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Original Research Article

## Role of plasminogen activator inhibitor type 1 (PAI-1) in PCOS patient

Shikha Sahay<sup>1</sup>, Madhu Jain<sup>1\*</sup>, D. Dash<sup>2</sup>, Lavina Choubey<sup>1</sup>, Shuchi Jain<sup>1</sup>, T. B. Singh<sup>3</sup>

<sup>1</sup>Department of Obstetrics and Gynecology, <sup>2</sup>Department of Biochemistry, <sup>3</sup>Department of Community Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India

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**\*Correspondence:**

Dr. Madhu Jain,

E-mail: [drmadhujainbhu@gmail.com](mailto:drmadhujainbhu@gmail.com)

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### ABSTRACT

**Background:** There has been few studies done demonstrating elevated level of PAI-1 in women with Polycystic Ovarian Syndrome (PCOS). PAI-1 has been associated with insulin resistance, obesity, anovulatory infertility, increased risk of cardiovascular disease in PCOS patient. The objective of the study was to find out the plasma level of PAI-1 in PCOS and compare with healthy age matched control. To correlate PAI-1 with various demographic, anthropometric, biochemical and hormonal parameters in PCOS patient and specific relation of PAI-1 with the insulin resistance, obesity, hyperandrogenemia.

**Methods:** A prospective case control study was carried out in 50 patients having PCOS (fulfilling Rotterdam Criteria, 2003). 25 healthy age matched control were taken. Blood samples were taken for estimation of fasting glucose, fasting insulin, lipid profile, LH, FSH, Prolactin, Testosterone, insulin sensitive indices (HOMA-IR, glucose: insulin ratio). Plasma level of PAI-1 was estimated with Human ELISA invitrogen kit. The data were statistically analysed with SPSS 16.0 version (student T test, Pearson ranked correlation coefficient, linear regression analysis was applied) and PAI-1 was correlated with various parameters.

**Results:** Mean level of PAI-1 was significantly raised in PCOS patient (893.36±234.97) pg/mL than in control (259.68±97.75) pg/mL (p<0.001). PAI-1 significantly correlated with insulin resistance, obesity; that is; PAI-1 significantly correlated with BMI (r=0.557; p<0.001), waist: hip ratio (r=0.550; p<0.001), fasting glucose (r=0.429; p=0.002), fasting insulin (r=0.357; p=0.001), triglyceride (r=0.492; p=0.000), LDL (r=0.604; p=0.001), HOMA-IR (r=0.467; p=0.001). On regression analysis LDL, fasting insulin, HOMA-IR altogether explained 54.9% of total variability of PAI-1.

**Conclusions:** Plasma level of PAI-1 is elevated in PCOS patient and it is significantly correlated with insulin resistance and obesity.

**Keywords:** Insulin resistance, Obesity, PAI-1, PCOS

### INTRODUCTION

Till now, only few studies have been carried out to show association between PAI-1 and PCOS, so we picked PAI-1 in our study to establish its definite role in PCOS. PCOS is a complex metabolic, endocrine and reproductive disorder affecting around 5-10% of the female population in developed countries. Now a day the

prevalence of PCOS is rising in developing countries like India, where there is now rapid nutritional transitions due to westernized diets and lifestyle.

Plasminogen activator inhibitor-1(PAI-1), is inhibitor of tissue-type and urokinase –type plasminogen activators (tPA and uPA), which convert plasminogen to plasmin. PAI-1 is a member of serine protease inhibitor

superfamily, also known as Serpin E-1. PAI-1 is synthesized by many tissue and cell types, free PAI-1 is relatively inactive in its free form and readily converts into its latent form.

The plasminogen activator system through degrading fibrinolytic activities can be explained in the pathogenesis of polycystic ovary syndrome (PCOS). Increased plasminogen activator inhibitor-1 (PAI-1) or tissue plasminogen activator (tPA) activity promote thrombosis by inhibiting the production of fibrinolytic enzyme plasmin, which is significant risk factor for cardiovascular disease.

## METHODS

This study was prospective case control study, carried out in which 50 patients having polycystic ovarian syndrome (fulfilling Rotterdam Criteria, 2003) from outpatient Department of Obstetrics and Gynecology, Sir Sunderlal Hospital between 20013 and 2015 in collaboration with the Department of Biochemistry were included in the study and 25 healthy age matched volunteers were taken as controls. The study was approved by the Institute Ethical Committee and informed consent was taken by the study subjects having following inclusion and exclusion criteria:

### *Inclusion criteria*

Rotterdam Criteria (2003) was used to diagnose PCOS.

### *Exclusion criteria*

- Patient with symptoms of Cushing's syndrome, non-classical congenital adrenal hyperplasia, Hyperprolactinemia, primary hypothyroidism, acromegaly, premature ovarian failure, virilising adrenal or ovarian tumour, primary hypothalamic amenorrhea
- OCPs use within last 4 months and
- Adolescent patient not attended menarche yet or who had attained within 6 months.

For control group, regular menstrual cycle, absence of hirsutism, alopecia and acne, absence of polycystic ovary on sonography and normal hormonal parameters including TSH, testosterone, prolactin, LH, FSH, LH: FSH ratio were included in the study.

A detailed history of patients was taken. Examination was done to look for any features suggestive of acne, hirsutism, acanthosis nigerians, androgenic alopecia, thyroid swelling, galactorrhea with other gynaecological examination. BMI, Waist hip ratio was calculated.

Blood investigations were taken for both cases and controls: serum LH, FSH, Prolactin, TSH, Testosterone, fasting glucose, fasting insulin, cholesterol, triglyceride, HDL, LDL. ultrasound pelvis.

Quantitative determination of serum PAI-1 concentration was measured using HUMAN PAI-1 ELISA (Enzyme Linked Immunosorbent Assay) kit manufactured by Invitrogen.

### *Statistical analysis*

The analysis was done with the help of SPSS 16.0 version for windows. Numerical data were presented in the form of mean + standard deviation and quantitative data were shown in the form of number and percentage. Student-t-test was used to compare the significant difference in mean values between cases and control groups. Parametric One-way analysis of variance test was applied to find out the significant difference in mean values if groups were more than two. If this test showed the significant difference then posthoc test (Student newmanKuel test) was applied to find pairwise difference. Chi square test was used to test the significant association between the qualitative variables. Correlation were determined by Pearson ranked correlation coefficient. Linear correlation coefficient was calculated to see the amount and direction of relationship between quantitative variables. To estimate the value of dependent variable on the basis of known values of independent variable, if correlation was significant, linear regression analysis was used. P-value <0.05 considered as statistically significant.

## RESULTS

The demographic characteristics of each group are compared in Table 1. The mean PAI-1 level in PCOS was 893.36±234.97 pg / mL and in control group the means level was 259.68±97.75 pg/mL (p<0.001). The difference was significantly increased in PCOS group as compared to control.

Serum PAI-1 level at 370.1 pg/mL has 100% sensitivity and 92% specificity with confidence interval 0.9921 to 1.003, area under curve = 0.9976 (likelihood ratio =12.5). To correlate demographic parameters like age, parity, marital status, socioeconomic status, menstrual pattern, acne and hirsutism with PAI-1 there was significant positive correlation was found with age (r=0.003, p=0.003) and parity (r=0.046, p=0.046) in PCOS cases. The correlation of biochemical and hormonal parameters with PAI-1 in PCOS cases was depicted in Table 2 and Figure 1. Among cases, PAI-1 had significant positive correlation with BMI (p<0.001); Waist: Hip ratio (p <0.001); Fasting glucose (p=0.002); Fasting insulin (p=0.011); Triglyceride (p=0.000); HDL (p=0.005); LDL (p=0.001); HOMA -IR (p=0.001). Among cases, PAI-1 had significant negative correlation with glucose: insulin ratio (p=.003); HDL (p=0.005) that is PAI-1 level decreases with increase in these values. A regression analysis was applied keeping PAI-1 as dependent variable and all those positive predictive parameters (BMI; waist: hip ratio; fasting glucose; fasting insulin; HOMA IR; triglyceride; LDL) (Table 3).

**Table 1: Demographic, biochemical, hormonal parameters in study population (mean+SD).**

Parameters	Study Population		p-value
	PCOS (n=50)	Control (n=25)	
Age (yrs)	22.26±3.927	23.80±3.122	0.092
BMI (kg/m <sup>2</sup> )	23.74±3.91	20.01±2.32	<0.001
Waist: hip ratio	0.74±0.13	0.50±0.06	<0.001
Fasting glucose (mg/dL)	95.87±9.09	93.04±21.49	0.424
LDL (mg/dL)	87.06±14.182	60.96±14.117	<0.001
HDL (mg/dL)	42.92±8.538	52.60±5.074	<0.001
TRG (mg/dL)	181.48±31.701	152.96±18.288	<0.001
Chol (mg/dL)	153.94±19.81	150.28±16.05	0.426
LH (mIU/mL)	17.80±9.25	4.05±2.66	<0.001
FSH (mIU/mL)	5.48±2.25	5.74±2.90	0.663
LH: FSH ratio	3.27±1.06	0.73±0.34	<0.001
TSH (IU/mL)	2.94±1.88	2.80±1.02	0.727
PRL (ng/mL)	20.4088±24.71135	10.2879±7.43867	0.050
Testosterone (ng/dL)	28.99±30.93	14.19±12.05	0.024
Fasting insulin	7.9422±5.72596	1.7880±.65149	<0.001
HOMA IR	1.8831±1.29402	.4237±.24914	<0.001
Glucose insulin ratio	19.5072±15.29546	57.9260±20.93578	<0.001
PAI1 (pg/mL)	893.36±234.97	259.68±97.75	<0.001

**Table 2: Correlation PAI-1 versus all variables in cases.**

Parameters in cases	r (correlation coefficient)	P (predictive value)
BMI	0.557**	<0.001
Waist: hip ratio	0.550**	<0.001
LH	-0.156	0.280
FSH	-0.098	0.497
LH: FSH ratio	-0.211	0.141
PRL	0.032	0.824
TSH	-0.012	0.931
Testosterone	-0.010	0.947
FBS	0.429**	0.002
Fasting insulin	0.357*	0.011
Glucose: insulin ratio	-0.407**	0.003
Cholesterol	0.309*	0.029
TRG	0.492**	0.000
HDL	-0.392**	0.005
LDL	0.604**	<0.001
HOMA-IR	0.467**	0.001

Among these we found that LDL alone explained 36.5% of total variability of PAI-1.

When LDL combined with HOMA-IR: 43.5% and when fasting insulin also included: 54.9% of total variability of PAI-1 explained. If we take negative predictive parameters (HDL and glucose: insulin ratio) also then 60.5% of total variability of PAI-1 is explained.

**Table 3: Regression analysis.**

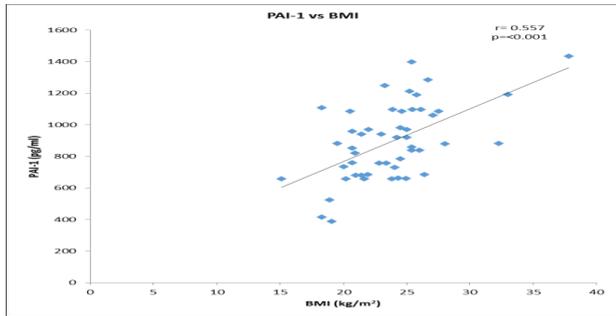
Independent variables in PCOS	Percent variation explained (r <sup>2</sup> x 100)	Regression coefficient (r)
LDL (mg/dL)	36.5%	0.604
HOMA-IR	7%	0.650
Fasting insulin (Iu/mL)	11.4%	0.741
LDL+HOMA-IR	43.5%	0.659
LDL+HOMA-IR + Fasting insulin	54.9%	0.741
HDL + Glucose/insulin ratio (negative predictive value)	60%	0.777

## DISCUSSION

In present study, we found that patients with PCOS had raised plasma PAI-1 levels as compared to controls. The mean level of PAI-1 in PCOS was (893.36±234.97 pg/mL) and in control (259.68±97.75pg/mL). The sensitivity and specificity of PAI-1 was calculated and it was found that the PAI-1 value at 370.1 pg/mL is having 100% sensitivity and 92% specificity.

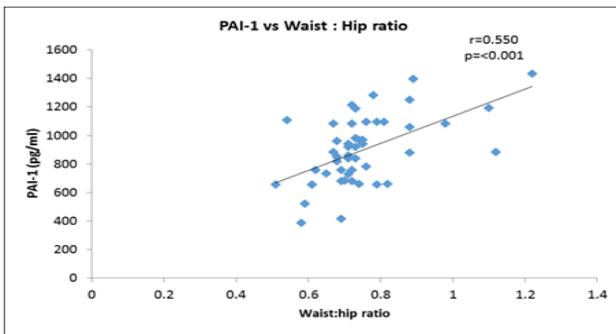
Atiomo WU, and Bates SA et al found that PAI-1 levels were significantly higher in PCOS groups than control: a higher PAI-1 activity (mean+SD, 19.7±2.12 arbitrary units (AU) per mL vs. 10.9±7.9 AU/mL).<sup>1</sup> Similarly Francesco, Stefano, Teresa et al found PAI-1 activity increased in PCOS than control having normal BMI

( $p < 0.05$ ); Tarkun, Canturk et al found raised PAI-1 activity in PCOS (12.8±3.12) U/mL and control (5.6±2.09) U/mL.<sup>2,3</sup>



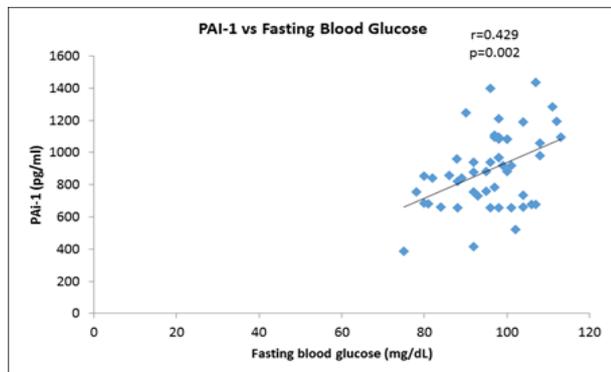
**Figure 1: PAI-1 versus BMI.**

The difference of PAI-1 level in our study from other is may be due to difference in dilution of sample during assay and the time of collection as PAI-1 level has circadian rhythm and its maximum activity is between 8:00 am to 10 a.m.

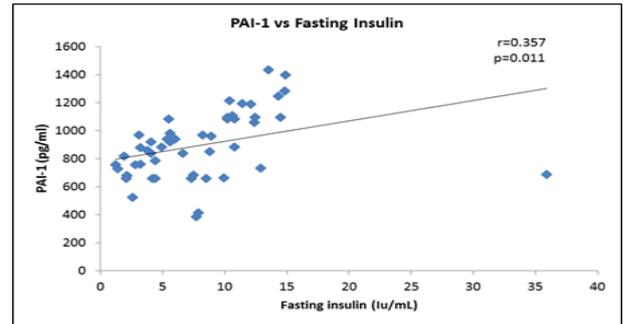


**Figure 2: PAI-1 versus Waist: Hip ratio.**

Plasminogen activator inhibitor 1 (PAI-1) is a member of the serine protease inhibitor (SERPIN) family, which act as a major regulator of the fibrinolytic system. It inhibits fibrinolytic activity of the tissue-type plasminogen activator (tPA), which generates active plasmin from plasminogen, that then eliminates the fibrin.<sup>4</sup>

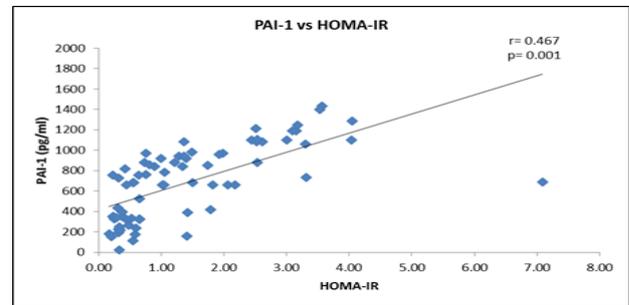


**Figure 3: PAI-1 versus fasting blood glucose.**



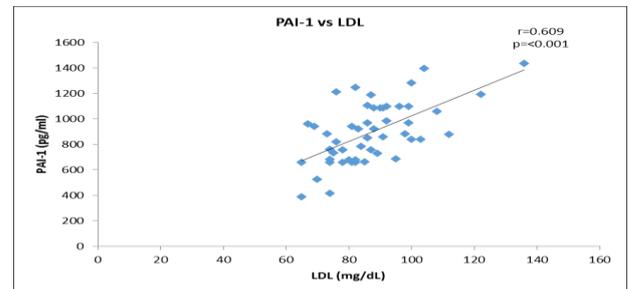
**Figure 4: PAI-1 versus fasting insulin.**

The PAI-1 plays an important role in development of PCOS. A complex dynamic interrelationship exists between factors such as insulin resistance, obesity, gonadotrophins, insulin like growth factors, the renin angiotensin system and the interleukins and PAI-1.<sup>5</sup>



**Figure 5: PAI-1 versus HOMA-IR.**

The raised level of PAI-1 explains the cause of ovarian dysfunction, ultimately leading to disturbed and endothelial, metabolic, and reproductive dysfunction.<sup>5</sup> It causes disordered folliculogenesis in PCOS as there is insulin-driven overproduction of PAI-1 with reduction in the amount of plasmin available for extracellular proteolysis.<sup>1,6</sup>

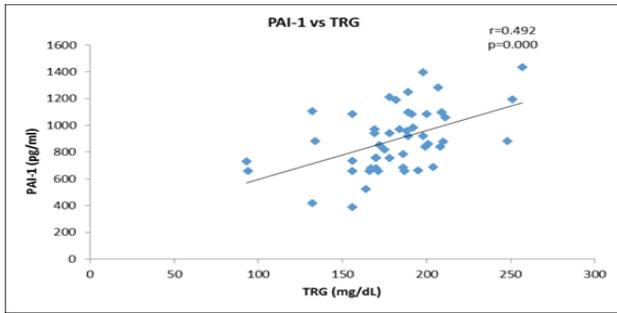


**Figure 6: PAI-1 versus LDL.**

The majority of PAI-1 is produced within theca (interstitium), whereas expression of plasminogen activators is specific to the granulosa cells.<sup>7</sup>

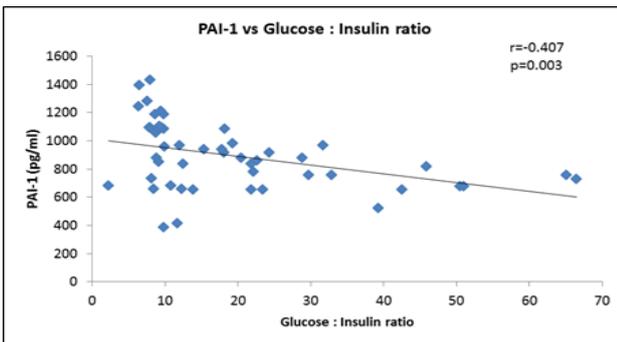
PAI-1 activity, may also play a key role in fibrinolytic activity in the early stages of placentation.<sup>8</sup> Antiphospholipid antibodies, known to be associated with

recurrent pregnancy loss, may exert some of their effect through increasing PAI-1.<sup>9</sup>



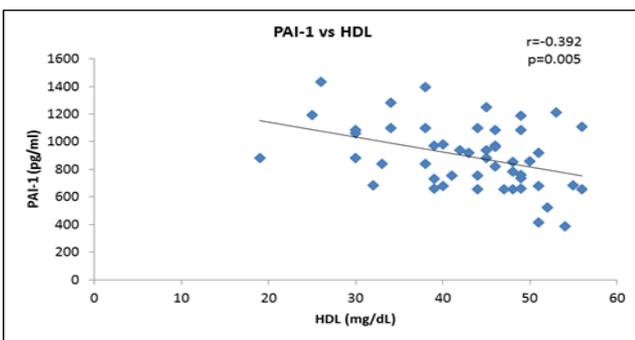
**Figure 7: PAI-1 versus TRG.**

High-PAI-1 levels are one mechanism that explain link between the finding of polycystic ovaries and recurrent miscarriage. The finding of high PAI- levels in many women with recurrent.<sup>10</sup> Hyperandrogenism is characteristic of PCOS which impairs follicular development and inhibits ovulation. This occurs due to imbalance in plasminogen.<sup>11</sup> This resulting in hypertrophied theca (interstitium) prompts a deleterious feedback loop, which then perpetuates testosterone production.



**Figure 8: PAI-1 versus glucose: insulin ratio.**

There is strong positive correlation between PAI-1 and insulin resistance in normal PCOS, obese PCOS and type 2 DM. This relation is independent of body mass and probably reflect insulin stimulated hepatic PAI-1 production.<sup>12</sup>



**Figure 9: PAI-1 versus HDL.**

It has been previously determined that major factor influencing PAI-1 concentration in women was insulin resistance.<sup>5,6</sup>

The mean BMI in present cases was (23.74±3.91) and in control was (20.01±2.32) kg/m<sup>2</sup>. BMI in cases was significantly increased (p<0.001). BMI significantly correlated with PAI-1 (r=0.557; p=0.001). The mean waist: hip ratio in cases was (0.74±0.13) and in control was (0.50±0.06). W: H ratio was significantly increased in cases (r= 0.550; p<0.001). In cases 7 were having W:H ratio > 0.85 (14%). In our study group, 26% of PCOS patients were overweight (BMI 25-29 kg/m<sup>2</sup>) while 6% were obese (BMI >30 kg/m<sup>2</sup>).

When PCOS patient was compared with control of same BMI group (BMI between 20 to 25), it was found that for same BMI, PAI-1 was however relatively higher in PCOS patient (840.11±166.87) than control (262.37±99.80) (p=0.001).

This finding is relatively consistent with the study of Tarkun I et al where cases (23.46 + 2.06) and control (22.9 + 2.7) have almost similar BMI but PAI-1 activity was found more in PCOS patient (p= 0.05).<sup>3</sup>

Similarly, in study of Francesco, Stefano, Palomba et al, normal weight PCOS (BMI= 23.0+0.3) compared with normal weight control (22.6+0.5) it was found that PAI-1 activity was elevated in PCOS even after adjustment of BMI (p<0.005).<sup>2</sup>

In present study, insulin resistance was assessed by fasting glucose; fasting insulin; glucose insulin ratio and HOMA IR (homeostasis model assessment for insulin resistance); lipid profile (LDL, HDL, cholesterol, triglyceride).

In current study, PAI-1 positively correlated with fasting glucose (r=0.429 p= 0.002). 32% PCOS patients in our study had raised fasting insulin levels (i.e. more than 9 IU/mL). When mean level of glucose: insulin ratio of cases (19.5072±15.29546) was compared with controls (57.926±20.935) a significant difference was found (p<0.001). Glucose: insulin ratio inversely correlated with PAI-1 (r= - 0.407, p= 0.003). In present study, fasting insulin positively correlated with PAI-1 (r=0.357; p= 0.011).

The fasting insulin in present cases was (7.9422±5.72596) IU/mL and in control (1.7880±0.65149) IU/mL and significantly correlated with PAI-1 (r=0.357; p=0.011). Thus, fasting insulin was raised in cases than in control (p<0.001). It was raised among those cases whose BMI was >25 kg/m<sup>2</sup> (p=0.002), this finding is again consistent with the study of Ilhan Tarkun et al, the fasting insulin in cases (9.3+3.4) was raised in comparison to control (6.08+2.09) (p <0.05) and moderately correlated with PAI-1 (r=0.315; p=0.021).<sup>3</sup> Similarly, we in this study found that serum triglyceride

(cases: 181.48±31.701 mg/dL control: 152.96±18.288 mg/dL) and LDL (cases: 87.06±14.182 mg/dL control: 60.96±14.117mg/dL) levels were increased and HDL was decreased (cases: 42.92±8.538 mg/dL control: 52.60±5.074mg/dL) in PCOS group as compared to controls (p value <0.001). There was no significant change in serum cholesterol.

PAI-1 significantly correlated with triglyceride (r=0.492 p=0.000); LDL (r=0.604, p<0.001; inversely correlated with HDL (r= -0.392, p= 0.005).

Based on measurements of fasting glucose and insulin levels, is the homeostatic model assessment (HOMA-IR). Resistance to insulin is diagnosed at HOMA-IR levels ≥3. In our study 22% of cases had HOMA IR value >3.0.<sup>13</sup> In this study, they have taken HOMA –IR cut off value 3.8 and 26% of cases had value more than 3.8.

In our study PAI-1 significantly correlated with HOMA-IR (r=0.467; p= 0.001).

A regression analysis was applied keeping PAI-1 as dependent variable and all those positive predictive parameters (BMI; Waist: hip ratio; fasting glucose; fasting insulin; HOMA IR; triglyceride; LDL) as independent variables and we found that LDL alone explained 36.5% of total variability of PAI-1. When LDL combined with HOMA IR: 43.5% of PAI-1 variability explained, and when fasting insulin also included: 54.9% of variability explained.

When negative predictive parameters also taken along with positive (glucose: insulin ratio and HDL) then 60.5% variability of raised PAI-1 level can be explained.

Whereas in study of Glueck, Sieve, Zhu et al, found following BMI -10.6%, (p<0.001); Insulin 13.4% (p<0.001); TRG 15.5% (p=0.0009) as independent variable affecting PAI-1.<sup>14-18</sup>

Hence raised PAI-1 in PCOS is affected by various parameters: obesity, insulin resistance, dyslipidemia contributes in raised level of PAI-1 in PCOS.

PAI-1 were more likely to have incident diabetes five years later and that PAI-1 may be considered as a predictive factor for the development of type 2 diabetes, independently of insulin resistance and other known risk factors for diabetes.<sup>17</sup> Previous studies showed that insulin increases PAI-1 synthesis and metformin inhibits insulin-mediated PAI-1 synthesis in vitro.<sup>18,19</sup> Recently, Ma et al noted prevention of obesity and insulin resistance in mice lacking PAI-1.<sup>20</sup>

Limitations of study: Sample size was small (n = 75, 50 PCOS patients and 25 controls) and less variation in parameters. We did not include other components of fibrinolytic activities that is plasminogen activators: tPA (tissue type plasminogen activator) and uPA (urokinase

type plasminogen activator). We did not observe intra ovarian activity of PAI-1. We did not perform genetic analysis of PAI-1 synthesis.

## CONCLUSION

The elevation of PAI-1 were directly correlated with insulin resistance in PCOS patient; so clinical strategies aimed at reducing insulin resistance may prevent development of atherosclerosis leading to various cardiovascular disease and several menstrual disturbances and infertility in PCOS.

It is required to develop new pharmacological agents that will antagonize PAI-1 and these agents will have the potential to restore proteolytic balance in tissues such as the ovary in order to correct ovulation, treatment for the prevention of PCOS to improve the fertility of patient and to prevent its complications leading to cardiovascular diseases like hypertension, myocardial infarction, type 2 diabetes mellitus etc.

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*Ethical approval: The study was approved by the Institutional Ethics Committee*

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