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Original Article

Evaluation of hematologic and coagulation system disorders in adolescents with polycystic ovary syndrome

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Abstract

Aim: Polycystic ovary syndrome (PCOS) is characterized by hyperandrogenism, ovulatory dysfunction, insulin resistance, and obesity, affects 8-26% of adolescent girls. The effects of polycystic ovarian syndrome on the hematologic and coagulation systems have received little attention. We aimed to investigate the hematologic and coagulation system disorders in PCOS.
Materials and Methods: The study included 40 adolescents with PCOS and 41 healthy controls. Hemostatic and coagulation system parameters evaluated in both groups and were compared with metabolic parameters.
Results: Adolescent's with PCOS had a significantly higher insulin, HOMA-IR levels, and Hematocrit (Hct) levels than the control group, but no significant difference was found in D-dimer, fibrinogen, protein C, protein S, Antitrombine III levels. A positive correlation was found between insulin and HOMA-IR values and hemoglobin (Hgb), Hct, white blood cell (WBC) levels (r=0.32 p=0.003; r=0.33 p=0.002; r=0.36 p=0.001, respectively); also a positive correlation was found between high-density lipoprotein cholesterol (HDL) and WBC values (r=0.26 p=0.01). A positive correlation was found between follicle stimulating hormone (FSH) and Protein C and Protein S (r=0.41 p=0.008; r=0.31 p=0.04); total testosterone and fibrinogen levels (r=0, 32 p=0.04); Dehydroepiandrostenedione sulfate (DHEAS) and protein S levels (r=0.31 p=0.04).
Conclusion: There was no significant difference in the hematologic and coagulation parameters between PCOS and healthy controls. Hypercoagulated state in PCOS is associated with obesity, BMI, inflammation, and insulin resistance, not specific to the disease.

Keywords: Adolescent, coagulation, hematologic, polycystic ovary syndrome

INTRODUCTION

Polycystic ovary syndrome (PCOS), characterized by hyperandrogenism, ovulatory dysfunction, insulin resistance, and obesity, affects 8-26% of adolescent girls (1-3). The pathophysiology of this condition is influenced by genetic factors, changes in follicle-stimulating hormone (FSH) and luteinizing hormone (LH), steroid synthesis and release, and disorders of insulin secretion and action (4).

PCOS, a multifactorial endocrine condition, is associated with decreased fibrinolytic capacity and mild to moderate prothrombotic tendency, with its pathophysiology still unknown. PCOS patients often experience prothrombotic states due to multifactorial factors including visceral obesity, insulin resistance, dyslipidemia, and dysglycemia, which often overlap with metabolic disorders involving both acquired and hereditary factors (5-7). Changes in the coagulation system are believed to contribute to thromboembolic events and atherosclerosis

progression in PCOS (8), with abnormalities causing increased thrombosis and decreased plasma fibrinolytic activity. However, it is important to note that the current literature is limited to a small number of studies, small sample sizes, and contradictory findings regarding hemostatic parameters in PCOS (9). White blood cell (WBC), red cell distribution width (RDW), platelet count, mean platelet volume (MPV), protrombin time (PT), activated partial tromboplastin time (aPTT), D- dimer, fibrinogen, plasminogen activator inhibitor-1 (PAI-1), and Thrombin activatable fibrinolysis inhibitor (TAFI) parameters were generally evaluated in studies investigating hemostasis in PCOS patients, with a few series including Hemoglobine (Hgb), hematocrite (Hct), protein C, protein S, and Antitrombine III (AT III) levels. Previous studies show insulin resistance in 44%-70% of PCOS patients, with dyslipidemia being the most common metabolic disorder, characterized by high triglyceride, low high-density lipoprotein (HDL), and high low-density lipoprotein (LDL) levels (9,10).

PCOS, a condition characterized by abnormal hormonal and metabolic systems, has been linked to hematologic and coagulation system disorders, with limited research in adolescent individuals. The aim of our study is to evaluate the hematological and coagulation parameters in adolescents with PCOS and correlate with metabolic parameters.

MATERIALS AND METHODS

Study Population

A prospective randomized-controlled study, was conducted in a pediatric endocrinology outpatient clinic from May 2020 to July 2021. The study protocol was approved by the hospital's institutional review board (2011-KAEK-25 2020/03–15) in accordance with the principles of the Helsinki declaration. Written informed consent to participate in this study was obtained from the children and/or parents or legal guardians of the children after explaining the nature and purpose of the study. The study included 40 patients diagnosed with polycystic ovary syndrome according to the Rotterdam criteria (11) and 41 control groups of similar age and weight who had regular menstruation for at least 2 years. The participants in both groups ranged in age from 12 to 18 years. The study excluded patients with hematological and endocrinological comorbidities, drug use history, and impaired thyroid, liver, and renal functions.

Study Protocol

Physical examination and anthropometric measurements of all patients in the study were performed. Height, weight measurements were taken by an experienced pediatric nurse. Body mass index (BMI) standard deviation (sd), weight sd and height sd were calculated according to the age- and sex-specific reference values (12). The first menstruation year and presentation complaints of the patients were noted. Ferriman Galwey score was used to evaluate signs of hirsutism (13). Serum glucose, insulin and lipid profile levels were measured after at least 8 hours of fasting. The insulin resistance index was calculated as homeostatic model assessment–insulin resistance (HOMA-IR) which was calculated as fasting plasma glucose (mg/dl) × fasting serum insulin (μU/ml)/405 (14). Blood samples that had previously been collected from participants at an early follicular phase (days 3–5) of menstruation were noted (LH, FSH, estradiol (E2)). The following hormonal parameters were evaluated for differential diagnosis of hyperandrogenism findings: total and free testosterone, dehydroepiandrosterone sulphate (DHEAS) and Δ4-androstenedione, and 17-OH progesterone. All patients' pelvic USG images were evaluated. All patients' PT, aPTT, International normalized ratio (INR), protein C, protein S, ATIII, MPV, WBC, homocysteine, D-dimer, and fibrinogen levels were measured to assess coagulation parameters and fibrinolytic activation. The metabolic parameters and hematological parameters of PCOS and control groups were compared, and the relationship between changing metabolic and hormonal parameters and hematological parameters was investigated.

Laboratory Analysis

For the hemogram, blood was taken into a purple capped tube with EDTA (ethylene diamine tetra acetic acid) and studied with the impedance method in the 'Mindray BC 6000' device without centrifugation. Blood is taken into a sodium citrate blue capped tube and centrifuged at 3000 rpm for 10 minutes, then PT, aPTT, fibrinogen by coagulometric method with 'Sysmex CS 5100' device, D-dimer by immunoassay method with 'Sysmex CS 5100' device. Protein C, protein S, AT-III, measurements were made with the 'Sysmex CS 5100' chromogenic method.

Statistical Analysis

IBM SPSS Statistics 22 program was used for statistical analysis. The suitability of the parameters to the normal distribution was evaluated by Kolmogorov-Smirnov and Shapiro-Wilks tests. While evaluating the study data, in addition to descriptive statistical methods (mean, standard deviation, median, frequency), Student's t-test was used for the comparison of normally distributed parameters between two groups, and Mann Whitney U test was used for comparisons of non-normally distributed parameters between two groups. Paired Sample T test was used for in-group comparisons of normally distributed parameters, and Wilcoxon Sign Test was used for in-group comparisons of non-normally distributed parameters. Fisher's Exact Chi-Square test and Continuity (Yates) Correction were used to compare qualitative data. Relationships between different variables with normal distribution were analyzed with Pearson correlation. Significance was evaluated at the $p<0.05$ level.

RESULTS

Our study consisted of 81 adolescents aged between 12 and 18, 40 of whom were in the "PCOS" group and 41 of them were in the "Control" group. Oxological and laboratory characteristics

of the groups are shown in Table 1, and the hormone profile of PCOS cases is shown in Table 2.

Both groups were of similar age, weight, and height. Insulin and HOMA-IR values were higher in the PCOS group than in the control group (p<0.001 and p=0.004, respectively). Again, High-density lipoprotein cholesterol (HDL-C) value of the PCOS group was found to be lower than the control group (p=0.02) (Table 1).

When the hematological data from both groups were compared, the median hematocrit (Hct) value of the PCOS group was 40.3% (40.12±3.13), while the control group had 39.01% (38.35±3.90). When the Hct levels of the two groups were compared, the PCOS group had a higher levels than the control group (p=0.02) (Table 1).

Evaluation of hormonal parameters of the PCOS Group was in Table 2.

Table 1. Comparison of the oxological and laboratory characteristics of the groups

	PCOS (n=40)	Control (n=41)	p
Age (years)	15.73±1.28 (15.9)	15.29±1.37 (15.2)	0.13*
Weight (kg)	70.71±20.87 (71.3)	63.45±13.14 (62)	0.13¶
Weight sd	1.50±2.34 (1.8)	0.96±1.04 (0.74)	0.19¶
Height (cm)	160.92±6.29 (161)	161.91±5.36 (161)	0.99*
Height sd	-0.13±1.0 (-0.01)	-0.08±0.92 (0.01)	0.85*
BMI(kg/m²)	27.11±7.57 (27.9)	24.67±5.07 (23.8)	0.20¶
BMI sd	1.31±1.88 (1.80)	0.98±1.21 (0.88)	0.26¶
Blood glucose (mg/dl)	84.35±9.55 (83)	85.34±6.27 (86)	0.58*
Insulin (µU/L)	20.31±12.57 (16.75)	12.20±8.97 (9.9)	**<0.001¶**
HOMA-IR	4.70±4.50 (3.20)	2.55±1.90 (2.10)	**0.004¶**
TK (mg/dl)	156.70±29.81 (153.5)	156.22±26.09 (149)	0.90¶
TG (mg/dl)	97.42±42.96 (88.5)	97.56±55.08 (84)	0.71¶
HDL-K (mg/dl)	56.65±21.85 (52.6)	60.92±13.61 (59)	**0.02¶**
LDL-K (mg/dl)	79.25±28.680 (81.90)	72.94±27.16 (68.4)	0.31*
PT (sn)	11.81±0.66 (11.8)	11.75±0.63 (11.7)	0.67*
aPTT (sn)	24.27±1.80 (24.05)	24.79±2.26 (24.4)	0.25*
INR	0.94±0.06 (0.93)	0.96±0.06 (0.96)	0.16¶
D-Dimer (mg/L)	0.26±0.11 (0.19)	0.26±0.12 (0.21)	0.55¶
Fibrinogen (mg/dl)	315.92±94.2 (288.5)	310.92±85.72 (292)	0.95¶
Protein-C (%)	100.87±28.24 (100.1)	105.17±37.93 (94.7)	0.88¶
Protein-S (%)	125.68±88.01 (99.45)	130.62±80.19 (105)	0.28¶
Antitrombin III (%)	34.41±3.23 (34.8)	34.03±4.66 (34.5)	0.67*
Hemoglobin (gr/dl)	13.41±1.17 (13.5)	12.83±1.60 (13.4)	0.23¶
Hematocrit (%)	40.12±3.13 (40.3)	38.35±3.90 (39.01)	**0.02***
MPV (fL)	10.03±1.22 (10.05)	9.6±0.99 (9.5)	0.08*
WBC (/mm³)	7277.0±1448.12 (7255)	7319.51±2287.22 (7000)	0.92*

Data are shown as mean±sd (median). ¶Mann-Whitney U test *Student's t test
PCOS: polycysticover syndrome, sd: standard deviation, BMI: body mass index, HOMA-IR: homeostasis model assessment of insulin resistance, TK: total cholesterol, TG: triglyceride, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, PT: prothrombin time, aPTT: activated partial thromboplastin time, INR: international normalized ratio, MPV: mean platelet volume, WBC: white blood cell

Table 2. Evaluation of hormonal parameters of the PCOS group

Parameters	Mean±sd (median)
FSH (µU/ml)	5.53±1.52 (5.4)
LH (µIU/ml)	14.42±12.16 (11)
Estradiol (pg/ml)	50.59±29.97 (42.45)
DHEAS (µg/dl)	292.07±152.21 (252.5)
Total testosterone (ng/dl)	52.92±21.81 (50.95)
17 OH Progesterone (ng/ml)	0.59±0.39 (0.5)
Androstenedione (ng/ml)	1.76±0.67 (1.7)

sd: standard deviation, FSH: follicle stimulating hormone, LH: luteinizing hormone, DHEAS: dehydroepiandrostenedione sulfate

When the correlation analysis of metabolic parameters with hematological parameters was performed, a positive correlation was found between insulin level and Hemoglobin (Hgb), Hct and WBC levels in the PCOS group (r=0.32, p=0.003; r=0.33, p=0.002; r=0.36, p=0.001) while PT, PTT, INR, D-dimer, fibrinogen, protein C, protein S, AT III, MPV levels were not correlated. There was a positive correlation between HOMA-IR level and Hgb, Hct, WBC levels in the PCOS group (r=0.35, p=0.001; r=0.35, p=0.01; r=0.29, p=0.007) while no correlation was found between PT, PTT, INR, D-dimer, fibrinogen, protein C, protein S, AT III, MPV levels (Table 3). There was a positive correlation between HDL level and WBC levels in the PCOS group (r=0.26, p=0.01) while no correlation was found between PT, PTT, INR, D-dimer, fibrinogen, protein C, protein S, AT III, MPV levels (Table 3).

Table 3. Correlation analysis of metabolic parameters with hematological parameters

Parameters	Insuline		HOMA-IR		HDL	
	r	p*	r	p*	r	p*
PT (sn)	-1.45	0.19	-0.14	0.19	-0.07	0.52
PTT (sn)	-.02	0.8	-0.07	0.49	0.15	0.16
INR	-.032	0.7	-0.12	0.28	0.07	0.50
D-Dimer (mg/L)	0.10	0.36	0.00	0.98	-0.19	0.07
Fibrinogen (mg/dl)	0.20	0.06	0.08	0.46	-0.11	0.28
Protein-C (%)	-0.00	0.97	-0.07	0.51	0.01	0.93
Protein-S (%)	-0.00	0.9	-0.05	0.6	-0.06	0.54
Antitrombin3 (%)	-0.08	0.4	-0.06	0.56	-0.05	0.66
Hemoglobin (gr/dl)	**0.32**	**0.003**	**0.35**	**0.001**	0.13	0.23
Hematocrit (%)	**0.33**	**0.002**	**0.35**	**0.01**	0.14	0.18
MPV (fL)	0.21	0.06	0.10	0.36	0.03	0.76
WBC (/mm^3)	**0.36**	**0.001**	**0.29**	**0.007**	**0.26**	**0.01**

Pearson Correlation test; PT: prothrombin time, aPTT: activated partial thromboplastin time, INR: international normalized ratio, MPV: mean platelet volume, WBC: white blood cell, HDL-C: high-density lipoprotein cholesterol

While a positive correlation was found between FSH level and Protein C and Protein S levels in the PCOS group (r=0.41, p=0.008; r=0.31, p=0.04), No correlation was found between PT, PTT, INR, D-dimer, fibrinogen, AT III, Hgb, Hct, MPV and WBC levels. While a positive correlation was found between total testosterone level and fibrinogen levels in the PCOS group (r=0.32 p=0.04), No correlation was found between PT, PTT, INR, D-dimer, protein C, protein S, AT III, Hgb, Hct, MPV and WBC levels. While a positive correlation was found between DHEAS level and protein S levels in the PCOS group (r=0.31, p=0.04), No correlation was found between PT, PTT, INR, D-dimer, protein C, AT III, Hgb, Hct, MPV and WBC levels. No correlation was found between LH and androstenedione levels and hematological parameters in the PCOS group (Table 4).

Table 4. Correlation analysis between hormone profile and hematological parameters

Parameters	FSH		LH		TT		DHEAS		Androstenedione	
	r	p*	r	p*	r	p*	r	p*	r	p*
PT (sn)	0.98	0.54	-0.02	0.87	-0.20	0.22	0.01	0.90	-0.05	0.73
PTT (sn)	0.26	0.87	0.07	0.96	0.09	0.54	-0.25	0.11	0.20	0.20
INR	0.16	0.31	0.05	0.75	-0.12	0.46	-0.05	0.76	0.01	0.94
D-Dimer (mg/L)	-0.10	0.52	-0.16	0.30	-0.12	0.43	-0.16	0.32	-0.23	0.13
Fibrinogen (mg/dl)	0.13	0.42	0.19	0.22	**0.32**	**0.04**	-0.02	0.85	-0.03	0.83
Protein-C (%)	**0.41**	**0.008**	0.11	0.49	0.02	0.90	0.25	0.11	-0.02	0.85
Protein-S (%)	**0.31**	**0.04**	0.28	0.07	0.09	0.56	**0.31**	**0.04**	-0.03	0.85
Antitrombin3 (%)	-0.08	0.60	-0.04	0.80	0.01	0.93	-0.13	0.39	-0.05	0.74
Hemoglobin (gr/dl)	-0.04	0.78	-0.08	0.62	-0.01	0.94	-0.08	0.61	-0.01	0.91
Hematocrit (%)	0.02	0.89	-0.11	0.47	0.08	0.96	-0.08	0.59	-0.05	0.75
MPV (fL)	-0.01	0.92	0.09	0.54	0.11	0.47	-0.27	0.08	0.15	0.35
WBC (/mm^3)	0.22	0.89	0.01	0.92	-0.13	0.42	-0.04	0.78	-0.17	0.27

Pearson Correlation test, PCOS: polycystic over syndrome, sd: standard deviation, FSH: follicular stimulating hormone, LH: luteinizing hormone, DHEAS: dehydroepiandrostenedione sulfate, PT: prothrombin time, aPTT: activated partial thromboplastin time, INR: international normalized ratio, MPV: mean platelet volume, WBC: white blood cell

DISCUSSION

The study found that patients with PCOS had significantly higher insulin, HOMA-IR levels, and lower HDL levels compared to the control group. This supports the common metabolic disorder of dyslipidemia, which is characterized by high triglyceride, low HDL, and high LDL levels (13,14). We also found that the patients with PCOS had a significantly higher Hct value than the control group, but no significant difference was found in other hematological parameters (Hgb, MPV, WBC, D-dimer, fibrinogen, PT, APTT, protein C, protein S, ATIII). Studies by Alhabardi et al. and Ucakturk et al. also found no significant difference (15,16). PCOS patients had higher Hgb levels had a positive correlation with testosterone levels, attributed to testosterone's erythropoiesis stimulating effect (17). Increased platelet count and higher BMI values may be linked to diabetes, insulin resistance, and cardiovascular disease (18).

Many studies show higher D-dimer levels in PCOS patients compared to control groups, with no differences in fibrinogen levels. Local coagulation depletes fibrinogen, leading to increased D-dimer levels. Manneres Holm et al. found no difference in D-dimer levels between PCOS and control groups, but fibrinogen levels were higher in the PCOS group (19-21). Karakurt et al.'s study found higher plasma TAFI, values in non-obese women with PCOS, but no significant differences in D-dimer and fibrinogen values (22). Kelly et al.'s study found that obese PCOS patients had higher levels of t-PA, while D-dimer and fibrinogen levels did not differ (23). Our study found no significant difference in D-dimer and fibrinogen levels between groups.

Research indicates higher MPV levels in PCOS patients, with a positive correlation between MPV, serum androgen levels, and insulin resistance. Luque-Ramírez et al.'s study found no significant difference in MPV levels between groups, a finding similar to our own research (24-28). High MPV and WBC counts increase coagulation, disrupt fibrin networks, and increase D-dimer levels, potentially contributing to cardiovascular risk in patients with PCOS (27).

We found no significant difference in PT and a PTT levels between PCOS patients and controls in our study, consistent with previous research (9,22,28). Sun et al. developed a model to predict PCOS risk based on PCOS-related coagulation parameters. Significant differences in PT values were found between groups, indicating the potential of anti-clotting therapies to reduce adverse outcomes (3).

We found no significant difference in Protein C, Protein S, and ATIII values between PCOS and control groups. Schancez et al.'s study found higher Protein S levels in PCOS patients, but no difference in Protein C or Antithrombin III levels. The cardiovascular risks increased in women with PCOS, but the role of the hemostatic system and coagulation remains unclear (29). Atiomo et al. found no significant difference in APC resistance in PCOS patients, and no abnormalities in Protein C, Protein S, and AT III levels in those with a thrombosis family history (30). Moini et al. found higher Protein C deficiency prevalence in non-obese PCOS patients, and thrombophilic disorders were more common in women with PCOS (31).

We found a positive correlation between insulin and HOMA-IR values and Hgb, Hct, and WBC levels, and a positive correlation between HDL value and WBC. Research indicates a positive correlation between Hbg and Hct level and insulin resistance, suggesting high Hct levels as a risk factor for atheromatous vascular disease (32,33). High WBC levels in women with PCOS, positively predicting insulin resistance, and a positive correlation with BMI, insulin, and HOMA-IR values (34-36). Obesity's metabolic consequences on hypercoagulable state of PCOS were studied, higher levels of plasminogen activator inhibitor-1, fibrinogen, fibrinogen gamma chain, fibronectin, von Willebrand factor, D-dimer, P-selectin plasma kallikrein, found in PCOS patients. Hyperinsulinemia and high PAI-1 levels in PCOS patients are linked to low fibrinolytic activity, increased cardiovascular disease, and a significant association between PAI-1, fibrinogen levels, and insulin resistance.9However, two anticoagulant proteins, vitamin K-dependent protein-S and heparincofactor-II were elevated and prothrombin decreased. As a result PCOS is not correlated with coagulation proteins, but hypercoagulated state is associated with obesity, BMI, inflammation, and insulin resistance, not specific to the disease (37).

We found a significant positive correlation between FSH and Protein C and Protein S; total testosterone and fibrinogen A; also DHEAS and Protein S levels. In PCOS patients, LH levels increase and FSH decreases, leading to an increase in protein C/S, a protective factor against thrombosis. Studies show a positive correlation between androgen levels and fibrinogen levels, as found in our study (19).

CONCLUSION

As a result, adolescents with PCOS had significantly higher insulin, HOMA-IR levels, and lower HDL levels while there was no significant difference in the hematologic and coagulation parameters between PCOS and healthy controls. Hypercoagulated state in PCOS is associated with obesity, BMI, inflammation, and insulin resistance, not specific to the disease. More studies are planned to understand hormonal and metabolic parameters, coagulation, and fibrinolytic system in adolescent PCOS patients to prevent future complications.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
The study protocol was approved by the Bursa Yüksek İhtisas Training and Research Hospital Clinical Research Ethics Committee (2011-KAEK-25 2020/03–15) in accordance with the tenets of the declaration of Helsinki.

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