

Serum D-dimer level in women with polycystic ovary syndrome

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Abstract

Background: Women with polycystic ovary syndrome (PCOS) have hyperandrogenemia and insulin resistance, which predispose them to prothrombotic conditions. D-dimer is a global marker of hemostatic dysfunction that has a contentious relationship with PCOS.

Objective: To assess the association of D-dimer with PCOS and its manifestations.

Methods: This case-control study enrolled 44 women with PCOS based on the International Evidence-based Guideline, 2018, and an equal number of matched healthy controls by convenient sampling. After obtaining informed consent, participants' clinical data was taken, and fasting blood was drawn to measure glucose, lipid profile, hormones, and D-dimer. D-dimer was analyzed by latex immunofluorescence assay.

Results: The D-dimer levels (mg/L) and status were statistically similar between the study groups [PCOS vs. control: 0.11 (0.10-0.17) vs. 0.13 (0.10-0.22), median (IQR), $p = 0.673$]. D-dimer levels did not vary according to the different characteristics of women with PCOS ($p > 0.05$). D-dimer levels had no significant correlations with various clinical and biochemical characteristics among women with PCOS ($p > 0.05$).

Conclusion: This study found that D-dimer has no significant association with PCOS or its manifestations.

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Keywords: Polycystic ovary syndrome, D-dimer, Prothrombotic condition

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Introduction

Polycystic ovary syndrome (PCOS) is a common chronic condition in women with heterogeneous presentations.¹ During their reproductive years, affected women typically report cutaneous and reproductive issues; later in life, they may experience cardiovascular morbidities.² Atherosclerosis and inflammation-induced cardiovascular morbidities are exacerbated by changes in sex-steroid levels, increased insulin resistance, metabolic syndrome, and hemostatic abnormalities in women with PCOS.³ Abnormal platelet activation, endothelial dysfunction, hypercoagulability, and poor fibrinolysis are among the hemostatic abnormalities. Every one of these processes causes a prothrombotic

condition in PCOS.⁴ Moreover, one of the common treatments for PCOS, combined oral contraceptives (COCs), increases the risk of venous thromboembolism.⁵ Women with PCOS are also more likely to have a family history of venous thrombosis.⁶ Furthermore, spontaneous abortion is a possible outcome of the prothrombotic condition.⁷ Therefore, for therapeutic management and cardiovascular disease prevention, the hemostatic assessment in women with PCOS is crucial. The clotting cascade includes both coagulation and fibrinolysis, which result in blood clot production and removal from the system via two distinct paths known as the intrinsic and extrinsic pathways. The intrinsic process begins with the activation of blood clotting

factors XI and XII, whereas the extrinsic pathway begins with the production of tissue factor (TF), which leads to the activation of Factor X. These two processes eventually lead to the development of fibrin (clot), which is degraded by plasmin into D-dimer.^{8,9} Its measurement evaluates the fibrinolytic and coagulation systems comprehensively. Conflicting findings from earlier research linked D-dimer to PCOS and its symptoms. Since our race predominates metabolic phenotypes, evaluating the connection would be pertinent.¹⁰ Our study's goals were to evaluate the relationship between PCOS and D-dimer in reproductive-aged women.

Methods

This case-control study was done in the Department of Endocrinology, Bangabandhu Sheikh Mujib Medical University (BSMMU) between September 2020 and August 2022. The Institutional Review Board of BSMMU (R/N no: 3582; BSMMU/2021/7642, date: 24/08/2021) provided the ethical clearance for the study. Informed consent was taken from each participant.

Considering the following formula [$n = (Z_{\alpha} + Z_{\beta})^2 \times (\sigma_1^2 + \sigma_2^2) \div (\mu_1 - \mu_2)^2$], using the mean and SD (PCOS: 280.6±69.4, control: 227.6±73.9, ng/mL) from a previous study, and considering 95% confidence interval and 90% power, the sample size was 38.¹¹ We enrolled 44 women aged 18-35 years with PCOS and an equal number of age-matched healthy controls. We diagnosed PCOS

according to the International Evidence-based Guideline, 2018.¹² Healthy controls were those who had regular cycles, no hyperandrogenism symptoms, and normal ovarian morphology. Everyone who had comparable endocrinopathies, severe and uncontrolled systemic illnesses, a history of COVID-19 within the last four months, had used aspirin, COCs, antiandrogens, insulin sensitizers, or an anticoagulant within the previous six months, or who was pregnant or breastfeeding was excluded. After taking relevant clinical information from PCOS women, fasting blood was drawn to measure glucose, insulin, and D-dimer. Glucose was measured by glucose oxidase, insulin by chemiluminescence immunoassay, D-dimer by latex immunofluorescence assay by GeteIn 1100 immunofluorescence quantitative analyzer, GeteIn Biotech, Inc., China. The minimum detectable level was 0.1 mg/L with an inter- and intra-assay coefficient of variation of below 10%. Insulin resistance was calculated from homeostatic model assessment (HOMA) and a cut-off of 2.6 was set.¹³ A D-dimer level below 0.5 mg/L was considered normal.¹⁴

Version 25.0 of SPSS software was used to analyze the data. Qualitative factors were expressed in frequency (%), whereas quantitative data were expressed in mean ± SD or median (IQR) depending on their distributions. Fisher's exact test was used to analyze the qualitative variables and the Student's t-test or Mann-Whitney U test was used to analyze the associations between

Table-I: Characteristics of the study participants (n= 88)

Variables	PCOS, n= 44	Control, n= 44	p
Age, years	25.0 (20.3-27.0)	26.5 (22.3-30.0)	0.070†
BMI, kg/m ²	28.4±6.4	23.5±4.8	<0.001*
Systolic BP, mm-Hg	110.0 (100.0-120.0)	110.0 (100.0-110.0)	0.020†
Diastolic BP, mm-Hg	70.0 (70.0-80.0)	70.0 (62.5-70.0)	0.030†
Waist circumference, cm	88.5 (82.0-99.3)	78.0 (71.0-88.8)	<0.001†
Modified Ferriman-Gallwey score	11.0 (9.0-14.8)	1.0 (0.0-2.0)	<0.001†
Free androgen index, %	9.8 (6.2-17.5)	1.1 (0.7-1.8)	<0.001†
Fasting P. glucose, mmol/L	4.9±0.4	4.9±0.6	0.812*
2H-OGTT glucose, mmol/L	6.5±1.5	6.0±1.3	0.109*
Total cholesterol, mg/dL	171.5 (146.8-192.5)	167.5 (143.5-185.8)	0.649†
HDL-cholesterol, mg/dL	39.0 (35.0-47.8)	44.0 (38.3-50.0)	0.064†
LDL-cholesterol, mg/dL	106.2±26.9	103.2±23.0	0.575*
Triglyceride, mg/dL	101.0 (82.3-158.3)	85.5 (66.3-141.5)	0.083†
HOMA-IR	2.3 (1.4-3.6)	1.5 (1.0-2.3)	0.006†
D-dimer, mg/L	0.11 (0.10-0.17)	0.13 (0.10-0.22)	0.673†
Elevated D-dimer ≥0.5 mg/L	5 (11.6%)	3 (6.8%)	0.484‡

Data were expressed in mean±SD, median (IQR), or frequency (%) as appropriate

*Independent samples t-test, †Mann-Whitney U test, or ‡Fisher's exact test was done as appropriate

Table-II: D-dimer levels with different characteristics of women with PCOS (n=44)

Variables	Subgroups	No.	D-dimer levels, mg/L	p
Body mass index	Lean (<23 kg/m ²)	11	0.10 (0.10-0.11)	0.301
	Overweight/obese (≥23 kg/m ²)	33	0.11 (0.10-0.19)	
Biochemical hyperandrogenism	Absent (FAI <5%)	8	0.11 (0.10-0.20)	0.915
	Present (≥5%)	36	0.11 (0.10-0.17)	
Glycemic status	Normal glucose tolerance	32	0.10 (0.10-0.19)	0.968
	Abnormal glucose tolerance	12	0.11 (0.10-0.15)	
Insulin resistance	Absent (HOMA-IR <2.6)	26	0.10 (0.10-0.16)	0.366
	Present (≥2.6)	18	0.11 (0.10-0.22)	
Metabolic syndrome	Absent (<3/5 criteria)	34	0.11 (0.10-0.15)	0.505
	Present (≥3/5)	10	0.12 (0.10-0.63)	
LH/FSH ratio	Normal (≤2)	25	0.11 (0.10-0.18)	0.914
	Altered (>2)	19	0.10 (0.10-0.17)	
Polycystic ovarian morphology	Absent	13	0.10 (0.10-0.32)	0.744
	Present	31	0.11 (0.10-0.17)	

Mann-Whitney U test was done

various quantitative variables and PCOS or its symptoms. The Spearman's correlation test was used to see whether D-dimer and certain PCOS characteristics were correlated. Any two-tailed p-value below 0.05 was considered statistically significant.

Results

The characteristics of the study participants showed that women with PCOS had poorer metabolic profiles (higher BMI, systolic & diastolic blood pressure, waist circumference, and HOMA-IR) than healthy control. The D-dimer levels and status were statistically similar between the study groups (Table-I). D-dimer levels did not vary according to the different characteristics of women with PCOS (Table-II). D-dimer levels had no significant correlations with different clinical and biochemical characteristics among women with PCOS (Table-III).

Discussion

Women with PCOS possess several metabolic risk factors and hyperandrogenism that predispose them to a prothrombotic state. Measuring D-dimer levels may provide a clue about the patient's risk of thrombosis especially while initiating COCs.¹⁵ In this context, we measure the D-dimer levels to see its association with PCOS and its characteristics. However, we found no association of D-dimer with PCOS and its different characteristics.

We found similar levels of D-dimer between PCOS and healthy control. The findings regarding the connection between PCOS and D-dimer levels are contradictory.

Table-III: Correlation between D-dimer and different characteristics among women with PCOS (n=44)

Variables	r _s	p
Age, years	0.17	0.268
BMI, kg/m ²	0.16	0.315
Waist circumference, cm	0.18	0.256
Systolic BP, mm-Hg	0.21	0.178
Diastolic BP, mm-Hg	0.15	0.326
Modified Ferriman-Gallwey score	-0.28	0.062
Free androgen index, %	-0.13	0.417
Fasting P. glucose, mmol/L	0.14	0.360
2H-OGTT glucose, mmol/L	0.03	0.833
Total cholesterol, mg/dL	0.04	0.815
HDL-cholesterol, mg/dL	0.001	0.995
LDL-cholesterol, mg/dL	0.01	0.928
Triglyceride, mg/dL	-0.02	0.879
LH/FSH ratio	-0.06	0.705
HOMA-IR	0.15	0.321

Spearman's correlation test was done

Several investigations revealed a similar conclusion.¹⁶⁻¹⁸ Others, however, found that women with PCOS had higher levels of D-dimer than a healthy control group.^{11,19,20} Higher D-dimer levels suggest increased subclinical fibrin synthesis rather than a breakdown in the setting of decreased global fibrinolytic activity.²¹ While some researchers discovered no association at all or an association that varied depending on age and BMI, others discovered an independent positive association between D-dimer and PCOS.^{22,23} The prevalence of elevated D-dimer status was higher in our study than in the control group, although the differences were not statistically significant. We could not find any research

that contrasts the frequency of high D-dimer status between PCOS patients and healthy controls. The absence of thrombotic characteristics in individuals with elevated D-dimer levels could potentially be attributed to a low grade of chronic inflammation.²⁴ However, we did not measure any markers of inflammation in this indexed study.

We did not find any association or correlation between D-dimer levels and several features of PCOS. The association between D-dimer levels and different characteristics of PCOS is not evaluated adequately in the literature. Kebapcillar et al. (2009) found a positive correlation between D-dimer levels with HOMA-IR and free testosterone levels.¹⁹ However, the association remained significant only with free testosterone in a linear regression model. Similarly, Moin et al., (2021) found an insignificant association of D-dimer levels with BMI and HOMA-IR.²⁵

The cross-sectional design and single-center tertiary care sample collecting site of this study are its limitations. Besides, we could not measure other markers of coagulation and fibrinolytic pathways as well as the markers of inflammation.

Conclusion

In summary, there is no discernible association between D-dimer and PCOS or its many manifestations. To determine the precise disruptions in the hemostatic system in PCOS-affected women, prospective studies may be recommended to evaluate additional hemostatic parameters and their correlation with thrombotic status.

Conflict of interest

The authors have no conflicts of interest to disclose.

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Disclosure

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Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author and are available from the corresponding author on reasonable request.

Ethical Approval and Consent to Participate

This study was approved by the Institutional Review Board (IRB) of BSMMU, Reg: No: 3582; BSMMU/2021/764. Informed written consent was obtained from each of the participants included in the study.

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