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Original Article

Does vitamin D status correlate with insulin resistance in obese prediabetic patients? An Egyptian multicenter study

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ABSTRACT

Background: The link between Vitamin-D deficiency and type 2 diabetes (T2D) is well-established. Since prediabetic obese populations have the greatest risk to develop to T2D, it was important in our study to examine serum 25(OH) D3 concentration among prediabetic obese patients and to evaluate the correlation between serum level of vitamin D and BMI, FBS, HOMA IR and HbA1c among prediabetes patients.
Methods: A multicenter case control study was carried out among 101 prediabetic persons & 50 controls, after obtaining consent from subjects and clearance from institutional ethics committee. Serum vitamin D level, Plasma levels of glycosylated hemoglobin (HbA1c) and fasting insulin levels were measured by ELISA in both groups enrolled in the study.
Results: The prevalence of vitamin-D deficiency/insufficiency was (73.3%) (n = 74) among 101 prediabetic obese individuals. Also, A significant inverse correlation was observed between vitamin D levels & body mass index(r = - 0.28, P = 0.004); fasting blood sugar (r = - 0.22, P = 0.002); HOMA insulin resistance (r = - 0.25 P = 0.01); HbA1C (r = - 0.2, *P* = 0.004).
Conclusions: High prevalence of vitamin D deficiency exists among obese prediabetic individuals and there is significant inverse correlation between BMI, FBS, HOMA IR, HbA1c and vitamin D level.

1. Introduction

Vitamin D is considered to be a fundamental micronutrient hormone with a major role in human health [1].During the last decades, there was increased concern amongst the general public and medical fraternity about studying the implication of vitamin deficiency as a risk factor in many autoimmune, metabolic, neoplastic and pregnancy disorders [2,3].

Prediabetes is defined as a precursor stage before diabetes mellitus encompassing both impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). The rate of progression to diabetes depends on the degree of insulin resistance and deficiency of Insulin secretion and other risk factors such as age, family history and overweight or obesity [4,5].

There are some great challenges in studying the important role of Vitamin D to be a risk factor in development of insulin resistance and the pathogenesis of type 2 DM by affecting either insulin sensitivity and Beta cell function or both [6]. Vitamin D may have a valuable effect on insulin action either by directly stimulating the expression of insulin receptors and improving insulin responsiveness for glucose transport, or by indirectly regulating extracellular

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calcium and ensuring normal calcium influx through cell membranes [7].Many studies have been reported that Vitamin D supplementation may improve the ability of the cells of the islets to manufacture many proteins de novo and to convert proinsulin to insulin [8,9].

Obesity is a major public health problem and considered to be an important risk factor for many somatic disorders, cardiovascular disease, type 2 diabetes mellitus and cancer [10]. Recently, the prevalence of obesity (body mass index (BMI) ≥30) has been increased to reach about 11–29% among men and 9–38% among women, with a median level of 20% [11]. Previously, obesity has been demonstrated as a risk factor in vitamin D deficiency [12]. There is strong evidences that serum level of 25(OH) D, the main circulating vitamin D metabolite is reversely associated with obesity [13].

Herein this study we assayed the vitamin D level among newly detected prediabetic obese patients and compared to control healthy group. Also, we studied the relationship between serum level of vitamin D and some anthropometric parameters.

2. Patients and methods

A hospital based descriptive cross sectional study was conducted to collect 101 Egyptian prediabetic patients, were recruited from diabetic outpatient's clinic of Helwan, Sohag and Assiut university hospitals. The study protocol was approved by the institutional ethics committee and explained to all participants and only those who gave informed written consent were included in the study. In addition, this study includes 50 age matched, healthy control group.

Individuals with history of any oral antidiabetic medications, insulin use and calcium or vitamin-D supplementation in the last one year were excluded. Also, individuals with associated disorders like primary hyperparathyroidism, chronic kidney disease, liver disease, malignancy, chronic drug use like antiepileptic agents, oral contraceptive pills, steroids which are likely to interfere with vitamin-D metabolism were excluded.

2.1. Methods

Data of the patients including, age, sex, height, weight, BMI, waist circumference (WC), Systolic Blood pressure (SBP), Diastolic Blood pressure (DBP)was collected.

Fasting blood samples were collected and centrifuged within 1 h and divided into two aliquots. One set was stored at −20 °C until the time of batch analysis. While the other set was used immediately for determination of fasting blood glucose level. Plasma levels of glycosylated hemoglobin (HbA1c) were measured by ELISA. Fasting insulin levels were determined by ELISA kit (Calbiotech Inc., USA, Catalog No.: IS098D). Serum 25(OH) D3 levels were determined using ELISA kit (Calbiotech Inc., USA, Catalog No.: VD220B).

Insulin resistance was also calculated by homeostasis model assessment of insulin resistance (HOMA-IR) as described by Mathews et al. [14] were HOMA-IR = fasting insulin concentration (mU/mL) xFPG (mmol/L)/22.5.

According to the American Society of Endocrinology, vitamin D status in obese prediabetic patients who are at risk for vitamin D deficiency have been categorized using the serum circulating 25-hydroxyvitamin D [25(OH)D] level, measured by a reliable assay, as follow:

1 Vitamin D deficiency when [25(OH)D] level below (20 ng/ml)
2 Vitamin D insufficiency when [25(OH)D] level range between (21–29 ng/ml)
3 Vitamin D sufficiency when [25(OH)D] level > (29 ng/ml)

3. Statistical analysis

Data are presented as range (minimum, maximum); and mean ± SD. Continuous variables age, height, weight, BMI, HOMAIR, WC, LDL, SBP and DBP were expressed as the arithmetic mean ± SD and were compared between the enrolled patients using Student's *t*-test, or Wilcoxon Rank Sum Test, as appropriate with a significance value at $p \leq 0.05$. The ANOVA test was used to examine the difference between groups of the enrolled subjects, as appropriate. Correlations between parameters measured were calculated using Spearman's correlation coefficient. All statistical analyses were completed with the help of Graph Pad Prism 7 Software (San Diego, California, USA).

4. Results

4.1. Characterization of the enrolled subject

The demographic and clinical characteristics of the enrolled patients are summarized in Table 1. Two groups were enrolled in this study; the first group included a total of 101 Egyptian prediabetes patients with 45.5% (n = 46) male and 54.4% (n = 54) female while the second group included 50 healthy control group with 40% (n = 20) male and 60% (n = 30) female. There was no significant difference in the mean age between the study population group and the healthy control group (34.01 ±7.47 *vs* 33.58 ±7.44), *P* = 0.7. mean weight, BMI, WC, FBG, HOMA IR, LDL, HbA1C, SBP, DBP, TC and TG were significantly high in the prediabetic patients than healthy control group (Table 1). However, there was no significant difference in the mean height and insulin between the two groups (P = 0.2, P = 0.9) respectively (Table 1). On the other hand, Serum vitamin D level was significantly higher in healthy control group than prediabetic patients (51 ±13.19 *vs* 25.64 ± 10.64), P < 0.0001 (Table 1).

4.2. Prevalence of vitamin D status among prediabetic patients

Among 101 obese prediabetic patients there was 32.7%with vitamin D deficiency (n = 33), 40.6% with vitamin D insufficiency (n = 41) and 26.7% with vitamin D sufficiency (n = 27) as shown in Fig. 1.

4.3. Correlations between vitamin D status and anthropometric parameters

The correlation between serum level of vitamin D 25(OH) and some anthropometric measurements are summarized in Table 2. Among 101 obese prediabetic patients, results show a significant negative correlation between serum level of vitamin D and BMI (r = - 0.28, ?? = 0.004) (Fig. 2 a). Also, there was a significant negative correlation between serum level of vitamin D and FBG (r = - 0.22, *P* = 0.002) (Fig. 2b). There was a significant inverse correlation between serum level of vitamin D and HOMA IR (r = - 0.25, P = 0.01) (Fig. 2c). Also, there was a significant inverse correlation between serum level of vitamin D and HbA1C (r = - 0.2, P = 0.04) (Fig. 2d).

5. Discussion

Vitamin D has sparked global interest in the pathogenesis and prevention of diabetes. As the major regulator for calcium homeostasis, vitamin D directly and or indirectly improves insulin exocytosis via activating calcium-dependent endopeptidases. The present study provided an additional evidence that the prevalence of vitamin D deficiency among obese prediabetic patients is high, as

Table 1
Demographic and laboratory characteristics of enrolled groups.

P value	Healthy control n = 50	Total prediabetic Patients n = 101	Parameter
P = 0.7	33.58±7.44	34.01±7.47	Age (years) (mean ± SD)
Ns	20: 30 40%: 60%	46: 55 45.5%: 54.4%	Gender Male: female
P = 0.2	1.58±0.04	1.59±0.02	Height (m) (mean ± SD)
P < 0.0001*	79.36 ± 8.41	88.51± 6.56	Weight (kg) (mean ± SD)
P < 0.0001*	32.12 ± 1.90	34.97 ± 2.68	BMI (obese >25) (kg/cm^2) (mean ± SD)
P < 0.0001*	89.24 ± 9.39	100.9 ± 5.86	Waist circumference (cm) (mean ± SD)
P < 0.0001*	51 ±13.19	25.64 ± 10.64	Vitamin D (ng/ml) (mean ± SD)
P < 0.0001*	4.428±0.33	5.925±0.22	HbA1C % (mean ± SD)
P = 0.03 *	122.6± 9.82	126.6±10.94	SBP (mmHg) (mean ± SD)
P = 0.0009*	73.52±6.31	77.93±8.10	DBP (mmHg) (mean ± SD)
P < 0.0001*	172.9± 8.54	191.7±18.82	TC (mg/dl) (mean ± SD)
P = 0.003*	91.1±8.38	98.69±14.12	LDL(mg/dl) (mean ± SD)
P < 0.0001*	123.4 ± 13.82	176.8± 72.05	TG(mg/dl) (mean ± SD)
P < 0.0001*	4.57 ± 0.49	116.8 ± 5.13	FBG (mmol) (mean ± SD)
P < 0.0001*	2.05 0.41	3.01 ± 0.63	HOMA IR (mean ± SD)
P = 0.9	10.12 ± 1.74	10.26 ± 2.36	Insulin (mean ± SD)

BMI=Body Mass Index; SBP = systolic Blood pressure; DPB = Diastolic Blood Pressure; HbA1c = Glycated hemoglobin; FBG=Fasting Blood glucose; TC = Total Cholesterol; LDL-C = Low Density Lipoprotein Cholesterol.
*significant.

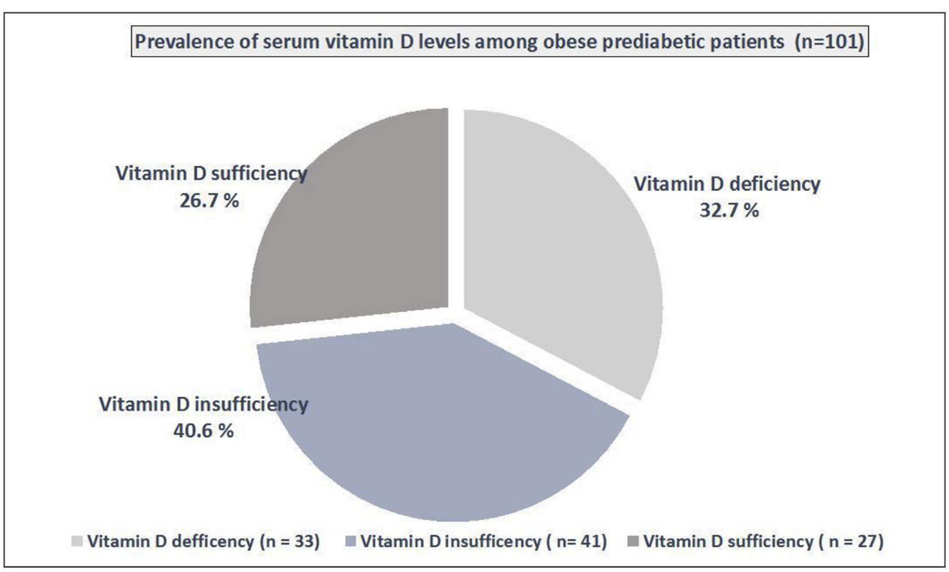

Fig. 1. Pie chart show the prevalence of different vitamin D status among 101 obese prediabetic patients. The prevalence of vitamin D among obese prediabetic patients was 32.7% with vitamin D deficiency (n = 33), 40.6% with vitamin D insufficiency (n = 41) and 26.7% with vitamin D sufficiency (n = 27).

we reported 73.3% of total patients were vitamin D deficient. Our results come in accordance with *Dutta* et al. and Modi et al. studies; who found that the prevalence of vitamin D deficiency/insufficiency was 73.25% and 77% respectively among prediabetic patients [15], [16].This result can be explained by the fact that obese people may not get enough sun exposure due to limited mobility or clothing habits and so their bodies does not easily release vitamin D because it is stored in the body fat compartments. Also, due to their greater weight they are not able to meet the requirement for vitamin D due to the decreased bioavailability of 25(OH)D [17].

The present study revealed that there was a significant difference in the mean serum level of 25 (OH) D between obese

Table 2
Correlation between body mass index, FBG, HOMA IR and HbA1c and vitamin D levels among study patients(n = 101).

P-value	Pearson's correlation coefficient	
P = 0.004 *	r = −0.28	BMI
P = 0.002*	r = −0.22	FBG
P = 0.01*	r = −0.25	HOMA IR
P = 0.004*	r = −0.2	HbA1C

*significant BMI=Body Mass Index; FBG=Fasting Blood glucose; HOMA IR= Homeostatic model assessment.
Insulin resistance; HbA1c = Glycated hemoglobin.

prediabetic population and control group which highlight that lower serum 25(OH)D levels were usually positively associated with pre-diabetes adults and that there is more risk of developing pre-diabetes in adults with vitamin D deficiency.

Our results indicated that there was a significant inverse correlation between serum level of vitamin D and BMI which come in accordance with some previous studies that demonstrated a significant inverse relationship with BMI [18–20]. Our findings could be explained by the fact that persons with high BMI usually have decrease in the bioavailability of 25(OH)D3 as body fat act as a reservoir for lipid-soluble vitamin D. Previously, it has been shown in animal models that body adipose tissue can accumulate about 10–12% of a supplemented dose of vitamin D. At the same time, it is known that vitamin D is stored in adipose tissue and slowly released with time.

Several previous studies tried to study the correlation between vitamin D status and insulin resistance among prediabetic patients. In our study we reported a significant inverse relationship between serum level of vitamin D and insulin resistance, which come in accordance with Dutta et al. study among prediabetic patients, those having severe vitamin D deficiency (<10 ng/ml), had the worst insulin resistance (HOMA2-IR, QUICKI and 1/fasting insulin) as compared to those having higher levels, with an inverse correlation between vitamin-D status and insulin resistance [15]. In contrast to our results, Kown et al. reported a significant positive correlation between HOMA IR and serum vitamin level [21] There are multiple potential pathways underlying the relationship between vitamin D and glucose metabolism [6]. Several longitudinal prospective studies are warranted to assess whether this worsened insulin resistance in prediabetes individuals with lower vitamin-D actually results in increased progression to diabetes.

The inverse correlation between serum 25(OH)D levels and HbAlc found in the present study has been reported. Our findings were in accordance with Ramos et al. study who found a significant inverse correlation between serum 25(OH)D levels and glucose parameters, i.e., FBS and HbAlc [22].Also A. Salehpour et al. reported a significant inverse correlation between 25(OH)D serum level and HbA1C [23].Thus our findings confirm that that patients with uncontrolled hyperglycemia had low vitamin D levels and giving vitamin D supplements in such patients might help to improve the glycemic control to a certain extent.

Our study also documented the inverse correlation between fast blood glucose (FBG) and serum level of vitamin D which was observed by Srinath KM et al. and Haidari. F et al. in their studies [24,25].On the other hand in Deepika G et al. study there was a non-significant negative correlation between fasting blood glucose and Vitamin D. Hypovitaminosis D may be a significant risk factor for glucose intolerance in some but not all populations.

In conclusion, the present study provided additional support for previous studies which found a high prevalence of vitamin D deficiency among obese prediabetic patients with strong significant inverse relationship to some anthropometric parameters as BMI, FBG, HOMA IR and HbA1C.

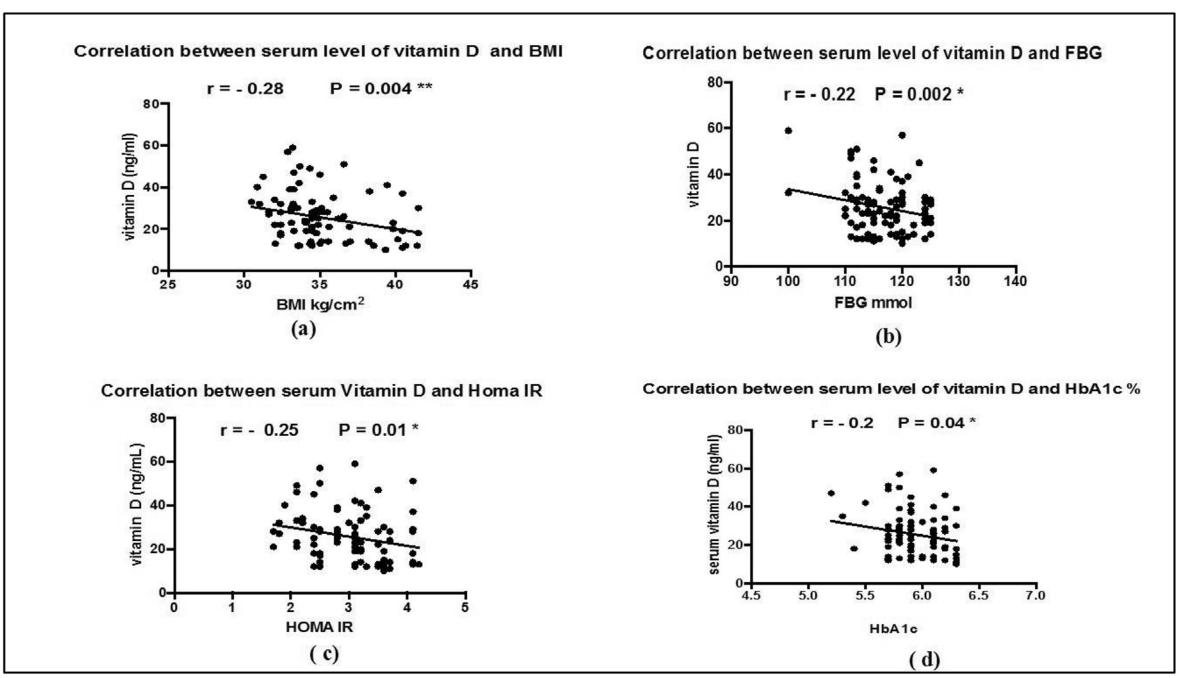

Fig. 2. Correlation between serum level of vitamin D and (a) BMI (b) FBG (c) HOMA IR (d) HbA1C. A significant negative correlation was found between serum levels of vitamin D and each of the following (a) BMI (r = - 0.28, P = 0.004), (b) FBG (r = - 0.22, P = 0.002), (c) HOMA IR (r = - 0.25, P = 0.01)) , (d) HbA1C (r = - 0.20. P = 0.04).

Conflicts of interest

No conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2019.07.043.

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