant to remove the heavy clothes and shoes. Their height was read while the back of the head, shoulder blades, buttocks, and heels were touching the stadiometer. Waist and hip circumference as the indexes of central obesity was measured by Measuring Tape. Waist was read in the horizontal plane midway between the lowest rib and the iliac crest. The body composition components such as fat percentage and fat-free mass were measured with the bioelectrical impedance analyzer (TANITA BC-418, Japan) while they are fast with an empty bladder.

Table 1. Baseline Characteristics of Patients with Morbid Obesity.

Variables	Value
Age, mean± SD, Year	39.1± 11.1
Female Sex, no (%)	3340 (79.3)
Weight, mean± SD, Kg	122.43± 22.38
Hip Circumference, mean± SD, Cm	136.65± 13.87
Waist Circumference, mean± SD, Cm	122.0± 15.06
BMI, mean± SD, Kg/m2	45.59 ± 6.41
Fat Percentage, mean± SD, %	46.66 ± 5.49
Visceral Fat Level, mean± SD, Level	16.27 ± 5.17
Fat free mass, mean± SD, Kg	65.21 ± .47
Hb, mean± SD, g/dL	13.72 ± 1.52
Ferritin, mean± SD, ng/mL	81.00 ± 9.17
FBS, mean± SD, mg/dL	112.43 ± 36.35
HbA1c, mean± SD, %	5.98 ± 1.28
c-Peptide, mean± SD, ng/mL	3.97 ± 4.41
SGPT, mean± SD, IU/L	24.39 ±15.56
SGOT, mean± SD, IU/L	30.67 ± 23.00
Insulin, mean± SD, µIU/mL	22.94 ± 19.63
TSH, mean± SD, mIU/L	2.95 ± 5.14
Cholesterol, mean± SD, mg/dL	192.18 ± 40.23
HDL, mean± SD, mg/dL	46.33 ± 13.6
LDL, mean± SD, mg/dL	123.61 ± 31.92
TG, mean± SD, mg/dL	170.31 ± 112.32
Vitamin D3, mean± SD, ng/mL	15.93 ± 10.63
PTH, mean± SD, pg/mL	55.80 ± 35.35
HOMA-IR, mean± SD	7.35 ± 5.21
HOMA-B, mean± SD	160.12 ± 170.34
QUICKI , mean± SD	0.55 ± 0.49

BMI: Body Mass Index, FBS: Fasting Blood Sugar, Hb: Hemoglobin, HbA1c: Hemoglobin A1c, HDL: high-density lipoprotein, LDL: Low-density lipoprotein, PTH: Parathyroid hormone, SGOT: Aspartate Transaminase, SGPT: alanine aminotransferase, TG: triglyceride

The clinical laboratory tests including fasting blood sugar, insulin, lipid profile, liver function test (SGOT and SGPT), and serum 25(OH) D3 are extracted from Iran National Obesity Surgery Database which had been evaluated by the enzyme-linked immunosorbent assay (ELISA). HOMA-IR and QUICKI, the insulin resistance and insulin sensitivity indices, were computed based on the standard formula. Vitamin D3 level has been measured by ELISA measurement of 25(OH) D3 using fasting blood samples of participants. Currently a level of at least 30 ng/ml 25(OH) D3 is considered as sufficient, values between 20-29 ng/ml as insufficiency, levels less than 20 ng/ml as deficiency and levels below 10 ng/ml as severe deficiency (10). In the present study the serum level of 20 ng/ml was considered as the vitamin D3 cut-off point.

Study Size, Statistical Methods: We included all the patients with morbid obesity of waiting list of bariatric surgery whose data were recorded in the database. The quantitative variables were expressed as mean ± SD and qualitative factors were presented as number and percentage. Statistical tests including independent-sample t-test, Mann-Whitney U, logistic regression, chi-square was conducted by SPSS software (version.22) in our analysis. The effect of baseline differences was adjusted using ANCOVA. A P-value lower than 0.05 was considered significant.

Results

Participants and Descriptive Data: Among 4214 obese patients of the waiting list for bariatric surgery, 3750 cases were finally entered in our analysis after exclusion of the patients who did not pass our exclusion criteria. Approximately 79% (n=2962) of subjects were female and 21% (n=788) were male. The mean age of patients was 39.1± 11.1 years old. The mean weight and BMI of the morbidly obese bariatric candidates were 122.43± 22.38 (Kg) and 45.59 ± 6.41 (Kg/m^2). The mean fat percentage, FBS, and A1C of participants were 46.66±5.49, 112.43±36.35, and 5.98±1.28, respectively. All other baseline characteristics of patients are listed in Table 1.

Vitamin D3, Adiposity and Metabolic syndrome indicators: In general, 69.6% (n=2588) of patients have a deficient level of 25(OH) D3. The younger persons (37.45±10.2 vs. 42.06±10.76, years old) were vitamin D3 deficient. The weight and BMI mean in 25(OH) D3 deficient patients was significantly higher than others (122.99±23.21 vs. 117.42±21.48, Kg) and (47.11±4.51 vs. 42.73±6.26, Kg/m^2) ($p<0.05$ for all). The patients with 25(OH) D3 deficiency had a significantly elevated level of visceral fat level, fat percentage, FBS, A1C, SGOT, SGPT, insulin, C-peptide, LDL, TG (Triglyceride) ($p<0.05$ for all). Despite The higher level of HOMA-IR and HOMA-β in 25(OH) D3 deficient patients, these differences were not statistically significant. Furthermore, 25(OH) D3 deficient patients have a lower level of insulin sensitivity (QUICKI) but, these differences were not statistically significant (Table 2).

Multivariable Analysis of Vitamin D3 Predictors:

Based on multivariable analysis using logistic regression, fat percentage and BMI of candidates of bariatric surgery was a significant predictor of vitamin D3 deficiency (OR= 1.19; % CI: 1.12, 1.26) and (OR=1.11; % CI: 1.06, 1.23), respectively. So that per each unit level increase in fat percentage and BMI, the probability of vitamin D3 deficiency increases by 19% and 11%, respectively. Potential confounder variables including age and sex were adjusted in multivariable analysis (Table 3).

Discussion

In the present cross-sectional study, we investigated the associations between vitamin D3 serum level and adiposity indicators of fat distribution, as well as lipid profile, liver function tests and insulin resistance in morbidly obese patients of waiting-list of bariatric surgery. After potentially confounder variables were controlled and adjusted for, a lower vitamin D3 level was related to higher increases in BMI and indices of central adiposity including hip and waist circumference.

Our findings confirm some recent investigation regarding that vitamin D3 deficiency could be related to adiposity and metabolic syndrome indicators (11, 12). On the other hand, the result of some randomized clinical trials showed that vitamin D3 supplementation could not improve insulin resistance and other glucose metabolism parameters (13, 14). Further randomized clinical trials are required to clarify the potential causal relationship between vitamin D3 and metabolic syndrome indicators. Vitamin D3 is known to affected insulin secretion (15), although hypo-vitaminosis D3 predicts glucose intolerance, insulin resistance, and other features of metabolic syndrome in normo-glycemic subjects (16). However, we didn't find a relationship in patients with morbid obesity between vitamin D3 level and insulin resistance indices including HOMA-IR and QUICKI. It may be due to the high prevalence of diabetes and/or insulin resistance which is more common in patients with morbid obesity rather than the healthy population.

The mechanisms by which Vitamin D3 may influence adiposity are not exactly clear, and possible explanations are still speculative. In vitro experiments suggested that vitamin D3 may prospectively influence the risk of obesity by modulating the catabolic and anabolic activity

Table 2. Characteristics of patients based on vitamin D3 status.

	Vitamin D3 Deficient (<20) n=2588	Vitamin D3 non- Deficient (≥20) n=1162	P-Value
Age (mean± SD), year	37.45 ± 10.25	42.06 ± 10.76	<0.001
Weight, mean± SD, Kg	122.99 ± 23.21	117.42 ± 21.48	<0.001
Hip Circumference, mean± SD, Cm	138.80 ± 13.12	134. 48 ± 12.35	<0.001
Waist Circumference, mean± SD, Cm	124.21 ± 14.26	120.17 ± 12.56	<0.001
Sex (n), %			0.07
Male	1558 (61)	1009 (39)	
Female	1992 (77)	267 (23)	
BMI (mean± SD), kg/m^2	47.11 ± 4.51	42.73 ± 6.26	<0.001
Fat Percentage (mean± SD), %	46.35 ± 3.75	41.99 ± 5.62	0.03
Visceral Fat Level (mean± SD), %	16.4 ±3.98	13.2 ±5.26	0.05
FBS (mean± SD), mg/dL	115.03 ± 34.95	107.00 ± 33.54	<0.001
A1c (mean± SD), %	6.47 ±1.24	5.62 ± 1.28	0.04
SGPT (mean± SD), IU/L	25.37 ± 17.86	22.12 ± 12.13	<0.001
SGOT (mean± SD), IU/L	31.81 ± 24.96	27.58 ± 21.51	<0.001
Insulin (mean± SD), µIU/mL	23.96 ± 12.62	20.89 ± 19.33	0.05
c-Peptide (mean± SD), ng/mL	4.80 ± 1.61	3.43 ± 7.55	0.02
Cholesterol (mean± SD), mg/dL	193.46 ± 39.53	176.58 ± 36.77	0.88
HDL (mean± SD), mg/dL	39.70 ± 11.30	46.46 ± 11.19	0.63
LDL (mean± SD), mg/dL	139.83 ± 32.89	114.13 ± 30.62	0.05
TG (mean± SD), mg/dL	160.66 ± 71.68	142.17 ± 74 ± 65	0.03
PTH (mean ±SD), pg/mL	58.01 ± 40.57	45.75 ± 36.47	<0.001
HOMA-IR (mean ±SD)	7.52± 4.74	6.22± 6.24	0.07
HOMA-β (mean ±SD)	164.25± 89.61	155.29± 220.11	0.15
QUICKI, mean± SD	0.43 ± 0.32	0.56 ± 0.38	0.08

n: number, WC: Waist Circumference, HP: Hip Circumference, Fat%: Fat Percentage, FFM: Fat free Mass, VFL: Visceral Fat Level, BMI: Body Mass Index, FBS: Fasting Blood Sugar, HbA1c: Hemoglobin A1c, HDL: high-density lipoprotein, LDL: Low-density lipoprotein, PTH: Parathyroid hormone, SGOT: Aspartate Transaminase, SGPT: alanine aminotransferase, TG: triglyceride, HOMA-IR: homeostatic model assessment-insulin resistance, HOMA-β: homeostatic model assessment- β-cell function, QUICKI : Quantitative insulin sensitivity check index

Table 3. Multivariable Analysis[¥] of Vitamin D3 Deficiency Predictors [a.]

Independent Variable	Odds Ratio (95% CI)	Model P-value, R-square
BMI	1.11 (1.06, 1.23)	<0.001, 19.1
Fat percentage	1.19 (1.12, 1.26)	

[¥]: Based on Logistic Regression

[a] Adjusted for Age and sex.

of adipocytes (17). Studies have shown that intracellular calcium concentrations modulate lipolytic activity in isolated human adipocytes (18), which raises the possibility that vitamin D3 could influence body weight and energy expenditure through calcium regulation (16). In vitro studies have also shown that vitamin D3 can inhibit the expression of a key adipogenesis regulator, peroxisome proliferator-activated receptor-gamma (19). Our results suggested that inadequate vitamin D3 status could be a risk factor for exacerbation of adiposity and metabolic syndrome in patients with morbid obesity possibly through its potential role in lipolysis and adipogenesis (17).

Significant strengths of the present study are detailed anthropometric indices and metabolic syndrome indicators measured in a large group of morbidly obese patients in the waiting- list for bariatric surgery. The bio-impedance analysis was used for body-composition assessment in our study and the HOMA-IR and QUICKI index for insulin resistance and sensitivity, which these methods are widely used and correlate well with more valid methods. The limitations of our study included its cross-sectional study design, which causality did not conclude from its finding. Furthermore, the lack of data on lifestyle habits factors (including dietary pattern, sun exposure) that could affect the patient's vitamin D3 status. Also, outdoor physical activity could be a confounder variable for the association between vitamin D3 level and adiposity or metabolic syndrome which was not available for consideration in our study.

Conclusion

In conclusion, vitamin D3 status may be an important micro-nutritional factor for weight and adiposity status and also metabolic syndrome component in morbidly obese patients. This is alarming considering the high prevalence of vitamin D3 deficiency among morbidly obese patients globally. This observation, therefore, warrants further research to determine whether the association is causal and whether impaired glucose homeostasis and metabolic syndrome indices could be treated or better managed by vitamin D3 supplementation before bariatric surgery. Moreover, future studies are required to answer this question whether the higher level of vitamin D3 in morbidly obese patients could play a role in the increase in the rate of diabetes or hyperlipidemia remission after bariatric surgery.

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