

Magnesium, calcium and vitamin D levels in polycystic ovarian syndrome: a retrospective single center study

Resul Kılıç¹, Mehmet Erdem², Mehmet Aslan²

¹Department of Internal Medicine, Çınar State Hospital, Diyarbakır, Türkiye

²Department of Internal Medicine, Faculty of Medicine, Yüzüncü Yıl University, Van, Türkiye

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ABSTRACT

Aims: Polycystic ovary syndrome (PCOS); it is an endocrine-gynecological disorder that affects many women of reproductive age, with chronic anovulation and androgen elevation. Although many pathophysiological processes have been discovered in the development of PCOS; the exact etiology and pathophysiology have not been fully elucidated. Vitamin D is synthesized differently from other vitamins and vitamin D has a hormonal function in the body. Vitamin D is known to have a role in many diseases, as well as its effects on bone metabolism in the body. We aimed to examine the relationship between PCOS and serum vitamin D, calcium and magnesium levels.

Methods: A total of 80 cases, including 40 patients diagnosed with PCOS according to the Rotterdam criteria and 40 cases in the normal population, were included in the study. The cases were examined retrospectively. Magnesium, calcium and vitamin D levels of all cases were compared. Additionally, the hemogram parameters, insulin, glucose, insulin resistance, HbA1c (hemoglobin A1c test), high-density lipoprotein, low-density lipoprotein, triglyceride, total cholesterol, parathyroid hormone (PTH) and phosphorus levels of the cases were compared.

Results: There was no difference in magnesium, calcium, vitamin D values between cases with and without polycystic ovary syndrome, and no difference in hemogram parameters, HbA1c, glucose, insulin, PTH and phosphorus levels between the same groups ($p>0.05$). When lipid levels were compared, total cholesterol and low-density lipoprotein levels were found to be significantly higher in those without PCOS ($p=0.042$). The average age was found to be significantly lower in patients with PCOS ($p<0.001$).

Conclusion: In our study, no significant difference was seen between the two groups in terms of magnesium, calcium and vitamin D levels. Prospective observational studies and randomized controlled studies are needed to more clearly explain the relationship between hormonal and metabolic irregularities and magnesium, calcium and vitamin D levels in PCOS.

Keywords: Polycystic ovary syndrome, vitamin D, magnesium, calcium, lipid profile

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a clinical entity characterized by menstrual irregularities and androgen elevation. Most women with PCOS are in their fertile period and its prevalence worldwide ranges from 6% to 21%. Most women with PCOS have metabolic disorders such as ovarian dysfunction, insulin resistance, androgen elevations, and dyslipidemia.¹ The etiology of PCOS is unknown. However, the high ratio between Luteinizing hormone (LH) and follicle stimulating hormone (FSH) and the increased frequency of gonadotropin-releasing hormone (GnRH) are the main underlying factors in pathophysiology. Current data; genetic-environmental factors, androgen elevation, insulin resistance are suggested to play a serious role in the development of PCOS as internal and external factors.²

Approximately 40-80% of women with PCOS are overweight or obese. A high body mass index negatively affects the patient's sexual activity, psychological and metabolic status. PCOS can cause serious complications such as diabetes

mellitus, hypertension, coronary artery disease, endometrium cancer and infertility in the long term.³

One of the criteria used in the diagnosis of PCOS is the Rotterdam criteria and consists of three criteria. The presence of at least two of the Rotterdam criteria is diagnostic. Rotterdam criteria: 1-ovulatory dysfunction, 2-hyperandrogenism and 3-polycystic ovary morphology.⁴

Currently, there are four commonly recognized phenotypes of PCOS: type A, polycystic ovary (PCO), chronic oligo-anovulation (OA) and hyperandrogenism (HA); type B, OA and HA; type C, PCO and HA; and type D, PCO and OA. Insulin resistance is present in all phenotypes. Insulin resistance is the most common classical phenotype (types A and B) (80%), followed by ovulatory PCOS (65%) and non-hyperandrogenemic PCOS (38%).⁵

Vitamin D deficiency may be a risk factor for PCOS. The prevalence of vitamin D deficiency is 20-48%. However,

Corresponding Author: Mehmet Erdem, dr.mehmet_erdem@hotmail.com



the prevalence of vitamin D deficiency is higher in patients diagnosed with PCOS.^{3,4} One of the vitamins produced in the human body is vitamin D. It has effects on calcium and bone metabolism as well as hormonal effects on many systems. Vitamin D deficiency is thought to play a role in the emergence of autoimmune diseases, rheumatoid arthritis, inflammatory bowel disease, DM, multiple sclerosis, some malignancies and heart diseases.^{6,7} In a study, low vitamin D levels were found to be associated with metabolic syndrome, but high vitamin D levels were positively correlated with insulin sensitivity.⁸ A positive effect has been detected in women with PCOS who receive calcium and vitamin D treatment in cases such as menstrual disorders, weight loss, and androgen elevation.⁹ In this study, we aimed to determine whether PCOS is related to calcium, magnesium and vitamin D levels. In case of a negative correlation, we predict that giving calcium, magnesium and vitamin D to women with PCOS for treatment may reduce some negative effects.

METHODS

Ethics

The study was carried out with the permission of the Van Yüzüncü Yıl University Non-interventional Clinical Researches Ethics Committee (Date: 19.08.2022, Decision No: 2022/08-06). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients

In our study, the files of individuals who applied to the Internal Medicine and Endocrinology polyclinic of Van Yüzüncü Yıl University Faculty of Medicine Dursun Odabaş Training and Research Hospital between 01.01.2020 and 30.09.2022 were retrospectively examined.

80 cases (40 cases with PCOS and 40 cases without PCOS) were included in the study. Patients diagnosed with PCOS in previous examinations and imaging studies and a healthy control group were included in the study, regardless of age range.

Inclusion criteria for the study: Being over 18 years of age, being female, not being pregnant, and having been diagnosed with PCOS according to the Rotterdam criteria.

Exclusion criteria for the study: Lack of laboratory results such as vitamin D, calcium, magnesium and parathyroid hormone; using steroids, sex hormones or drugs that may cause electrolyte imbalance in the last six months; having diseases such as congenital adrenal hyperplasia, Cushing syndrome, thyroid gland diseases and cancer.

Methods

Demographic characteristics of all individuals (age and gender), calcium, magnesium, vitamin D, phosphorus, parathyroid hormone (PTH), mean platelet volume (MPV), erythrocyte distribution volume (EDV), white blood cells (WBC), neutrophil count, lymphocyte count, platelet count, neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), glucose, insulin, HbA1c (hemoglobin A1c test), low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride (TG) and total cholesterol (TK) levels was recorded.

The Architect i2000 system (Abbott Laboratories, USA) uses chemiluminescent microparticle immunoassay (CMIA) technology. The hormone assays performed by this analyser included tests for cortisol, follicle-stimulating hormone (FSH), carcinoembryonic antigen (CEA), α -fetoprotein (AFP), ferritin, PTH, free thyroxin (FT4), vitamin B12, folic acid, prolactin, progesterone, luteinising hormone (LH), and β -human chorionic gonadotrophin (β hCG).

In our total laboratory automation (TLA) setting, two Architect c16000 platforms are used to automatically measure HIL indices on all plasma and serum samples on which chemistry and immunochemistry tests are requested. Both instruments are used and maintained by strictly following the manufacturer's instructions. In particular, the Architect c16000 analyzer measures HI through the dilution of samples with saline solution and the polychromatic photometric detection of the interferent.

Statistical Analysis

Descriptive statistics for the features emphasized; expressed as mean, standard deviation, minimum and maximum values. Independent samples T test was performed to compare group means in terms of continuous variables. To determine the relationship between these variables, Pearson correlation coefficients were calculated separately in the groups. In the calculations, the statistical significance level was taken as 5% and the SPSS (ver: 21) statistical package program was used for the calculations.

RESULTS

A total of 80 cases, 40 cases diagnosed with PCOS and 40 healthy cases, were included in the study. The average age of PCOS cases was 27 ± 6 years, and the average age of healthy cases was 36 ± 12 years. The average age of patients with PCOS was found to be significantly lower ($p=0.001$). While the average magnesium of PCOS cases was 1.9 ± 0.36 mg/dl, calcium 9.4 ± 0.5 mg/dl, phosphorus 3.42 ± 0.58 mg/dl, PTH 73 ± 25 pg/ml and vitamin D 14.09 ± 8.2 pg/ml; The average magnesium of the control group cases was 1.9 ± 0.29 mg/dl, calcium 9.4 ± 0.4 mg/dl, phosphorus 3.38 ± 0.46 mg/dl, PTH 76 ± 42 pg/ml and vitamin D 10.16 ± 8.4 pg/ml. No statistically significant difference was detected between the groups. Magnesium, calcium, phosphorus, PTH and vitamin D levels of the cases are given in **Table 1**.

Table 1. Comparison of magnesium, calcium, phosphorus, vitamin D and parathormone levels of cases with and without polycystic ovary syndrome

Parameters	With PCOS cases (n=40)	PCOS without (n=40)	p
Magnesium (mg/dl)	1.9 ± 0.36	1.9 ± 0.29	0.124*
Calcium (mg/dl)	9.4 ± 0.5	9.4 ± 0.4	0.652*
Phosphorus (mg/dl)	3.42 ± 0.58	3.38 ± 0.46	0.713*
Parathormone (pg/ml)	73 ± 25	76 ± 42	0.659*
Vitamin D (pg/ml)	14.09 ± 8.2	10.16 ± 8.4	0.061*

*Student T test, PCOS: Polycystic ovary syndrome

While the average total cholesterol of the PCOS cases was 165.6 ± 44.4 mg/dl and LDL was 92.5 ± 32.6 mg/dl, the total cholesterol of the control group cases was 186.3 ± 36.7 mg/dl and LDL was 109.0 ± 29.2 mg/dl. Total cholesterol and LDL levels of patients without PCOS were found to be statistically significantly higher. While the average triglyceride of the PCOS

cases was 125.3±85.3 mg/dl and HDL was 51.4±16.2 mg/dl, the triglyceride of the control group cases was 119.6±71.6 mg/dl and HDL was 54.3±13.4 mg/dl. No statistically significant difference was detected between the groups (**Table 2**).

Table 2. Comparison of lipid levels in cases with and without polycystic ovary syndrome

Parameters	With PCOS cases (n=40)	PCOS without (n=40)	p
TG (mg/dl)	125.3±85.3	119.6±71.6	0.776*
LDL (mg/dl)	92.5±32.6	109.0±29.2	0.04*
HDL (mg/dl)	51.4±16.2	54.3±13.4	0.444*
TK (mg/dl)	165.6±44.6	186.3±36.7	0.05*

*Student T test, PCOS: Polycystic ovary syndrome, TG: Triglyceride, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, TK: Total cholesterol

No statistically significant difference was detected between the groups in hemogram parameters, HbA1c, glucose, insulin and insulin resistance level (**Table 3**).

Table 3. Comparison of laboratory values in cases with and without polycystic ovary syndrome

Parameters	With PCOS cases (n=40)	PCOS without (n=40)	p
WBC (mm ³)	7.552±2.332	7.201±1.844	0.458*
Neutrophil (mm ³)	4.447±1.541	3.976±1.163	0.127*
Lymphocyte (mm ³)	2.445±778	2.469±782	0.894*
Platelet (10 ³ /mm ³)	293.800±63.450	299.080±60.456	0.704*
Neutrophil/lymphocyte	2.08±1.65	1.69±0.56	0.158*
Platelet/lymphocyte	138.3±87.7	128.7±35.5	0.521*
MPV (fL)	10.3±0.90	10.3±0.88	0.940*
EDV (fL)	13.07±1.17	13.5±1.14	0.141*
Insulin (IU/l)	12.8±8.0	12.3±10.6	0.818*
Glucose (mg/dl)	95.3±32.4	97.6±33.0	0.749*
HbA1c (mmol/mol)	5.4±0.5	5.5±1.4	0.563*

*Student T test, PCOS: Polycystic ovary syndrome, WBC: White blood cells, MPV: Mean platelet volume, EDV: Erythrocyte distribution volume, HbA1c: Hemoglobin A1c test

DISCUSSION

Infertility, oligo-amenorrhea, and abnormal menstrual bleeding due to ovarian dysfunction may occur in PCOS. Moreover, symptoms such as hirsutism and skin acne due to high androgen levels are common. The prevalence of obesity in women with PCOS is approximately 40-60% (**Table 4**). Menstrual cycles of at least 45 days or fewer than 9 periods per year; presence of findings related to high androgen levels such as acne, hirsutism, alopecia, acanthosis nigricans; or laboratory findings of high androgen levels are considered criteria for chronic oligo-amenorrhea.¹⁰

Table 4. Frequency of signs and symptoms of polycystic ovary syndrome

Signs and symptoms of polycystic ovary syndrome	Frequency
Hirsutism	60-90%
Oligomenorrhea	50-90%
Infertility	55-75%
Polycystic ovary	50-75%
Obesity	40-60%
Amenorrhea	25-50%
Dysfunctional uterine bleeding	30%
Acne	25%
Normal menstrual pattern	22%

Several scientific studies have examined the nutrition of women with PCOS. It was observed that 25% of these women had insufficient magnesium consumption.¹¹ Asemi et al.¹² showed that women with PCOS consumed an average of 233 mg/day of magnesium. This is below the average of 320 mg/day for women ≥19 years of age.

Vitamin D deficiency emerges as a significant health problem for patients with PCOS. Various studies show that vitamin D plays a critical role in hormonal balance and insulin metabolism. In individuals with PCOS, deficiency of this vitamin can increase insulin resistance, which can lead to complications such as metabolic syndrome, obesity and other hormonal imbalances. Demographic characteristics of PCOS women diagnosed with DM and metabolic syndrome were evaluated. A negative correlation was observed between magnesium and insulin resistance in these patients. It has been observed that low magnesium is associated with insulin resistance. Insulin resistance is believed to be the main pathogenic factor associated with the increased rate of metabolic disorders among women with PCOS.¹³

In 2016, Rajeswari et al.¹⁴ 80 premenopausal women with PCOS were compared with 40 women without PCOS. Women with PCOS (116.65±11.15 compared to 89.10±5.89 mg/dl, p=0.0001) had lower magnesium levels (1.210 mg/dl) than the control group. Moreover, found significantly higher fasting blood sugar levels in women with PCOS. (While it was 2.087±0.189 mg/dl in the control group, it was 1.210±0.239 in the PCOS group, p=0.0001). In this study, there was an inverse relationship between glucose and magnesium (r=-0.412, p=0.0001) levels in patients with PCOS. In our study, blood magnesium levels were found to be similar between patients with PCOS and the other group (p>0.05).

Some studies have shown that vitamin D deficiency is a problem in patients with PCOS.^{15,16} It has been observed that there is a relationship between low vitamin D levels and the criteria of metabolic syndrome in women with PCOS.¹⁷ The regulatory effect of vitamin D on insulin-mediated intracellular and extracellular calcium plays a critical role in many biological processes. Vitamin D can strengthen the effects of insulin by increasing insulin resistance at the cellular level. Additionally, vitamin D can regulate calcium levels both inside and outside cells by increasing calcium absorption from the gastrointestinal tract and urinary tract. Calcium is vital for cellular signaling and various metabolic pathways. This regulatory role of vitamin D becomes even more important, especially in diseases with hormonal imbalances such as PCOS.¹⁸ Another hypothesis is examining the effects of vitamin D on gene expression related to insulin receptors. Research shows that vitamin D may promote the transcription of certain genes and increase the production of insulin receptors by these genes. Thus, vitamin D deficiency can lead to increased insulin resistance and metabolic risk.¹⁹ In summary, many studies have shown that there may be a relationship between PCOS and vitamin D and calcium. In our study, no significant difference was found between the group with PCOS and the group without PCOS in terms of parameters such as vitamin D, calcium, PTH and phosphorus (p>0.05 for all).

In individuals with PCOS, hormonal imbalances and metabolic disorders, combined with factors such as treatment and oxidative stress, may cause adverse vascular disorders.

Additionally, high androgen levels may further increase the risk of blood pressure increases. These metabolic abnormalities can increase the risk of diseases such as heart disease and stroke.²⁰ Dyslipidemia is also common in PCOS. In a meta-analysis conducted by Wild et al.,²¹ it was reported that TG levels were 26 mg/dl and LDL 12 mg/dl higher, and HDL concentrations were 6 mg/dl lower in women with PCOS compared to the control group. In some studies, the prevalence of dyslipidemia was found to be up to 50-70% higher in women with PCOS.²² Another study found that 72.4% of non-hispanic women with PCOS had dyslipidemia and elevation in LDL was most common, with important predictors being age, insulin, and testosterone.²³ In our study, LDL and TC values of the group without PCOS were found to be higher and significant ($p < 0.05$ for all). There was no difference between the two groups in terms of insulin.

C-reactive protein (CRP) is a disease-produced protein produced by the liver and is an acute phase reactant that is increased in inflammatory events. CRP levels rise when an infection or inflammatory response occurs in the body. The normal range of neutrophil lymphocyte ratio (NLR) is considered to be 1-2. In adults, values higher than 3.0 and lower than 0.7 are pathological. Values between 2.3-3.0 may be a sign of chronic inflammatory diseases. NLR has been shown to positively correlate with CRP levels.²⁴ NLR is a cost-effective marker that could be an alternative to CRP for inflammation. There are also several studies reporting increased leukocyte counts in patients with PCOS.^{25,26} In some studies, MPV can be used as a marker to detect inflammation. It has been shown that the MPV value in patients with PCOS is higher than in the control group.²⁵ In our study, when PCOS cases were compared with the control group, leukocyte count, neutrophil count, lymphocyte count, NLR, platelet count, platelet-lymphocyte ratio and MPV value were similar ($p > 0.05$ for all).

Limitations

One of the most important limitations was that our study was single center and this was one of the main factors of the low number of patients. Another limitation was that our study was retrospective. Therefore, most patients diagnosed with PCOS did not have the laboratory parameters we wanted. We believe that prospective and multicenter studies on PCOS will contribute more to the literature.

CONCLUSION

In our study, magnesium, calcium and vitamin D levels were found to be similar between the PCOS group and the other group. More studies are needed to clarify the relationship between PCOS and magnesium, calcium and vitamin D levels. However, we think that there may be a significant difference when done with a larger number of patients.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was approved by the the Van Yüzüncü Yıl University Non-interventional Clinical Researches Ethics Committee (Date: 19.08.2022, Decision No: 2022/08-06).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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