TURKISH JOURNAL OF INTERNAL MEDICINE
ISSN:2687-4245
Original Article

Evaluation of Insulin Resistance and Vitamin D Levels in Patients With Polycystic Ovary Syndrome

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ABSTRACT

Background Polycystic ovary syndrome (PCOS) is associated with many long term health problems such as increased risk of obesity, type 2 diabetes, metabolic syndrome and cardiovascular risk factors. Several reports indicated that PCOS patients have lower vitamin D status compared to healthy subjects. In our study we aimed to investigate whether vitamin D deficiency has effect on the pathogenesis of insulin resistance in PCOS.

Material and Methods Fourty eight patients with PCOS and 24 healthy controls were included in the study. Following the physical examination and anthropometric measurements of the patients and healthy subjects, glycemic control data, lipid values, parathormone, vitamin D status and hormonal parameters were studied.

Results In our study, vitamin D levels were significantly lower in PCOS patients (19.7±26.9 ng/mL) compared with controls (31.9±35 ng/mL, $p<0.01$). Vitamin D levels were found to be lower in the obese PCOS group compared to those with non-obese, but not significant. Statistically significant inverse correlation was found between vitamin D levels and body mass index (BMI). It was also found between vitamin D and low density cholesterol (LDL-C).

Conclusions Our findings revealed increased likelihood of metabolic and dyslipidemic manifestations in PCOS patients compared to control group, while no significant difference was noted in vitamin D levels among PCOS patients in terms of co-morbid obesity. The detection of lower vitamin D levels in PCOS patients suggested that this may be one of the causes of insulin resistance and metabolic complications in these patients.

Turk J Int Med 2022;4(2):66-72
DOI: 10.46310/tjim.1027019

Keywords: *Polycyctic ovary syndrome, vitamin D levels, obesity, insulin resistance.*

Received: November 22, 2021; Accepted: January 16, 2021; Published Online: January 29, 2022

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Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine diseases in women of reproductive age with an incidence of 5-15%.[1] The prevalence of PCOS may change depending on the criteria used for diagnosis and decrease with age.[2] The Rotterdam criteria frequently used for the diagnosis of PCOS include the presence of polycystic ovaries on ultrasound with oligomenorrhea or oligo-ovulation, clinical and/or biochemical hyperandrogenism. After excluding other causes of hirsutism, the presence of the two criterias, enough for diagnosis as PCOS.[3]

Although the etiology of PCOS is not well known despite intensive research, it is known that inflammation leading to oxidative stress and endothelial damage with genetic factors play a role in the ethiopathogenesis of the disease.[4] Chronic inflammation in PCOS is thought to cause a potential link between PCOS and long-term metabolic and cardiovascular complications.[5]

PCOS is associated with many long term metabolic and cardiovascular problems such as increased risk of obesity, type 2 diabetes and cardiovascular risk factors.[3] Moreover, it was reported that dyslipidemia and metabolic syndrome is higher in PCOS patient with insulin resistance (IR) compared to those without IR.[6] Hyperinsulinemia causes excess production of several adipokines such as leptin, adiponectin and resistin. These adipokines play a role in intraabdominal fat accumulation and diabetogenic processes.[7]

Vitamin D is a lipid solubl molecule that accumulates in adipose tissue. It also has it's receptors in human ovaries, endometrium, placenta and decidual cells. Previous reports indicated that PCOS patients have lower vitamin D status compared to healthy subjects.[8,9] Moreover, It has been suggested that vitamin D deficiency may be associated with metabolic disorders in PCOS.[10,11] The association between vitamin D levels and IR since a causative relation from a pathological point of view cannot be given due to the study design. In our study we aimed to investigate whether vitamin D deficiency has effect on the pathogenesis of IR in PCOS.

Material and Methods

A total of 72 subjects, 48 of whom were PCOS patients and 24 healthy participants, were included in the study. The PCOS group consisted of patients who were diagnosed with PCOS according to the 2004 revised Rotterdam Criteria. Provided that releated disorders are excluded, the patients who had two out of the following could be diagnosed as PCOS; ovulatuar disturbance, hyperandrogenism (clinical and/or biochemical) and polycystic ovaries confirmed via ultrasonography (USG). Hirsutism was evaluated using Ferriman–Gallwey score and menstrual disturbance (none, oligomenorrhea, amenorrhea) was evaluated based on medical history in all subjects. We excluded pregnant women, women with incomplete PCOS diagnosis and received hormone preparations such as oral contraseptive drugs within the last six months. Twenty-four healty subjects participated in the study. The study was performed in accordance with the Helsinki Declaration, and approved by the local ethical committee of our institution. Written informed consent was obtained from all the participants.

Data on antropometric measurements were recorded in each participant. Body mass index (BMI) was calculated based on weight and height (weight/height^2). For subgroup comparisons, patients with a BMI of 30 and above were classified as obese-PCOS, and those below 30 were classified as non-obese PCOS. Weight measurement was done with a classic weighing machine. Waist and hip circumference was performed with an inelastic tape measure while the patients were standing upright. Body fat ratio was measured with a body analyzer using the bioelectrical impedance method. Patient files were analyzed in detail and plasma levels of glycemic and lipid parameters, vitamin D, parathormone and other hormonal parameters were recorded. IR status was evaluated by calculating the homeostatic model assessment for IR (HOMA-IR).

Statistical Analysis

SPSS version 21 (IBM corp) program was used for statistical analysis. Demographic, basal characteristics and vitamin D levels are summarized with mean±standard deviation for

continuous variables, frequency and percentages for categorical variables. Chi-square test was performed for comparison of the categorical data. The continuous data between the study and control groups were analized with Student's t test for normally disturbed variables and Mann–Whitney U variance analysis tests for not normally distributed others. Two-way Spearman's correlation analysis was used to examine the relationship between variables. The significance level of p value less than 0.05 was regarded as statistically significant.

Results

Mean age were insignificant between the two groups. The mean body weight, BMI and body fat ratio of the PCOS patients were 76.2±20.2 kg, 28.7±7.8 kg/m^2 and 35.6±9.4% respectively. In the control group, mean body weight, BMI and body fat ratio of the patients were 61.5±7.5 kg, 22.1±2.6 kg/m^2 and 28.1±5.4%, respectively. Body weight, BMI and body fat ratio were found to be significantly higher in the PCOS group. Waist and hip circumference were measured as 85.9±16.9 cm and 105.0±13.0 cm in the PCOS group, 74.2±5.9 cm and 96.2±6.2 cm in the control group, respectively. Waist and hip circumference values were found to be significantly higher in the PCOS group. While systolic blood pressure (SBP) was similar in both groups, diastolic blood pressure (DBP) measurements were statistically significantly higher in the PCOS group *(Table 1)*.

Plasma fasting glucose levels were significantly higher in PCOS group. HOMA-IR values which is an indication of IR were also higher in the PCOS group, as expected (p <0.001). Low density cholesterol (LDL-C) and triglyceride levels were higher and High density cholesterol (HDL-C) levels were lower in the PCOS group compared to the controls. Vitamin D levels were 19.7±26.9 ng/mL and 31.9±35 ng/mL in the PCOS and control groups, respectively. The difference between the two groups was statistically significant. In the hormonal evaluation; the level of total testosteron, dehydroepiandrosterone-sulphat (DHEA-S) and androstenedione were statistically significant higher in PCOS patients. *(Table 2)*.

When PCOS patients were subclassified as obese and nonobese, SBP and DBP found to be higher in the obese PCOS group. Obese PCOS group had higher levels of fasting blood glucose (FBG), LDL-C and triglycerides and lower levels of HDL-C levels compared to nonobes PCOS. The mean HOMA-IR was 3.6±1.5 in the obese PCOS group, while it was 1.8±0.8 in the non-obese PCOS group. Results were statistically significant. Vitamin D levels were found to be lower in the obese group but not significant (13.7±8.0 vs. 25.7±36.6 ng/mL) *(Table 3)*. In the

Table 1. Comparison of demographic data of the patients according to the groups.

	PCOS group (n=48)	Control group (n=24)	p value
Age (year)	26.8±7.1	28.2±4.2	0.1
Height (cm)	162.3±5.8	165.2±7.7	0.09
Weight (kg)	76.2±20.2	61.5±7.5	0.008*
BMI (kg/m^2)	28.7±7.8	22.1±2.6	0.003*
Waist circumference (cm)	85.9±16.9	74.2±5.9	0.03*
Hip circumference (cm)	105.0±13.0	96.2±6.2	0.009*
Waist-hip ratio	0.81±0.08	0.76±0.03	0.07
BFR (%)	35.6±9.4	28.1±5.4	0.001*
SBP (mmHg)	116.6±13.6	110.8±11.0	0.06
DBP (mmHg)	76.0±8.9	69.5±9.0	0.006*

*p <0.05, BMI: body mass index, BFP: body fat ratio, SBP: systolic blood pressure, DBP: diastolic blood pressure.

correlation analysis, a statistically significant inverse correlation was found between serum vitamin D levels and BMI values in the PCOS group (r=[-0.243], p=0.04), however, no correlation was found between vitamin D levels and HOMA-IR scores. In addition, while there was an inverse correlation between vitamin D and LDL-C (r=[-0.242], p=0.04), no significant correlation was found between vitamin D levels and other lipid parameters.

Discussion

PCOS, which is common in women of reproductive age, causes metabolic disturbances as well as reproductive disorders. Obesity, IR, dyslipidemia, and hypertension are seen in patients with PCOS and these pose a risk in terms of diabetes and cardiovascular diseases.[12] Approximately 30% of PCOS women are obese.[13] In our study, mean BMI was 28.7±7.8 kg/m² in PCOS group and it was statistically significantly higher than healthy control group. Waist and hip circumference and body fat ratio were significantly higher in PCOS patients. In our study, SBP was similar in both groups, while diastolic blood pressure measurements were significantly higher in patients with PCOS. In our study, LDL-C and triglyceride levels were higher and HDL-C levels were lower in the PCOS group. In addition, higher triglyceride and LDL-C levels and lower HDL-C levels were detected in the obese PCOS group compared to the non-obese PCOS group.

Accumulating evidence has shown that the prevalence of vitamin D deficiency is higher in women with PCOS compared to healthy controls.[9] Vitamin D deficiency is reported to be between 20-48% in the general population, and 67-85% in patients with PCOS.[14] Voulgaris *et al*.[15] shown that vitamin D levels were lower in obese women with

Table 2. Comparison of laboratory data of the patients according to the groups.

	PCOS group (n=48)	Control group (n=24)	p value
FBG (mg/dL)	86.8±9.2	73.4±12.2	0.000*
PPG (mg/dL)	96.0±19.7	75.1±13.6	0.000*
HDL-C (mg/dL)	50.5±12.1	58.7±9.9	0.001*
LDL-C (mg/dL)	117.5±37.2	97.0±18.9	0.06
TG (mg/dL)	115.4±83.4	68.1±21.0	0.006*
TG/HDL-C	2.5±2.4	1.1±0.4	0.002*
ALT (U/L)	16.8±8.5	16.0±8.8	0.6
Insulin (IU/mL)	12.7±6.6	6.7±2.4	0.000*
HOMA-IR	2.7±1.5	1.2±0.4	0.000*
Vitamin D (ng/mL)	19.7±26.9	31.9±35	0.005*
PTH (pg/mL)	79.6±29.9	55.6±22.6	0.000*
FSH (mIU/mL)	5.4±5.1	5.7±4.9	0.6
LH (mIU/mL)	8.9±12.6	5.7±7.2	0.04*
E2 (pg/mL)	104.2±102.9	64.0±44.6	0.09
Testosteron (ng/mL)	0.6±0.4	0.4±0.3	0.000*
DHEAS (µg/dL)	369.2±141.0	268.5±116.1	0.005*
Androstenedione (ng/mL)	4.0±1.4	2.2±0.9	0.000*

*p <0.05, FBG: fasting blood glucose, PPP: postprandial glucose, HDL-C: high density cholesterol, LDL-C: low density cholesterol, TG: triglyceride, ALT: alanine transaminase, HOMA-IR: homeostasis model assessment, PTH: parathormone, FSH: follicle-stimulating hormone, LH: luteinizing hormone, E2: oestradiol, DHEAS: dihydroepiandrosterone sulfate.

PCOS than in non-obese women with PCOS. In our study, vitamin D levels were 19.7±26.9 ng/mL and 31.9±35 ng/mL in PCOS and control groups, respectively (p=0.005). When PCOS patients were classified as obese and non-obese, vitamin D levels were lower in the obesity group, but not significant (13.7±8.0 vs. 25.7±36.6 ng/mL).

The vitamin D receptor gene, which regulate approximately 3% of the human genome and vitamin D receptors, modulate the expression of many genes in various tissues, including the pancreas and ovaries. Thus, vitamin D has a wide range of effects including the effects on the metabolism of glucose and lipid, and the regulation of blood pressure.[16,17] Several reports suggest that some proinflammatory mediators, such as tumor necrosis factor, are important in pathogenesis of PCOS independent of excess weight. Hence, PCOS is currently considered as a chronic, low-grade inflammatory disorder.[18,19] Hyperglycemia and higher levels of free fatty acids can increase reactive oxygen species and oxidative stress, leading to dysfunction and cell death.[20]

The prevalence of IR approximately 50-70% in PCOS women.[16] Although serum insulin levels are lower in non-obese women with PCOS compared to obese ones, IR is a common clinical finding in these women.[21] In our study, plasma fasting glucose levels and HOMA-IR were significantly higher in PCOS with obesity compared to the control group. Similar statistically significant results was also present in PCOS with obesity compared to non-obese ones.

Increasing number of studies have shown that vitamin D and HOMA-IR levels are inversely related in PCOS.[16] Although the effects of vitamin D on glucose metabolism are not clear, it can be explained that it increases insulin synthesis and insulin receptor expression and decreases some inflammatory cytokines.[22] Hann *et al.*[23] reported that vitamin D levels were lower in women with PCOS who had IR. Wehr *et al.*[11] shown that vitamin D has been an independent predictor of IR and sensitivity. In our study, no significant relationship was found between IR and vitamin D levels in PCOS patients.

Table 3. Comparison of demographic and laboratory data of the PCOS patients according to the BMI.

	Obese PCOS group (n=24)	Non-obese PCOS group (n=24)	p value
SBP (mmHg)	124.7±12.5	108.5±9.2	0.000*
DBP (mmHg)	79.3±7.4	72.7±9.2	0.01*
FBG (mg/dL)	88.9±10.1	84.7±7.9	0.07*
PPG (mg/dL)	101.3±23.1	90.2±13.5	0.1
HDL-C (mg/dL)	43.9±8.9	57.3±11.2	0.000*
LDL-C (mg/dL)	128.7±37.5	105.8±33.8	0.01*
TG (mg/dL)	161.0±94.3	67.9±25.1	0.000*
TG/HDL-C	3.8±2.8	1.2±0.5	0.000*
ALT (U/L)	21.5±7.8	12.1±6.3	0.000*
Insulin (IU/mL)	16.5±7.0	8.7±2.7	0.000*
HOMA-IR	3.6±1.5	1.8±0.8	0.000*
Vitamin D (ng/mL)	13.7±8.0	25.7±36.6	0.2
PTH (pg/mL)	81.0±29.2	78.3±31.1	0.5

*p <0.05, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, FBG: Fasting blood glucose, PPP: postprandial glucose, HDL-C: High density cholesterol, LDL-C: Low density cholesterol, TG: triglyceride, ALT: alanine transaminase, HOMA-IR: Homeostasis model assessment, PTH: parathormone.

Based on accumulating reports, the relationship between vitamin D and obesity has been clearly demonstrated. Despite this, the causal relationship between low vitamin D levels and obesity remains unclear.[24] In a meta-analysis investigating the relationship between vitamin D deficiency and BMI, the prevalence of vitamin D deficiency in obese participants was found to be 35% higher than the non-obese group.[25] In another meta-analysis, vitamin D deficiency prevalence was correlated with obesity in Asians (OR 95% CI 3.70 [1.98-6.90]) and European-Americans (OR 95% CI 3.09 [1.89-5.04]).[26] In our study, a statistically significant relationship was found between low vitamin D and BMI.

Clinical studies have shown that vitamin D deficiency is related with arterial hypertension, due to the possible inhibitory effect of vitamin D on renin gene expression.[27] Wehr *et al.*[11] found significantly negative correlation of vitamin D levels SBP and DBP in PCOS patients. Dyslipidemia, with a prevalence of approximately 70%, is a frequent metabolic disorder in PCOS patients. Legro *et al.*[28] found significant elevations in LDL-C levels in women affected by PCOS, independent of obesity. Similarly, several studies have found an association between low vitamin D levels and increased total cholesterol, LDL-C, triglycerides, and low HDL-C.[29-31] In our study, an inverse relationship was found between vitamin D and LDL-C, but no significant relationship was found between vitamin D and other lipid parameters.

Limitations

Our study has a few limitations that should be noted. One of the major limitations of our study was its evaluation of IR with HOMA-IR. Secondly, the sample size was small.

Conclusions

As a conclusion, in our study, we showed that vitamin D levels were lower in PCOS patients and suggested that this may be one of the causes of IR and metabolic complications in these patients. A statistically significant relationship was found between BMI and low vitamin D levels. It was also found inverse correlation between vitamin D and LDL-C. However, our study revealed that IR increased in women with PCOS, but there was no significant relationship between IR and vitamin D levels.

Conflict of interest

The authors declare that they have no conflict of interest.

Authors' Contribution

Study Conception: OOG; Study Design: OOG; Supervision: OOG, SC; Data Collection and/or Processing: OOG, PS, SC; Statistical Analysis and/or Data Interpretation: SC, OOG; Literature Review: PS; Manuscript Preparation: PS; and Critical Review: OOG, SC.

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