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Original Research Article

Low serum vitamin D associated with prediabetes

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ABSTRACT

Background: This study is performed to evaluate vitamin D levels and metabolic parameters in patients with prediabetes, compared to healthy controls.
Methods: This study was conducted between October and December 2013 in İstanbul Haseki Training and Research Hospital, internal medicine department. We enrolled total 247 individuals, 122 prediabetic (PreDM) patients (79 female, 43 male) and 125 control healthy individuals (94 female, 31 male) between 20-65 ages who admitted randomizely to the outpatient clinic with non spesific complaints. FPG, urea, creatinine, calcium, phosphate, albumin, alkaline phosphatase, thyriod stimulan hormon (TSH), 25 hydroxy vitamin D (25[OH]D), parathormon (PTH), c-peptide, insulin were analyzed.
Results: Pre DM patients' mean plasma 25[OH]D level (25.7±14.9 nmol/l) was statistically lower than the control group (31.4±17.8 nmol/l). Pre DM patients' mean plasma insulin, c-peptide, calcium, PTH, HOMA-IR (10.8±8.7 IU/ml, 3.3±2.0 ng/ml, 9.7±0.4 mg/dl, 56.5±22.5 pg/ml, 3.0±2.68, respectively) levels were statistically higher than the control group's (6.3±3.8 IU/ml, 2.4±1.0 ng/ml, 9.5±0.5 mg/dl, 44.0±16.0 pg/ml, 1.4±0.8, respectively) mean levels. There were negative correlations between 25[OH]D and BMI (r:- 0.13, p:0.03), FBG (r:- 0.14, p:0.02) and plasma insulin (r:-0.16, p:0.01) values. A multivariate logisitic regression model for prediabetes was performed and variables as female gender, age, HOMA-IR and lower 25[OH]D values were risk factors for pre DM.
Conclusions: Serum low 25[OH]D level correlated with insulin resistance and metabolic parameters in prediabetic patients. Also, it may play an important role in the development of type 2 diabetes.

Keywords: Serum 25[OH] vitamin D, Prediabetes, Metabolic syndrome

INTRODUCTION

Prediabetes is the important predisposition to the development of type 2 diabetes mellitus. It is associated with increased cardiovascular risk and mortality. Prevention of prediabetes is important for protection from microvascular and macrovascular complications. According to Turkey Diabetes, Hypertension, Obesity and Endocrinological Diseases Prevalence Study (TURDEP-II) data, the incidence of prediabetes in Turkish adult population has reached 30,4%.[1] The incidence of prediabetes increases because of obesity, physical inactivity and metabolic syndrome. Up to 70% of prediabetic patients will develop diabetes mellitus in time.[2] Impaired fasting glucose (IFG) defined as fasting glucose levels between 100 and 125 mg/dl and impaired

glucose tolerance (IGT) as 2nd hour plasma glucose after 75 grams OGTT levels between 140 and 199 mg/dl. Vitamin D deficiency can increase the risk of developing prediabetes, osteopenia, osteoporosis, cancer, hypertension, dementia and metabolic syndrome.[3-5] Moreover, vitamin D is a risk factor for progression from prediabetes to diabetes.[6] There are several hypothesis for vitamin D in pancreatic beta-cell function and regulation of insulin secretion. Regulation of insulin secretion by vitamin D is associated with calcium concentration because vitamin D effects indirectly regulation of calcium flux through the beta cells.[7] Vitamin D stimulates the expression of insulin receptors and provides insulin sensitivity.[8] Vitamin D deficiency can cause to glucose intolerance, decrease insulin secretion via inflammation.[9] There is a strict relationship between serum vitamin D concentrations, diabetes and metabolic syndrome.[10] The aim of this study was to evaluate vitamin D levels and metabolic parameters in patients with prediabetes, compared to healthy controls.

METHODS

Study participants

This study was conducted between October and December 2013 in Istanbul Haseki Training and Research Hospital, internal medicine department. We enrolled total 247 individuals, 122 prediabetic (PreDM) patients (79 female, 43 male) and 125 control healthy individuals (94 female, 31 male) between 20-65 ages who admitted randomizely to the outpatient clinic with non spesific complaints. Informed consent of patients and hospital's local ethics commitee approvement were provided before the study. The American Diabetes Association (ADA) criteria for impaired fasting glucose were used to define PreDM as a fasting plasma glucose (FPG) level between 100 and 125 mg/dl. Individuals who had a chronic disease, infection, malabsorption, pregnants, drug addicts and smokers were excluded.

Anthropometric and laboratory measurements

Anthropometric measurements such as height (m), weight (kg), waist circumference (cm) were measured. Weight was measured with light clothing and without shoes. Waist circumference (WC) was measured between the lowest rib and the crista iliaca superior. Body mass index (BMI) was calculated as weight (kg) divided by height (m^2). Systolic and diastolic blood pressure was measured twice with a mercury sphygmomanometer from the right arm of patients in a sitting position after 5 minutes of rest and average value was calculated. Blood sample parameters were analyzed after a 8 hours fasting in the morning for all participants. FPG, urea, creatinine, calcium, phosphate, albumin, alkaline phosphatase were measured by using Beckman Coulter AU-2700 analyzer, UK. Thyriod stimulan hormon (TSH), 25 hydroxy vitamin D (25[OH]D), parathormon (PTH), c-peptide, insulin were measured by using Beckman Coulter DxI 800 analyzer, UK. Serum 25[OH]D levels were classified as; >75 nmol/l vitamin D sufficiency; 50–75 nmol/l vitamin D insufficiency and <50 nmol/l vitamin D deficiency. Within the deficiency category serum levels of 25[OH]D were further classified as; 25-49 nmol/l deficiency, <25 nmol/l severe deficiency. The homeostasis model assessment for insulin resistance (HOMA-IR) was calculated with the following formula; fasting blood glucose (mg/dl) × fasting insulin (mU/ml)/ 405.

Statistical analysis

Statistical analysis was carried out by using SPSS for Windows version 17.0. Results were expressed as mean ± standard deviation. Kolmogorov Smirnov Z test was performed to determine the distribution of variables for each patients group. Regular variances were assessed with t test and irregulars with Mann-Whitney U test. The Pearson and the Spearman tests were performed to analyze the correlation between variables. Chi square test was used to evaluate categorical variables. A p value <0.05 was statistically significant.

RESULTS

Participants were divided into four groups according to 25[OH]D and displayed a significant decrese in plasma 25[OH]D values (Table 1).

Table 1: Prediabetic patients and controls healthy groups' 25 Hydroxy Vitamin D values.

25 hydroxy vitamin D levels	Patient groups		Total
	Prediabetics (n)	Control (n)	
Severe deficiency (<25 nmol/L)	71	52	123
Deficiency (25-49 nmol/L)	43	53	96
Insufficiency (50-74 nmol/L)	7	13	20
Sufficiency (>75 nmol/L)	1	7	8
Total	122	125	247

Age was higher in prediabetic patients. Systolic and diastolic blood pressure, WC, BMI mean values were statistical significant increased in PreDM group according to controls, (Table 2). PreDM patients' mean plasma 25[OH]D level (25.7±14.9 nmol/l) was statistically lower than the control group (31.4±17.8 nmol/l). PreDM patients' mean plasma insulin, c-peptide, calcium, PTH, HOMA-IR (respectively;10.8±8.7 IU/ml, 3.3±2.0 ng/ml, 9.7±0.4 mg/dl, 56.5±22.5 pg/ml, 3.0±2.68) levels were statistically higher than the control group's (6.3±3.8 IU/ml, 2.4±1.0 ng/ml, 9.5±0.5 mg/dl, 44.0±16.0 pg/ml, 1.4±0.8, respectively) mean levels, (Table 3). Insulin, HOMA-IR, c-peptide and PTH levels

significantly elevated in female and male patients with PreDM (Table 4 and 5). There were negative correlations between 25[OH]D and BMI (r: 0.13, p: 0.03), FBG (r: 0.14, p: 0.02) and plasma insulin (r: 0.16, p: 0.01) values (Table 6). A multivariate logisitic regression model for prediabetes was performed and variables as female gender, age, HOMA-IR and lower serum 25[OH]D were risk factors for PreDM (Table 7).

Table 2: Comparison of age, anthropometric and blood pressure measurements to each groups.

Parameters	Groups	Mean value	Std. deviation	P value
Age (years)	Control	33.3	8.0	<0.001
	Prediabetics	39.9	8.8	
SBP (mmHg)	Control	106.0	6.4	<0.001
	Prediabetics	123.8	12.4	
DBP (mmHg)	Control	67.2	6.2	<0.001
	Prediabetics	76.8	9.5	
WC (cm)	Control	82.0	10.2	<0.001
	Prediabetics	95.5	10.7	
BMI	Control	24.4	4.1	<0.001
	Prediabetics	30.3	5.5	

(SBP: systolic blood pressure, DBP: diastolic blood pressure, WC: waist circumference, BMI: body mass index, Std: standard)

Table 3: Comparison of the laboratory parameters between each groups.

Parameters	Groups	Mean	Std. deviation	P value
FBG (mg/dl)	Control	87.26	7.60	<0.001
	Prediabetics	109.01	6.93	
Urea (mg/dl)	Control	24.93	7.33	0.058
	Prediabetics	26.69	6.95	
Creatinine (mg/dl)	Control	0.63	0.13	0.01
	Prediabetics	0.68	0.17	
25[OH]D (nmol/l)	Control	31.46	17.80	0.007
	Prediabetics	25.72	14.98	
İnsulin (IU/ml)	Control	6.31	3.58	<0.001
	Prediabetics	10.85	8.76	
C-peptide (ng/ml)	Control	2.45	1.04	<0.001
	Prediabetics	3.32	2.06	
Calcium (mg/dl)	Control	9.51	0.55	0.02
	Prediabetics	9.79	0.48	
Albumin (g/dl)	Control	4.41	0.32	0.38
	Prediabetics	4.33	0.30	
Phosphate (mg/dl)	Control	3.46	0.64	0.69
	Prediabetics	3.50	0.51	
ALP (mg/dl)	Control	67.34	20.87	<0.001
	Prediabetics	80.29	28.60	
PTH (pg/ml)	Control	44.05	16.03	0.001
	Prediabetics	56.52	22.58	
HOMA-IR	Control	1.47	0.82	<0.001
	Prediabetics	3.02	2.68	
TSH (mIU/L)	Control	1.69	0.87	0.26
	Prediabetics	1.85	1.33	

(Std: Standard, FBG: fasting blood glucose, 25[OH]D: 25 hydroxy vitamin D, ALP: alkaline phosphatase, PTH: parathormon, HOMA-IR: homeostasis model assessment for insulin resistance, TSH: thyroid stimulating hormon).

Table 4. Comparison of parameters of female participants.

Parameters	Groups	Mean	Std. deviation	P value
FBG (mg/dl)	Control	87.69	7.25	<0.001
	Prediabetics	107.96	6.26	
Urea (mg/dl)	Control	23.22	6.68	0.36
	Prediabetics	24.56	6.27	

Continued.

Parameters	Groups	Mean	Std. deviation	P value
Creatinine (mg/dl)	Control	0.58	0.09	0.42
	Prediabetics	0.58	0.10	
25[OH]D (nmol/l)	Control	28.34	16.07	0.002
	Prediabetics	21.28	13.36	
İnsulin (IU/ml)	Control	6.23	3.04	<0.001
	Prediabetics	10.96	7.78	
C-peptide (ng/ml)	Control	2.40	0.91	<0.001
	Prediabetics	3.11	1.32	
Calcium (mg/dl)	Control	9.54	0.53	0.17
	Prediabetics	9.66	0.42	
Albumin (g/dl)	Control	4.48	0.35	0.07
	Prediabetics	4.35	0.30	
Phosphate (mg/dl)	Control	3.42	0.51	0.45
	Prediabetics	3.52	0.54	
ALP (mg/dl)	Control	64.06	20.48	<0.001
	Prediabetics	81.24	32.31	
PTH (pg/ml)	Control	45.13	16.63	<0.001
	Prediabetics	59.30	21.15	
Homa-ır	Control	1.34	0.75	<0.001
	Prediabetics	3.09	2.36	
TSH (mıu/L)	Control	1.70	0.87	0.06
	Prediabetics	1.91	1.29	

(Std: Standard, FBG: fasting blood glucose, 25[OH]D: 25 hydroxy vitamin D, ALP: alkaline phosphatase, PTH: parathormon, HOMA-IR: homeostasis model assessment for insulin resistance, TSH: thyroid stimulating hormon).

Table 5: Comparison of parameters of male participants.

Parameters	Groups	Mean	Std. deviation	P value
FBG (mg/dl)	Control	85.82	8.66	<0.001
	Prediabetics	110.94	6.25	
Urea (mg/dl)	Control	30.67	6.59	0.73
	Prediabetics	30.70	6.45	
Creatinine (mg/dl)	Control	0.79	0.11	0.01
	Prediabetics	0.86	0.14	
25[OH]D (nmol/l)	Control	41,8	19.94	0.056
	Prediabetics	33,9	14.31	
İnsulin (IU/ml)	Control	6,9	4.96	0.08
	Prediabetics	10,5	10.33	
C-peptide (ng/ml)	Control	2.49	1.25	0.06
	Prediabetics	3.63	2.92	
Calcium (mg/dl)	Control	9.70	0.54	0.16
	Prediabetics	9.92	0.49	
Albumin (g/dl)	Control	4.41	0.37	0.56
	Prediabetics	4.55	0.32	
Phosphate (mg/dl)	Control	3.48	0.85	0.92
	Prediabetics	3.49	0.66	
ALP (mg/dl)	Control	78.41	18.43	0.98
	Prediabetics	78.53	20.84	
PTH (pg/ml)	Control	40.47	13.51	0.01
	Prediabetics	51.35	24.28	
HOMA-IR	Control	1.52	1.12	0.02
	Prediabetics	3.06	3.20	
TSH (mIU/L)	Control	1.64	0.85	0.06
	Prediabetics	1.73	1.41	

(Std: Standard, FBG: fasting blood glucose, 25[OH]D: 25 hydroxy vitamin D, ALP: alkaline phosphatase, PTH: parathormon, HOMA-IR: homeostasis model assessment for insulin resistance, TSH: thyroid stimulating hormon)

Table 6: Correlation between 25[OH]D and age with metabolic variables for all patients.

		Age	BMI	WC	FBG	c-peptide	Insulin
25[OH]D	r	-0.091	-0.135	0.022	-0.149	-0.120	-0.162
	P	0.154	0.037	0.734	0.020	0.116	0.012

Table 7: A multivariate logistic regression analysis for prediabetes with associated risk factors for all patients.

	P value	OR	95% CI
Gender (female)	0.004	3.22	1.45 – 7.18
Age	0.0001	1.10	1.06 – 1.15
HOMA-IR	0.0001	3.51	2.26 – 5.45
25[OH] D	0.008	0.97	0.94 – 0.99

(OR: odds ratio, 95% CI: confidence interval, HOMA-IR: homeostasis model assessment for insulin resistance, 25[OH]D: 25 hydroxy vitamin D).

DISCUSSION

The frequency of diabetes mellitus increases rapidly due to industrial life and nutrition. Prediabetes is the predisposition to the development of type 2 diabetes mellitus. Recent studies have shown a relationship between vitamin D deficiency and development of type 2 diabetes mellitus (DM). Lower serum vitamin D levels may play role in the pathogenesis of prediabetes.[11] Its protective effects perform through the immunological system and calcium metabolism.[12] PTH levels were statistically higher in prediabetic patients and parathormone increases as negative feedback to low vitamin D level. Lower serum vitamin D levels effect glucose homeostasis and parathyroid hormone concentrations in patients with prediabetes.[13,14] In this study, serum 25-OH vitamin D levels were sufficient in 5 patients (% 2.05), insufficient in 20 patients (% 8,2), deficient in 96 patients (% 39,36), severe deficient in 123 patients (%50,43). Plasma PTH, HOMA-IR, systolic and diastolic blood pressure, waist circumference and BMI values were statistically higher in PreDM patients compared to control group. There was an increase in the presence of metabolic parameters in patients with prediabetes. Gupta et al, suggested that 25[OH]D levels were lower in prediabetic patients and affected by age, sex and BMI.[15] There were negative correlations between serum 25[OH]D level and BMI and fasting blood glucose in the study. Moreover, low serum 25[OH]D level was strictly correlated with elevated insulin level (r: 0.162, p: 0.012). The risk of insulin resistance was increased in patients with vitamin D deficiency. Forouhar et al demonstrated that there is negative correlation between insulin resistance and 25[OH]D level.[16] In prediabetic patients, pancreatic early phase insulin release is impaired, together with increased serum insulin levels.[17,18] This situation accelerates the development of insulin resistance and overt diabetes in prediabetic patients.[19] In our study, the risk of developing insulin resistance in prediabetic subjects was found to be 3.5-fold increased. Female gender, age and 25[OH]D level were another additional risks for prediabetes.

CONCLUSION

Increase in serum vitamin D levels enhances the progression of prediabetes affecting insulin resistance. Low 25(OH)D levels might have contributed to the incidence of prediabetes.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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