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Prevalence of hypovitaminosis D and its relation to cardiovascular risk among elderly diabetic female patients

Walaa W. Aly[1], Hend M. Taha[1], Khalid E. Elsorady[1], Wessam E. Saad[2], Ahmed K. Mortagy[1]
[1]Geriatric and Gerontology Department, Faculty of Medicine, Ain Shams University.
[2]Clinical Pathology Department, Ain Shams University Hospitals.

ABSTRACT

Vitamin D deficiency is highly prevalent worldwide and certain groups as elderly persons women and institutionalized persons are particularly prone to severe deficiency. Objective: To identify the prevalence of hypovitaminosis D and its relation to cardiovascular risk among elderly diabetic female patients. Method: A cross sectional study conducted from the first of October 2014 to the end of March, 2016, where 163 elderly diabetic females who attended Ain shams university hospital at that time were included. They underwent careful history taking, body mass index calculation, blood pressure measurement and Serum 25(OH) D measurement, assessment of insulin secretion including fasting serum C-peptide and CPI measurement in addition to assessment of glycemic control by fasting blood sugar estimation. The level of 25 hydroxy vitamin D (25OHD) was measured. Results: The prevalence of vitamin D deficiency (25OHD level <20 ng/mL) and insufficiency (25OHD concentration of 20–29 ng/mL) among elderly Egyptian diabetic female patients are 71.2% and 28.2% resp. There is statistically significant association between vitamin D deficiency and low fasting C peptide level and c peptide index. The 3 independent predictor of the presence of vitamin D deficiency were types of diabetic medications, low C-peptide and CPI values and upon logistic regression analysis for these 3 variables, lower CP level was an independent predictor of the presence of vitamin D deficiency. Results showed a weak negative correlation between serum 25(OH)D, systolic BP, BMI and HOMA IR in studied subjects. Conclusion: Prevalence of vitamin D deficiency among elderly Egyptian diabetic female patients is 71.2%. There is statistically significant association between vitamin D deficiency and low fasting C peptide level and c peptide index.

Keywords:
Hypovitaminosis D, cardiovascular risk, diabetic females.

***Correspondence to Author:**
Hend M. Taha
Geriatric and Gerontology Department, Faculty of Medicine, Ain Shams University.

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INTRODUCTION

Hypovitaminosis D has become pandemic and is now seen in every country in the world. It has been estimated that more than one billion people worldwide are either vitamin D deficient or insufficient [1]. Older people are more likely to have lower serum 25(OH)D concentrations [2], partly due to reduced ability to synthesize vitamins with increasing age [3].

Alarming levels of vitamin D deficiency among Egyptian females across all age groups have been demonstrated, prevalence of hypovitaminosis D is approximately 77.2% among healthy geriatric population [1]. There is evident relationship between vitamin D adequacy and various human disease including skeletal and extra skeletal manifestations. As it has a role in many metabolic processes such as glucose metabolism [4]. Prevalence of hypovitaminosis D among diabetic patients exceeds 80 % in various population, also vitamin D status is inversely related to glycemic control. Thus, a poor glycemic control is associated with low vitamin D levels [5], as 25(OH)D plays an important role in glucose homeostasis via different mechanisms. It improves insulin sensitivity of the target cells (liver, skeletal muscle, and adipose tissue [6, 7]. In addition, recent research suggests that low 25(OH)D concentrations may be related to insulin resistance [9].

In addition to vitamin D role in the pathogenesis of DM, there is a growing body of evidence suggests that low levels of vitamin D may adversely affect the cardiovascular system through several mechanisms [10]. Analyzing data from the Third National Health and Nutrition Examination Survey (NHANES III) showed a strong association between hypovitaminosis D and cardiovasular risk factors including diabetes, high blood pressure and increased body mass index [11].

Hypovitaminosis D is associated with higher risk of metabolic syndrome, a cluster of abdominal obesity, hypertension, hyperglycemia and dyslipidemia which are a major risk factor for cardiovascular disease and mortality [12]. as it has an anti-inflammatory effect and negative regulator of the renin-angiotensin system that decreases blood pressure [13].

Insulin resistance is a hallmark of diabetes, obesity, cardiovascular diseases and metabolic syndrome [14]. A number of indices have been used to simplify and improve the determination of insulin resistance [14]. Fasting C-peptide could be used for determination of Insulin resistance, using HOMA modeling [15], as C-peptide concentrations in the peripheral blood are widely accepted as the most appropriate measure of insulin secretion because it is secreted in equimolar amounts with insulin [16, 17]. C peptide index (CPI) could be used as an index of endogenous insulin secretion and insulin resistance, it is not affected by exogenous insulin therapy, hence its value in patients with insulin therapy [18].

The aim of this study was to identify the prevalence of hypovitaminosis D and to detect its relation to cardiovascular risk among Egyptian elderly diabetic female patients.

SUBJECTS AND METHODS

Study design: A cross sectional study.

Setting: Inpatient wards, Ain Shams University Hospital.

Study participants: One hundred and sixty-three elderly diabetic females recruited from the first of October 2014 to the end of March 2016.

After obtaining an informed consent, all participants underwent careful history taking including history of DM and hypertension. All included patients were diabetics on antidiabetic treatment and the associated hypertension was evaluated based on history of hypertension and on blood pressure measurement with a calibrated sphygmomanometer at resting state, hypertension was defined as a systolic pressure above or equal 140 mmHg and/or a diastolic pressure above or equal 90 mmHg [19]**.** Blood Samples were withdrawn during

fasting state after about 8 hours fasting, then collected into plain tubes and centrifuged to separate serum that is stored at -70°C until analysis then referred to Ain shams university hospital blood lab for determination of serum 25(OH)D and fasting serum C-peptide.

Serum 25(OH) D measurement was done using 25(OH) D kits manufactured by DRG instruments GmbH, Marburg, Germany and were analyzed by ELISA methods. Level of 25(OH) D equal or more than 30ng/ml is considered to be sufficient, 10 to less than 30ng/ml is considered to be insufficient, and level less than 10ng/ml is considered as vitamin D deficiency [20].

Fasting serum C-peptide level was done using C-peptide kits manufactured by DRG instruments GmbH, Marburg, Germany and were analyzed by ELISA methods and according to the used C peptide kit, reference range was (0.5-3.2ng/ml), patients were divided into 3 categories:

High CP level: Serum C-peptide level > 3.2 indicating hyperinsulinemic state and insulin resistance,

Normal CP level: Serum C-peptide level 0.5–3.2

Low CP level: Serum C-peptide level <0.5 indicating insulin deficiency state.

All patients underwent assessment of glycemic control by fasting blood sugar estimation utilizing enzyme technique with glucosooxidasis. Glycemic control was categorized based on FBS value, normal values were taken as less than 100 mg/dl (normal FBS category) and high in cases with value over or equal to 100 mg/dl (high FBS category).

Assessment of insulin resistance done by HOMA2-IR index which was obtained by the program HOMA Calculator v2.2.2 (The Oxford Centre for Diabetes. Endocrinology & Metabolism. Diabetes Trial Unit. HOMA Calculator. Available from: http://www.dtu.ox.ac.uk/ Accessed March 2009). At the current study, HOMA 2 calculation couldn't be done for 60 patients whose serum C-peptide level less than 0.6 ng/ml as this value is not accessible at the program so estimation of insulin resistance done for 103 patients only.

HOMA-IR makes it possible to define persons with insulin resistance with a single glucose and C-peptide measurement in the fasting state, we used 2.0 as HOMA 2-IR cut-off point to diagnose insulin resistance. Patients with HOMA2-IR ≥ 2.0 were considered insulin resistant and patients with HOMA2-IR index < 2 were not considered insulin resistant [21, 22].

Estimation of B cell function, in addition to fasting serum C-peptide, CPI was used as an indicator for insulin secretion. CPI measurement was done for each participant. The C-peptide index (CPI) was calculated for all participants with the following formula: fasting C-peptide (ng/ml)/fasting glycemia (mg/dl) × 100 [23, 24]. We used CPI value cut off point at 1.1ng/ mg. Accordingly, patients were divided into 2 categories:

High CPI: C-peptide index (CPI) value ≥ 1.1 indicating hyperinsulinemic state and insulin resistance

Low CPI: C-peptide index (CPI) value < 1.1 indicating insulin deficiency state [25].

Ethical statement

There is no conflict of interest of any kind, all authors have no financial or any other kind of personal conflicts.

All authors meet the criteria for authorship and are in agreement with the content of the manuscript and have contributed significantly to this work.

STATISTICAL METHODS:

Values were presented as means ± SD or as numbers and proportions, as appropriate. The relations between qualitative variables were evaluated by Chi-square test or Fisher's exact test, as indicated. Means were compared with Student's test or analysis of variance.

Quantitative variables were correlated with the use of coefficient of correlation “r”. Variables that were statistically significant in univariate analysis were introduced in a logistic regression model to detect independent predictors of outcome. All tests were bilateral and a P value of 5% was the limit of statistical significance. Analysis was performed by statistical package software IBM- SPSS for MAC, version 24.

RESULTS:

This study was conducted at Ain Shams university hospitals during the time period of about 2 years, 163 elderly diabetic females were enrolled in the study, 71.8% (117) were on insulin therapy and 28.2% (46) were on oral hypoglycemic medication.

Estimation of B cell function and insulin resistance were done for 102 patients only as HOMA 2 calculation couldn’t be done for 60 patients whose serum C-peptide levels were less than 0.6 ng / ml as this value is not accessible at the program.

The study was conducted on 163 elderly diabetic females with a mean age of 66.19 ±5.72 years. Serum 25(OH)D was 9.01(±6.04), height was 153.68 cm (±7.22), weight was 79.69 kg (±21.56), and BMI was 33.65 (±8.36). Systolic BP was 128.56 (±19.35), diastolic BP was 79.39 (±11.08), fasting blood sugar was 174.20 (±84.58), serum C peptide (ng/mL) was 2.77 (±3.62), CPI was 1.84 (±2.64) and HOMA IR was 4.13 (±4.09) (Table 1). Prevalence of vitamin D deficiency was 71.2%, vitamin D insufficiency was 28.2% and vitamin D sufficiency was 0.6% (the case with sufficient vitamin D was not enrolled in subsequent comparisons) (Table 2).

There was statistically significant higher prevalence of vitamin D deficiency among diabetics on insulin therapy in comparison to those on oral hypoglycemic drugs. There was statistically significant difference between means of 25(OH)D as regards CP level and CPI. Low fasting serum C peptide level and CPI were found to be significantly related to lower vitamin D level. Vitamin D deficiency was more common among obese patients 79 person out of 110 (68.1%). In comparison to vitamin D insufficiency, vitamin D deficiency was significantly associated with the presence of lower CP level and CPI values. But there was no statistically significant difference between the 2 groups of vitamin D as regards presence of insulin resistance (Table 3). Upon logistic regression analysis done for the 3 variables associated with vitamin D deficiency, lower CP level was an independent predictor of the presence of vitamin D deficiency (Table 4). There was statistically significant association between low C peptide level and presence of vitamin D deficiency (P value 0.000) (Figure 1). There was a positive correlation between serum 25(OH)D and C peptide (ng/mL) and CPI and negative correlation between serum 25(OH)D and Systolic BP, BMI, and, HOMA IR, although not statistically significant. There was statistically significant difference between CP level categories as regards HOMA %B and HOMA IR. High CP level categories significantly associated with higher HOMA %B and HOMA IR. There was statistically significant association between high C peptide level and presence of insulin resistance (P value 0.000), as all patients (52) with high C peptide level are insulin resistant (Figure 2). Similarly, there was statistically significant difference between the 2 categories of CPI as regards fasting blood sugar, 25(OH)D (ng/mL), HOMA %B and HOMA IR. The lower CPI was significantly associated with lower 25(OH)D, C peptide, HOMA %B and HOMA IR (Table 5). There was significant association between high CPI and presence of Insulin resistance (P value 0.000) (figure 3).

There was no statistically significant difference between means of BMI as regards serum 25(OH)D, but the majority of obese patients are vitamin D deficient (P value 0.34).

Upon comparison between means of serum 25 (OH) D (ng/mL) in uncontrolled and controlled Systolic blood pressure were 7.77± 4.41 vs.

9.29 ± 5.77 and means of serum 25 (OH) D (ng/mL) in uncontrolled and controlled Diastolic blood pressure were 8.53 ± 5.43 vs. 8.93 ±5.40, respectively without statistically significant difference.

Table 1: The clinical characteristics of the study subjects

Variables	Descriptive Statistics					
	Range			Mean	±	SD
Age	60.00	-	85.00	66.19	±	5.72
Weight (kg)	33.00	-	225.00	79.69	±	21.56
Height (cm)	130.00	-	170.00	153.68	±	7.22
BMI	14.28	-	85.73	33.65	±	8.36
Systolic BP	80.00	-	210.00	128.56	±	19.35
Diastolic BP	50.00	-	100.00	79.39	±	11.08
Fasting blood sugar	43.00	-	460.00	174.20	±	84.58
C peptide (ng/mL)	0.001	-	19.55	2.77	±	3.62
C Peptide Index (CPI)	0.0005	-	19.78	1.84	±	2.64
Serum 25 OH Vit D (ng/mL)	0.01	-	44.00	9.01	±	6.04
HOMA %B	6.40	-	405.90	95.02	±	81.29
HOMA IR	0.48	-	31.25	4.13	±	4.09

Table 2: Serum 25(OH)vitamin D levels among participants

25(OH)vitamin D level			
Deficiency No. (%)	Insufficiency No. (%)	Sufficiency No. (%)	Total No. (%)
116 (71.20)	46 (28.20)	1 (0.60)	163 (100.00)

Vitamin D deficiency (25OHD level <20 ng/mL) and insufficiency (25OHD concentration of 20–29 ng/mL)

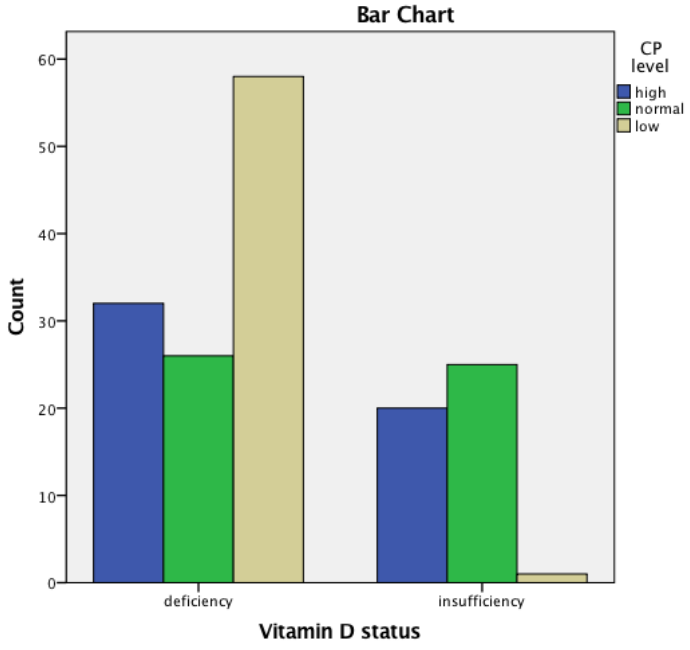

Figure 1: Comparison between 25(OH)D deficiency-insufficiency as regards C peptide level.

Table 3: Comparison between participants with sufficient and insufficient levels of 25(OH) vitamin D, stratified by CP level, CPI value and IR.

Quantitative Variables		Vitamin D status						Chi-Square	
		Deficiency		Insufficiency		Total			
		N (116)	%	N (46)	%	N (162)	%	X^2	*P*-value
C Peptide level	High	32.00	27.60	20.00	43.50	52.00	32.10	33.948[a]	0.000
	Normal	26.00	22.40	25.00	54.30	51.00	31.50		
	Low	58.00	50.00	1.00	2.20	59.00	36.40		
C Peptide Index (CPI) value	High	45.00	38.80	32.00	69.60	77.00	47.50	12.507[a]	0.000
	Low	71.00	61.20	14.00	30.40	85.00	52.50		
Insulin resistance*	Yes	39.00	56.50	30.00	43.50	69.00	67.60	0.010[a]	1.000
	No	19.00	57.60	14.00	43.10	33.00	32.40		
Type of diabetic medication	Insulin	90.00	77.60	27.00	58.70	117.00	72.20	5.859[a]	0.015
	oral hypoglycemic	26.00	22.40	19.00	41.30	45.00	27.80		
BMI Category	Obese	79.00	68.10	31.00	67.40	110.00	67.90	3.318[a]	0.345
	Overweight	26.00	22.40	8.00	17.40	34.00	21.00		
	Normal weight	11.00	9.50	6.00	13.00	17.00	10.50		
	Underweight	0.00	0.00	1.00	2.20	1.00	0.60		

* Insulin resistance were done for 102 patients.

Table 4: Independent predictors of the presence of vitamin D deficiency.

The 3 variables associated with vitamin D deficiency	B coefficient values	P value.
DM on insulin therapy	-0.760	0.088
Lower C Peptide level	4.022	0.000
Lower C Peptide Index (CPI) value	-0.021	0.971

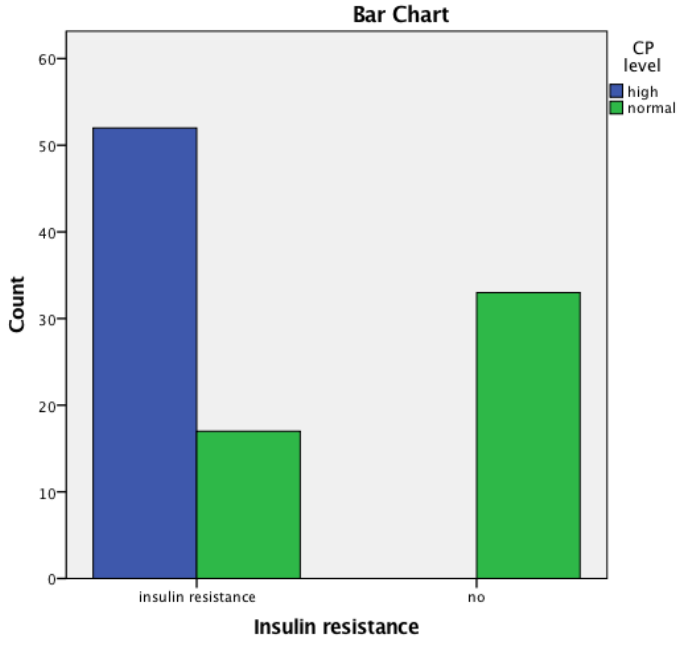

Figure 2: Association between C peptide level and presence of insulin resistance.

Table 5: Comparison between means of high and low CPI categories as regards other quantitative variables.

Other variables	CPI value						*P*-value
	High (n=77)			low (n=85)			
	Mean	±	SD	Mean	±	SD	
BMI	34.11	±	7.34	32.95	±	7.31	0.316
Systolic BP	127.47	±	16.19	129.76	±	21.87	0.446
Diastolic BP	78.96	±	10.04	80.00	±	11.85	0.547
Fasting blood sugar	159.16	±	74.72	188.62	±	90.95	0.025
C peptide (ng/mL)	5.26	±	3.91	0.54	±	0.78	0.000
25 (OH) D (ng/mL)	10.25	±	6.05	7.47	±	4.36	0.001
HOMA %B	117.12	±	81.88	26.95	±	13.65	0.000
HOMA IR	4.83	±	4.42	1.96	±	1.40	0.000

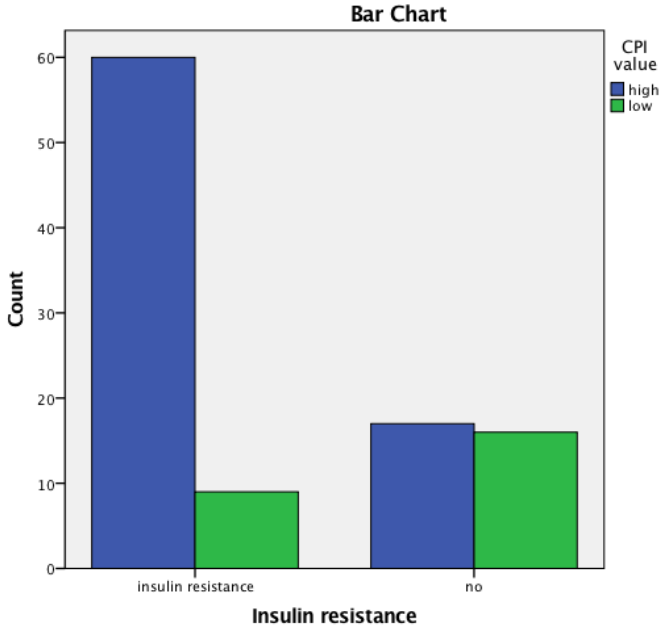

Figure 3: Association between C Peptide Index (CPI) and presence of Insulin resistance.

DISCUSSION:

The prevalence of hypovitaminosis D is common among postmenopausal women particularly those with diabetes [26]. The results of our study showed that the majority of diabetic elderly female non-supplemented patients have suboptimal vitamin D level. In our study, vitamin D insufficiency was defined as a 25(OH)D level < 30ng/ml, which is in accordance with the recommendation of International Osteoporosis Foundation (IOF). The study showed that the prevalence of vitamin D deficiency is 71.2%, vitamin D insufficiency is 28.2% and vitamin D sufficiency is 0.6%, these results support other previous studies in this field at various countries, including sunny regions of the world and neighboring countries [26, 27]**.** In a recent study, the prevalence of hypovitaminosis D was higher in diabetic patients than in control

subjects (90% vs. 83%; p<0.01) [28]. It affects 89% of non-supplemented postmenopausal women with T2DM [37]. Deepika *et al*. [29] showed that patients with T2DM have a very low serum 25(OH)D level and almost all of the patients had vitamin D insufficiency or deficiency.

Vitamin D deficiency is thought to influence DM pathogenesis by affecting either β-cell function, insulin sensitivity, or both [30].

Role of vitamin D in insulin secretion

Vitamin D deficiency is associated with impaired insulin secretion, which is a high-risk factor for diabetes [31]. The level of Vitamin D is reported to be lower in diabetic patients than in non-diabetics [9] as vitamin D plays an important role in beta cell functions [32]. Endogenous insulin secretion can be measured by several indices (indices of insulin secretion) including fasting serum C peptide level, HOMA %B and CPI [24, 33-34]. We found statistically significant higher prevalence of vitamin D deficiency among diabetics on insulin therapy in comparison to those on oral hypoglycemic drugs. There was statistically significant difference between means of 25(OH)D as regards CP level and CPI. Mean serum 25(OH)D (ng/mL) is higher among the high C peptide category than low C peptide one being 10.19 vs. 6.07 among the 2 categories, respectively (P value 0.00). Subsequently, there was significant difference as regards vitamin D status and fasting serum C peptide level categories as majority of patients with low C peptide level (98.3%) had vitamin D deficiency (P value 0.00), also mean HOMA %B was higher among the high C peptide category than the normal C peptide one, 126.06 vs. 62.74 resp with statistically significant difference (P value 0.00). Current study found a statistically significant association between low C peptide level and presence of vitamin D deficiency (P value 0.000), that is consistent with a large prospective, randomized, double-blind, placebo-controlled clinical trials [35 - 36]. The current study showed that in comparison to patients on oral hypoglycemic therapy, patients on insulin therapy had significantly lower serum 25(OH) vitamin D levels. There was statistically significant association between insulin therapy and vitamin D deficiency (P value 0.01) as the majority of patients on insulin therapy had vitamin D deficiency 90 patient out of 116 with odds ratio 2.4.

Similarly, considering CPI as an index of endogenous insulin secretion [18], we found a positive correlation between serum 25 (OH) D and CPI value and a significant association between low serum 25(OH)D levels and low CPI, mean serum 25(OH)D was 10.25 ± 6.05 vs. 7.47 ± 4.36 (P value 0.00) among high and low CPI categories, respectively.

Role of vitamin D in insulin sensitivity

To determine presence of insulin resistance, HOMA2 calculation was done for 102 patients, who had serum C peptide above 0.6ng/ml and showed that 69 patients (67.6%) had insulin resistance and 33 patients (32.4%) had no insulin resistance. Although the majority of studied population were insulin resistant, the present study couldn't demonstrate significant association between hypovitaminosis D and presence of insulin resistance, but we demonstrated a negative correlation between serum 25(OH)D and HOMA-IR (r = -0.048 , p value 0.62) that is supported by various studies including NHANES III which disclosed that serum 25(OH)D was inversely associated with measures of insulin resistance including HOMA IR [37]. Chandler *et al*. [35] reported that vitamin D intake was inversely associated with HOMA-IR and the relationship was independent of age, total body fat, and energy intake. In the Canadian Prospective Metabolism and Islet cell Evaluation (PROMISE) study cohort [38], a significant negative correlation was found between serum 25(OH)D and HOMA-IR (r = -0.29, p < 0.001).

Since insulin secretion and insulin resistance are positively correlated in type 2 diabetes, C-peptide is positively correlated with insulin resistance [39]. One of the valuable finding of

the current study is demonstration of the role of C peptide level as an indicator for insulin resistance that is supported by several findings. All patients with high C peptide had insulin resistance and patients with low C peptide had no Insulin resistance. There is statistically significant difference (P value 0.00) as regards C peptide level among BMI categories, being highest among obese patients. We demonstrated that mean HOMA IR was higher among high CPI category 4.83 ± 4.42 vs. 1.96 ± 1.40. with significant difference (P value 0.00) and significant association between high CPI value and presence of insulin resistance (Odds Ratio for Insulin resistance was 6.27).

Effect of hypovitaminosis D on glycemic control

At the current study, we used FBS as an indicator for glycemic control, and based on it, patients were divided into high FBS: FBS 100 mg/dl or more (no=136) and patients with normal FBS: FBS less than 100 mg/dl (no=26) to demonstrate any difference between the 2 groups as regards serum 25(OH)D, insulin status and cardiovascular risk including obesity and hypertension. There was no statistical difference in serum 25(OH)D level among the 2 categories as regards 25(OH)D. Mean serum 25(OH)D level is 8.95± 5.69 in the high FBS category and 7.97± 3.46 in the normal FBS category (P= 0.24).

Relation between hypovitaminosis D and obesity

One relevant finding of the present study was a negative correlation between serum 25 (OH)D and BMI (r = -0.059, p 0.457). Several studies have shown that patients with hypovitaminosis D had higher prevalence of overweight or obesity when compared to patients with normal 25(OH)D status [40]. Furthermore, obesity is associated with low serum 25(OH)D levels [41-42]. Raška *et al*. [27] found significant negative association between 25(OH)D levels and BMI (p=0.01)

We have demonstrated the relation between increased BMI and vitamin D status, insulin resistance, glycemic control and blood pressure for diabetic elderly women.

Concerning serum 25(OH)D level, mean 25(OH)D levels is lowest among obese and overweight women (p value 0.35), that is concordant with most of the published studies which report the inverse relation between BMI and vitamin D. Several clinical and epidemiological studies reported that obese subjects have lower serum concentrations of 25(OH)D with a negative correlation of vitamin D concentrations with BMI and waist circumference [43, 44]. There was also an inverse association between 25(OH)D concentration and BMI [45]. A study involving 243 adults reported a decrease of 0.74 nmol/l of serum 25(OH)D per 1 kg/m2 increase in BMI [46].

Relation between hypovitaminosis D and HTN

The majority of study population (114 patients) had history of hypertension and were on antihypertensive medication. We demonstrated a negative correlation between serum 25(OH)D level and systolic hypertension (r = -0.056, p 0.477). several observational studies [47, 48] have suggested links between low 25(OH)D levels and a subsequent higher risk for hypertension. The current study shows an inverse correlation between 25(OH)D and systolic blood pressure that is consistent with several studies which demonstrated association between arterial hypertension and hypovitaminosis D [49,50]. Previous studies showed negative correlation between serum 25(OH)D level and blood pressure [51,52]. The prevalence of arterial hypertension was also associated with reduced serum 25(OH)D levels in several studies [53, 54].

Relation between hypovitaminosis D and CVD

The Third National Health and Nutrition Examination Survey revealed that 25(OH)D

levels are associated with important cardiovascular disease risk factors. The prevalence of *diabetes mellitus* (odds ratio 1.98), obesity (odds ratio 2.29), and arterial hypertension (odds ratio 1.30) were all significantly greater in the lower quartiles of the 25(OH)D serum levels than in the higher quartiles (< 0.001 for all) [11]. Epidemiologic studies have reported a trend toward higher prevalence of ischemic heart disease and hypertension with increasing distance from the equator, and these higher rates are attributed to the higher rates of vitamin D deficiency in regions with less exposure to sunlight [55, 56]. At the current study, the failure to demonstrate the association between hypovitaminosis D and certain cardiovascular disease could be attributed to the absence of vitamin D sufficiency group to compare with hypovitaminosis D groups.

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