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Original Article

Investigation of plasminogen activator inhibitor-1 (PAI-1) levels in patients diagnosed with polycystic ovary syndrome

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ABSTRACT

Objective: The aim of this study was to investigate the plasma levels of plasminogen activator inhibitor -1 (PAI-1) known as a potent inhibitor of fibrinolysis in women with polycystic ovary syndrome (PCOS) and compare with healthy controls.

Material and methods: Forty women with PCOS diagnosed using 2003 revised Rotterdam criteria and 40 healthy women who attended to Adnan Menderes University Department of Obstetrics and Gynecology between July-October 2013 were recruited to this prospective study. We noted all participant's demographic features, calculated body mass index (BMI), waist hip ratio (WHR), and measured blood pressures. We performed modified Ferriman-Gallwey Score (mFGS) and calculated Luteinizing hormone (LH)/Follicle stimulating hormone (FSH) ratio and homeostatic model assessment insulin resistance (HOMA-IR) of participants. PAI-1 levels were measured by using the Human PAI-1 Elisa test. We used the student T test and Mann-Whitney U test as statistical methods. A p-value less than 0.05 was considered statistically significant.

Results: We found PAI-1 levels, fasting insulin levels, HOMA-IR index, BMI significantly higher in the PCOS group compared with the control group. Mean age of the participants was found lower in the PCOS group. Between the groups we found no statistically significant differences in terms of the LH/FSH ratio, fasting glucose, dehydroepiandrosterone and testosterone levels.

Conclusion: PAI-1 levels can be considered as a biochemical marker for risk assessment in cardiovascular disease in polycystic ovary syndrome.

Keywords: coagulation; plasminogen activator inhibitor 1; polycystic ovary syndrome

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Introduction

Polycystic ovary syndrome (PCOS) is a common endocrinological disease between women in the reproductive age, prevalence of up to 10%. The diagnostic criteria include polycystic ovarian morphology, hyperandrogenism and/or hyperandrogenemia and oligo-ovulation [1]. PCOS can be recognized as well as metabolic disease due to the increased prevalence of type 2 DM, cardiovascular disease and hypertension in PCOS patients [2]. Some coagulation markers have been found to be elevated in PCOS versus to controls and the coagulation parameters including prothrombin time, thrombin time and fibrin degradation products may be predictive of PCOS [3].

Recent studies in women with PCOS reported that plasminogen activator inhibitor-1 (PAI-1) which is one of the potent inhibitor of fibrinolysis are increased in level in both normal weight and overweight/obese women with PCOS compared with controls with matched body mass index (BMI) [4, 5, 6]. Serum PAI-1 activity is related to the BMI and homeostasis model assessment (HOMA) score which indices insulin sensitivity [7, 8]. So that, PAI-1 was found to be associated with insulin resistance, abdominal obesity, metabolic syndrome and type 2 diabetes mellitus [4]. PAI-1 levels have been shown to decrease after treatment with metformin and sibutramine in normal weight and overweight women with PCOS [5, 9]. Oligo-ovulation could not be understood sufficiently yet [10].

Some studies show that urokinase plasminogen activator plays an essential role in the early growing follicles during cell proliferation and migration, and in the early corpus luteum formation related to extracellular matrix degradation and angiogenesis [11]. PAI-1 is localized in the granulosa and theca cells, it may play a role in follicular ovulation [12]. PAI-1 is also thought as a predominant independent risk factor for miscarriages in PCOS [13]. High plasma PAI-1 levels are found to be associated with an increased risk for both type 2 diabetes mellitus and cardiovascular diseases [14-16]. In some populations as well as European, Turkish, and Asian people PAI-1 4G/5G polymorphism is associated with susceptibility to PCOS [17, 18]. PAI-1 has two fractions as a soluble and cellular component. 40% activity of PAI-1 is depend on cellular component. It can be possible to measuring activity or antigen level of PAI-1 [19]. In the current study we aimed to investigate PAI-1 antigen levels in PCOS and healthy control groups.

Material and methods

The present study was conducted as a prospective cohort study. According to revised 2003 Rotterdam criteria [20], forty PCOS patients who were admitted to Adnan Menderes University Department of obstetrics and gynecology between June and October 2013 were included in the PCOS group. Those with a known disease other than PCOS and those

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using drugs (oral contraceptive, anti-androgen, drugs for infertility etc.) of the kind that would change hormone assays in the last six months were excluded. Forty healthy volunteers with regular menstrual cycles, without clinical or biochemically hyperandrogenemia were included in the control study group. All participants were at reproductive age (18-45 year) span.

Modified Ferriman-Gallwey score was used to determine the hirsutism level of patients. Scores 8 and above were considered hirsute. Ultrasonographic polycystic ovary appearance was defined as having 12 or more 2-9 mm diameter follicles in an ovary and/or ovarian volume over 10 cm3 [20].

All participant's venous blood samples were taken in the early follicular phase of the menstrual period in the study. Serum PAI-1 antigen levels of the participants were measured using the Human PAI-1 Platinum (Ebioscience, San Diego, USA) ELISA kit. Ethics committee approval for the current study was received and informed consent was taken from all participants.

Statistical analysis

SPSS (Statistical Package for the Social Science, version 14.0) program was used for statistical analysis. Data were indicated mean ± standard deviation (± SD). We used the Student T test and Mann-Whitney U test as statistical methods. A p-value less than 0.05 was considered statistically significant.

Results

Demographic, anthropometric measurements and biochemical properties of PCOS and control groups are shown in Tables 1 and 2. The mean age of the PCOS and control groups were 22.8 ± 4.42 and 26 ± 5.87, respectively. PCOS group age was found to be smaller than the control group. This difference was statistically significant (p = 0.006). BMI was found to be 24.35 ± 5.68 in the PCOS group and 21.98 ± 3.27 in the control group. This difference was statistically significant (p=0.024). WHR was found 0.79 ± 0.64 in the PCOS group and 0.75 ± 0.62 in the control group and this difference was statistically significant (p=0.007). mFGS was found to be higher in PCOS group statistically (p<0.001).

Table 1. Demographic and anthropometric values of the PCOS and the control group

Parameters	PCOS group (n: 40) mean ± std	Control group (n: 40) mean ± std	P value
Age	22.8 ± 4.42	26 ± 5.87	0.006
BMI (kg/m^2)	24.35 ± 5.68	21.98 ± 3.27	0.024
WHR	0.79 ± 0.64	0.75 ± 0.62	0.007
Systolic BP (mm Hg)	115.75±10.595	110.25±9.997	0.019
Diastolic BP (mm Hg)	74.0 ± 7.528	70.75 ± 8.664	0.017
mFGS	8.90 ± 2.15	0.55 ± 1.709	0.001

PCOS: Polycystic ovary syndrome, BMI: Body mass index, WHR: Waist hip ratio, mFGS: modified Ferriman-Gallwey Score, BP: Blood pressure.

The systolic blood pressure was 115.75 ± 10.595 mmHg in the PCOS group and 110.25 ± 9.997 mmHg in the control group. The difference was statistically significant. Diastolic blood pressure was 74.0 ± 7.528 mmHg in the PCOS group and 70.75 ± 8.664 mmHg in the control group. Diastolic blood pressure was significantly higher in the PCOS group than the control group. HOMA-IR indexes were 4.64 ± 6.74 and 2.23 ± 1.99 in the PCOS group and the control group, respectively.

We found HOMA-IR indexes significantly higher in the PCOS group compared to the control group (p=0.033).

Table 2. Comparison of biochemical values of the PCOS and the control group

Parameters	PCOS group (n: 40) Mean ± std	Control group (n: 40) Mean ± std	P
Fasting Glucose (mg/dl)	90.1 ± 11.38	89.5 ± 10.87	0.811
Fasting Insulin (mU/ml)	19.13 ± 24.88	10.07 ± 8.68	0.033
LH/FSH ratio	1.6135 ± 0.97	1.3580 ± 0.99	0.248
DHEAS (ug/dl)	291.4 ± 163.38	306.68 ± 100.9	0.616
Testosterone (ng/ml)	4.057 ± 9.73	3.46 ± 7.64	0.762
PAI-1 (pg/ml)	2405.26 ± 1056.44	1913.48 ± 795.373	0.021
HOMA-IR index	4.64 ± 6.74	2.23 ± 1.99	0.033

PCOS: Polycystic ovary syndrome, LH: Luteinizing hormone, FSH: Follicle stimulating hormone, DHEAS: Dehydroepiandrosteron sulfate, PAI-1: Plasminogen activator inhibitor 1 HOMA-IR: Homeostatic Model Assessment Insulin Resistance.

When the PAI-1 levels were examined, the level of PAI-1 was found as 2405.26 ± 1056.44 pg / ml in the group with PCOS and 1913.48 ± 795.373 pg / ml in the control group. PAI-1 levels were significantly higher in PCOS group (p=0.021).

When the fertility status of the groups were examined, no statistically significant difference was found between the PCOS group and the control group (p=0.387).

Discussion

PCOS is considered as an etiological factor for multiple systemic disorders such as type 2 diabetes mellitus, obesity, dyslipidemia, cardiovascular dysfunction, infertility and endometrial cancer [21]. The prevalence of obesity in women with PCOS is 41%. It is typically defined as a rate of 30–75% central type of obesity associated with PCOS, which is also a reason for elevated risk of cardiovascular disorders. Insulin resistance is also obvious in these types of patients with PCOS [22]. In our study, HOMA-IR levels that indices insulin resistance were high in the PCOS group such as PAI-I. PAI-1 is an important inhibitor of tissue-type and urokinase type plasminogen activators. Toulis et al. had reported the results of a meta-analysis of eight studies evaluating the relation between PAI-1 and PCOS, and concluded that PAI-1 is elevated in women with PCOS than in controls [23].

On the other hand, a multivariate analysis showed that inflammation, insulin resistance and BMI were associated with elevated level of PAI-1, there was no correlation of PCOS with any of the coagulation proteins [24]. So that, the researchers concluded that the hypercoagulable state in PCOS is not related to the syndrome, it can be fully explained by presence of BMI, inflammation and insulin resistance. Blair et al. investigated CRP, PAI-1, serum amyloid A, neopterin and myeloperoxidase from inflammatory markers which would produce oxidative stress.

PAI-1 levels were higher in obese PCOS group than in obese control group [25].

Abolhasani et al. investigated the PAI-1 levels between 160 patient whom coronary artery disease and 20 healthy control in non PCOS population, they found that PAI-1 level was significantly higher in study group than the control [26].

González et al published an article in 2013, 12 PCOS (6 obese - 6 normal weight subgroups) and 12 controls (6 obese - 6 normal weight subgroup) were included in their study. They found PAI-1 levels higher in obese patients with or without PCOS [27]. A study conducted by Elci et al. from Turkey was concluded that PAI-1 antigen levels were statistically higher in obese and non obese PCOS patients than the control group [28].

Moran et al. in their study on PAI-1 levels, they compared 14 patients with overweight PCOS and 14 patients with non-PCOS overweight control group. They found PAI-1 levels were significantly higher in the PCOS group than the control group [29].

Atiomo et al. found no statistically significant difference between the two groups in terms of PAI-1 activity compared to 41 patients with PCOS and 25 healthy controls [30]. However, in a recent study, Moin et al. found the increased levels of PAI-1 in PCOS patients, their study had large number of participant (PCOS group; 146 vs Control group: 97) [24].

In a study, high BMI and WHR were found related with elevated PAI-1 levels [31]. Also our study showed that the PCOS group had high WHR and BMI, but when we look at the mean of BMI for the both group, the participants were not obese in the mean±std (table 1).

Combined oral contraceptive (COC) pills are used widely by PCOS patients. Although in a study, using some COC pills significantly decreased levels of PAI-1 in PCOS patients after six months, some other COCs did not decrease levels of PAI-1 significantly after three months of use [32]. As a result, reduction of PAI-1 may improve endothelial function in PCOS patients is still not clear. The poor negative effect of COCs on insulin resistance does not impair the estrogen- induced beneficial effects on PAI-1 [33]. Therefore, importance of targeted treatment is emerging.

One of the limitations in our study was that the groups differed in terms of weight. Another limitation of the study is that PAI-1 activity was not measured.

In conclusion, we found elevated PAI-1 levels in women with PCOS in non-obese population. Further research should be conducted on this topic. More extensive studies should be performed to research whether PAI-1 has a potential to be a biochemical screening parameter and inhibition of this antigen may offer a therapeutic option in cardiovascular diseases and reproductive pathologies in women with PCOS.

Disclosure

Authors have no potential conflicts of interest to disclose.

References

[1] Goodarzi MO, Dumesic DA, Chazenbalk G, Azziz R. Polycystic ovary syndrome: Etiology, pathogenesis and diagnosis. Nat RevEndocrinol.2011 Apr;7(4):219–31.
[2] Salley, K. E. et al. Glucose intolerance in polycystic ovary syndrome—a position statement of the Androgen Excess Society. J. Clin. Endocrinol. Metab. 92(12), 4546–4556 (2007).
[3] Sun, Q. et al. Coagulation parameters predictive of polycystic ovary syndrome. Eur. J. Obstet. Gynecol. Reprod. Biol. 240, 36–40 (2019).
[4] Cesari M, Pahor M, Incalzi RA. Plasminogen activator inhibitor-1 (PAI-1): A key factor linking fibrinolysis and age-related subclinical and clinical conditions. Cardiovasc. Ther.2010 Oct;28(5):e72-91.
[5] Koiou E, Tziomalos K, Dinas K, Katsikis I, Kandaraki EA, Tsourdi E, et al. Plasma plasminogen activator inhibitor-1 levels in the different phenotypes of the polycystic ovary syndrome. Endocr J. 2012;59(1):21-9.
[6] Koiou E, Tziomalos K, Katsikis I, Delkos D, Tsourdi EA, Panidis D. Disparate effects of pharmacotherapy on plasma plasminogen activator inhibitor-1 levels in women with the polycystic ovary syndrome. Hormones (Athens). 2013 Oct-Dec;12(4):559-66.
[7] Orio FJr, Palomba S, Cascella T, Tauchmanova L, Nardo LG, di Biase S, et al. Is plasminogen activator inhibitor-1 a cardiovascular risk factor in young women with polycystic ovary syndrome? Reprod Biomed Online. 2005 Feb;10(2):289.
[8] Tarkun I, Cantürk Z, Arslan BC, Türemen E, Tarkun P. The plasminogen activator system in young and lean women with polycystic ovary syndrome.Endocr J. 2004 Oct;51(5):467-72.
[9] Palomba S, Orio F. Jr, Falbo A, Russo T, Tolino A, Zullo F. Plasminogen activator inhibitor 1 and miscarriage after metformin treatment and laparoscopic ovarian drilling in patients with polycystic ovary syndrome. FertilSteril. 2005 Sep;84(3):761-5.
[10] Fauser BC, Tarlatzis BC, Rebar RW, Legro RS, Balen AH, Lobo R, et al. Consensus on women's health aspects of polycystic ovary syndrome (PCOS): The Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group. FertilSteril. 2012 Jan;97(1):28-38.e25.
[11] Liu YX. Plasminogen activator/plasminogen activator inhibitors in ovarian physiology. Front Biosci. 2004 Sep 1;9:3356-73
[12] Atiomo WU, Hilton D, Fox R, Lee D, Shaw S, Friend J, et al. Immunohistochemical detection of plasminogen activator inhibitor-1 in polycystic ovaries. GynecolEndocrinol. 2000 Jun;14(3):162-8
[13] Glueck CJ, Wang P, Fontaine RN, Sieve-Smith L, Tracy T, Moore SK. Plasminogen activator inhibitor activity: An independent risk factor for the high miscarriage rate during pregnancy in women with polycystic ovary syndrome. Metabolism. 1999 Dec;48(12):1589-95.
[14] Meigs JB, O'Donnell CJ, Tofler GH, Benjamin EJ, Fox CS, Lipinska I, et al. Hemostatic markers of endothelial dysfunction and risk of incident type 2 diabetes: The Framingham Offspring Study. Diabetes. 2006 Feb;55(2):530-7.
[15] Smith A, Patterson C, Yarnell J, Rumley A, Ben-Shlomo Y, Lowe G. Which hemostatic markers add to the predictive value of conventional risk factors for coronary heart disease and ischemic stroke? The Caerphilly Study. Circulation. 2005 Nov 15;112(20):3080-7.
[16] Yarmolinsky J, BordinBarbieri N, Weinmann T, Ziegelmann P.K, Duncan BB, Ines Schmidt M. Plasminogen activator inhibitor-1 and type 2 diabetes: A systematic review and meta-analysis of observational studies. Sci Rep. 2016 Jan 27;6:17714
[17] Sales MF, Soter MO,Candido AL, Fernandes AP, Oliveira FR, Ferreira AC, et al. Correlation between plasminogen activator inhibitor-1 (PAI-1) promoter 4G/5G polymorphism and metabolic/proinflammatory factors in polycystic ovary syndrome. Gynecol Endocrinol. 2013 Oct;29(10):936-9.
[18] Lee YH, Song, GG. Plasminogen activator inhibitor-1 4G/5G and the MTHFR 677C/T polymorphisms and susceptibility to polycystic ovary syndrome: A meta-analysis. Eur J Obstet Gynecol Reprod Biol. 2014 Apr;175:8-14.
[19] Morrow GB, Whyte CS, Mutch NJ. Functional plasminogen activator inhibitor 1 is retained on the activated platelet membrane following platelet activation. Haematologica. 2020 Dec 1;105(12):2824-2833
[20] Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome.FertilSteril. 2004 Jan;81(1):19-25.

[21] Cengiz H, Ekin M, Dagdeviren H, Kaya C, Kanawati A. Comparison of serum anti Mullerian hormone levels in normal weight and overweight–obese adolescent patients with polycystic ovary syndrome. Eur J Obstet Gynecol Reprod Biol. 2014 Sep;180:46-50.
[22] Stegenga ME, van der Crabben SN, Levi M,de Vos AF, Tanck MW, Sauerwein HP, et al. Hyperglycemia stimulates coagulation, whereas hyperinsulinemia impairs fibrinolysis in healthy humans. Diabetes. 2006 Jun;55(6):1807-12.
[23] Toulis KA, Goulis DG, Mintziori G,Mintziori G, Kintiraki E, Eukarpidis E, Mouratoglou SA, et al. Meta-analysis of cardiovascular disease risk markers in women with polycystic ovary syndrome. Hum Reprod Update. 2011 Nov-Dec;17(6):741-60.
[24] Moin ASM, Sathyapalan T, Diboun I, Elrayess MA, Butler AE, Atkin SL. Metabolic consequences of obesity on the hypercoagulable state of polycystic ovary syndrome. Sci Rep. 2021 Mar 5;11(1):5320
[25] Blair SA, Kyaw-Tun T, Young IS, Phelan NA, Gibney J, McEneny J. Oxidative stress and inflammation in lean and obese subjects with polycystic ovary syndrome.J Reprod Med. 2013 Mar-Apr;58(3-4):107-14.
[26] Abolhasani S, Shahbazloo SV, Saadati HM, Mahmoodi N, Khanbabaei N. Evaluation of Serum Levels of Inflammation, Fibrinolysis and Oxidative Stress Markers in Coronary Artery Disease Prediction: A Cross-Sectional Study. Arq Bras Cardiol. 2019 Aug 29;113(4):667-674.
[27] González F, Kirwan JP, Rote NS, Minium J. Elevated circulating levels of tissue factor in polycystic ovary syndrome. Clin Appl Thromb Hemost. 2013 Jan-Feb;19(1):66-72.
[28] Elci E, Kaya C, Cim N, Yildizhan R, Elci GG. Evaluation of cardiac risk marker levels in obese and non-obese patients with polycystic ovaries. Gynecol Endocrinol. 2017 Jan;33(1):43-47
[29] Moran LJ, Noakes M, Wittert GA, Clifton PM, Norman RJ. Weight loss and vascular inflammatory markers in overweight women with and without polycystic ovary syndrome.Reprod Biomed Online. 2012 Nov;25(5):500-3.
[30] Atiomo WU, Fox R, Condon JE, Shaw S, Friend J, Prentice AG, et al.Raised plasminogen activator inhibitor-1 (PAI-1) is not an independent risk factor in the polycystic ovary syndrome (PCOS).Clin Endocrinol (Oxf). 2000 Apr;52(4):487-92.
[31] Landin K, Stigendal L, Eriksson E, Krotkiewski M, Risberg B, Tengborn L, et al. Abdominal obesity is associated with an impaired fibrinolytic activity and elevated plasminogen activator inhibitor-1. Metabolism. 1990 Oct;39(10):1044-8.
[32] de Medeiros SF, de Medeiros MAS, Santos NS, Barbosa BB, Yamamoto MMW. Combined Oral Contraceptive Effects on Low-Grade Chronic Inflammatory Mediators in Women with Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis.Int J Inflam. 2018 Nov 25;2018:9591509.
[33] Teede HJ, Meyer C, Hutchison SK, Zoungas S, McGrath BP, Moran LJ. Endothelial function and insulin resistance in polycystic ovary syndrome: the efects of medical therapy.FertilSteril. 2010 Jan;93(1):184-91.