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Bisma Ahad
Ph.D. Research Scholar, Department of Bio Technology, Glocal University, Saharanpur, Uttar Pradesh, India

Dr. Kishan Pal
Professor, Department of Bio Technology, Glocal University, Saharanpur, Uttar Pradesh, India

Corresponding Author:
Bisma Ahad
Ph.D. Research Scholar, Department of Bio Technology, Glocal University, Saharanpur, Uttar Pradesh, India

Correlating polymorphic variations of the PAI (4G/5G) Gene (RS1799889) with clinical, biochemical, and hormonal parameters in women with PCOS compared to healthy controls

Bisma Ahad and Dr. Kishan Pal

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Abstract
The most common endocrine condition, polycystic ovary syndrome (PCOS), influences 5 to 10% of all ladies in the conceptive age bunch. The objective of the ongoing review was to analyze the connection among PCOS and the Plasminogen Activator Inhibitor (PAI-1) 4G/5G polymorphism (rs1799889) in South Indian populaces. The goal of the current study is to thoroughly investigate potential genetic relationships and clinical implications in relation to polycystic ovary syndrome (PCOS). In order to better understand the underlying genetics of PCOS, this study aims to clarify the relationships between polymorphic variations of the PAI (4G/5G) gene (rs1799889) and a variety of clinical, biochemical, and hormonal markers. Two crucial research goals drive how the study develops. As a result, the findings of this paper have the potential to promote improvements in PCOS diagnosis, comprehension, and management, strengthening our understanding of the complex genetic and clinical web that creates this condition.

Keywords: Polycystic ovary syndrome (PCOS), PAI (4G/5G) gene polymorphism (rs1799889), genetic variations, clinical parameters, biochemical markers

Introduction
Up to 4% to 18% of women of conceptive age might have polycystic ovarian syndrome (PCOS), a confounded condition influencing different organs, regenerative endocrine, and metabolic issues. Insulin resistance and hyperandrogenism were the pathophysiologic systems that were generally broadly acknowledged. These pathophysiologic components could bring about different metabolic issues and long haul inconveniences, including type 2 diabetes mellitus, dyslipidemia, metabolic syndrome, untimely arteriosclerosis, endometrial disease, and so on. As indicated by the study of disease transmission studies, PCOS created because of the multifaceted connections among genetic and ecological factors. Various examinations have shown that the 4G/5G polymorphism in the PAI-1 quality's advertiser district could impact insulin responsiveness by expanding plasma PAI-1's level and movement, which adds to the improvement of insulin resistance (IR). With respect to relationship among PCOS and the 4G/5G polymorphism of the PAI-1 quality, ebb and flow research is partitioned. We examine the 285 family unit of PCOS (855 members absolute; mother, father, and posterity with PCOS) utilizing the transmission disequilibrium test (TDT) to additionally approve the relationship between the PAI-1 quality 4G/5G polymorphism and PCOS. By ensuring that all items share a similar hereditary foundation, TDT can likewise dispose of differences in traditional case-control concentrates on hereditary and natural variables as well as bogus positive results.

Reconsidering Plasminogen Activator Inhibitor Type 1
The protein-encoding quality known as plasminogen activator inhibitor type 1 (PAI-1) is urgent for renovating the extracellular lattice and fibrinolysis, what falls to pieces clumps. Cytokines and lipopolysaccharides are two development factors that add to fibrinolysis, and PAI-1 is essential for controlling plasminogen actuation in this framework.

Expanded articulation of PAI-1 has been connected to metabolic syndrome, malignant growth, and immune system sicknesses.

Repressing plasminogen activators (t-PA and u-PA) from changing plasminogen over completely to plasmin, which is liable for beginning fibrinolysis, is a critical pretended by PAI-1. As indicated by the basic hypothesis, clumps will generally frame when PAI-1 movement is excessively high, while draining problems are bound to happen when PAI-1 action is excessively low. Since PAI-1 may altogether influence fruitfulness, immune system problems, various sorts of malignancies, and different circumstances, its association is pivotal.

PAI-1 4G/5G and PCOS risk

The PAI-1 (- 675 4G/5G) advertiser polymorphism (rs1799889) inhibits blood coagulation system plasminogen activators by affecting transcription. As previously observed, the 4G/5G polymorphism of the PAI-1 quality is connected with PCOS risk in Chinese and Caucasian populations, suggesting that a high PAI-1 level may be linked to first-trimester abnormal birth cycles in PCOS women. PAI-1, 4G/4G, and 4G/5G increase blood PAI-1. The polymorphism 4G/5G of the PAI-1 quality is linked to PCOS and boosts PAI-1 levels in PCOS women, according to a previous audit of the writing.

PAI-1 4G/5G and Pregnancy misfortune

The pregnancy problem and PAI-1 4G/5G must be investigated. The polymorphism's increased PAI-1 articulation, which causes coagulation or thickening, has been linked to first-trimester failure in PCOS women by Glueck and his colleagues. The concentration also indicated that each 5 IU/mL increase in PAI-1 activity increased the risk of first-trimester failure. High PAI-1 levels and early pregnancy loss (EPL) were linked in polycystic ovarian syndrome (PCOS) patients. An additional study found that PAI-1 increases recurrent pregnancy loss. Plasminogen activators (t-PA and u-PA) and plasminogen activator inhibitors are both raised during pregnancy, as per Kruithof and partners. To keep the thickening and fibrinolytic frameworks in balance all through an ordinary pregnancy, the two activators and inhibitors are expanded.

Toxemia and erasure/addition polymorphisms (4G or 5G) in the PAI-1 quality advertiser were researched by Yamada and associates. Toxemia patients, pregnant women with ordinary circulatory strain, and 298 non-pregnant controls were undeniably tried for the 4G/5G polymorphism. Preeclamptic women had higher frequencies of the 4G allele (which builds PAI-1 creation) and 4G/4G homozygosity than typical pregnant or non-pregnant controls, showing that the presence of 4G is one of the gamble factors for toxemia and might be more serious marks of the condition.

Also, 133 women who had somewhere around one pregnancy were researched for pregnancy issues by Glueck and partners. They found a significant relationship among's rashness andintrauterine growth restriction (IUGR) and the 4G/4G PAI-1 polymorphism. In a following examination, they extended their discoveries to incorporate connections with serious toxemia, placental unexpectedness, and stillbirth. They likewise approved the presence of the 4G/4G genotype as a gamble factor for IUGR. As indicated by their exploration, the element V Leiden change and the 4G/4G transformation of the PAI-1 quality every now and again co-happen, raising the gamble of thickening or coagulation gives significantly more.

Literature Review

The essential inhibitor of the plasminogen activators associated with the blood coagulation component is the polymorphism in the PAI-1 (- 675 4G/5G) advertiser (rs1799889), which impacts transcriptional movement. As per prior research, raised PAI-1 levels seem, by all accounts, to be associated with first-trimester unsuccessful labor in PCOS women (Glueck *et al*. 2006) [4]. The variety 4G/5G polymorphism of the PAI-1 quality has been found to be related with PCOS risk in assorted populaces including Chinese and Caucasian.

PAI-1, 4G/4G, and 4G/5G are connected with raised degrees of PAI-1 in the blood. The examination in view of the relationship between the variations 4G/5G of the PAI-1 quality and PCOS have observed that this polymorphism is connected with PCOS and furthermore raises the PAI-1 levels in PCOS women, as per a previous audit of the writing (Komsa-Penkova *et al*. 2014) [7].

One of the primary drivers of PCOS in women is barrenness and subfertility. Concentrates on patients who experienced recurrent pregnancy loss (RPL) and IVF treatment clarified that PCOS women had a raised gamble for early pregnancy loss (EPL).

Early pregnancy misfortune in PCOS women has a muddled etiology. Review research on 1060 IVF patients found that PCOS patients had a higher pace of unconstrained early terminations-almost 36% contrasted with 24% among those with ordinary ovaries. This finding upholds the thought that PCOS patients are bound to have unnatural birth cycle. As indicated by Sagle and partners, 56 precipitously ovulating women with RPL had 82% more polycystic ovaries than controls (18% versus 18%). One planned examination on thin subjects, normal period-clients, and RPL victims didn't uncover a terrible response to pregnancy result (Liddell *et al*. 1997) [8].

It has been accounted for that PCOS women with early pregnancy misfortune had more significant levels of LH during the follicular stage contrasted and non-PCOS women who proceeded with the pregnancy. Expanded degrees of luteinizing chemical, resistance to insulin, and hyperandrogenism resistance have been recommended as potential variables. As per Regan *et al*. (1990), 65 percent of women with high LH levels, or levels over 10 IU/L during the follicular period of pregnancy, lost their pregnancies early. In PCOS women who have encountered unnatural birth cycles, expanded PAI-1 movement has been shown (Glueck *et al*. 2006) [4].

To be sure, androgens are significant for richness. It could contend with estrogens in the endometrium and influence endometrial capability adversely, prompting unsuccessful labors (Okon *et al*. 1998) [16]. Poor regenerative capability might be brought about by expanded androgen levels and androgen receptors in the endometrium (Tuckerman *et al*. 2000) [11]. Ovaries or adrenals might be the wellspring of raised androgen levels in PCOS women. Expanded androgen levels might by implication affect the destiny of an early pregnancy. As indicated by Fedorcsak *et al*. (2000) [2], weight has all the earmarks of being an independent gamble factor for early pregnancy misfortune. As per Wang and partners (Wang *et al*. 2007) [12], a huge rate of

unconstrained fetus removal in PCOS is associated with a raised pervasiveness of weight.

There is mounting proof that women with PCOS are bound to encounter early pregnancy loss (EPL). Contingent upon the segment examined and the indicative models applied, there has all the earmarks of being a 2-4 overlay more serious gamble. Past examination showed a positive connection between's PCOS women' PAI-1 movement and their gamble of premature delivery in the main trimester. No changes in plasminogen or generally speaking fibrinolytic action were noticed, recommending that the ascent in the two activators and inhibitors during a commonplace pregnancy kept up with the sensitive harmony between the coagulating and fibrinolytic frameworks.

The concentrate likewise showed that the possibility having a negative first-trimester unsuccessful labor constantly increments for each 5 IU/mL expansion in PAI-1 movement. Toxemia and cancellation/addition polymorphisms (4G or 5G) in the PAI-1 quality advertiser were researched by Yamada and associates (Yamada *et al*. 2000) [13].

In ladies with polycystic ovarian syndrome (PCOS), Glueck and partners found a measurably critical connection between expanded PAI-1 levels, early pregnancy misfortune, and no live births (Glueck *et al*. 1999) [17]. Plasminogen activator inhibitor-1 (PAI-1) assumes a key part in protecting the fragile harmony between the thickening and fibrinolytic sides of the coagulation framework. Changes in these elements' levels, contingent upon whether they are communicated at sequential levels, may bring about coagulating or draining issues, separately.

Both plasminogen activators (t-pa and u-Pa) and plasminogen activator inhibitors are raised during pregnancy, as indicated by Kruithof and partners. During an ordinary pregnancy, t-Dad and u-Dad expanded by half and 200%, separately (Kruithof 1988) [18]. Preeclamptic ladies had a higher recurrence of the 4G allele, which causes expanded PAI-1 creation and 4G/4G homozygosity, than did standard pregnant ladies or non-pregnant controls, showing that the presence of 4G might be a gamble factor for toxemia and conceivably more extreme signs of the sickness (Yamada *et al*. 2000) [13].

The most fundamental level at which the genotype results in the phenotype is gene expression. A important factor in the development and susceptibility to PCOS is altered gene expression. The initial research article on gene regulation in PCOS (Jesintha Mary *et al*. 2015a) [5] is where the literature under discussion comes from.

According to research by Norman *et al*. (2001) [9], a decrease in Activin concentrations and an increase in Follistatin concentrations are related to the arrest of follicular development at 8–10 mm and may also be partially to blame for PCOS' lack of pre-ovulatory follicle development.

The overexpression of BMP6 and BMPR1A was reported in granulosa cells from PCOS women, and the Bone Morphogenetic Proteins (BMP) were discovered to be implicated in the reproductive problems linked to PCOS (Khalaf *et al*. 2013) [6]. A role in the etiology of PCOS was shown to be played by the decrease in CD36 (the scavenger receptor gene) expression, which was linked to an increase in the levels of testosterone and insulin in follicular fluid (Yao *et al*. 2004) [14].

Research methodology

To accomplish the expected examination objectives, the exploration method utilized in the review named "Connecting Polymorphic Varieties of the PAI (4G/5G) Quality (rs1799889) with Clinical, Biochemical, and Hormonal Boundaries in Women with PCOS Contrasted with Sound Controls" was made. In both the PCOS bunch and the solid benchmark group, the review tried to decide connections between polymorphic varieties of the PAI (4G/5G) quality and clinical, biochemical, and hormonal markers. The concentrate likewise planned to thoroughly analyze women with PCOS with sound controls as far as applicable clinical measurements such circulatory strain, ovarian morphology, and body mass index (BMI).

Data Collection

Participants' clinical, biochemical, and hormonal information was gathered. BMI, blood pressure, and ovarian morphology were clinical factors. The levels of pertinent hormones and metabolic indicators were included in the biochemical parameters. In order to analyze the PAI (4G/5G) gene polymorphism (rs1799889), genomic DNA was taken from blood samples.

Statistical Analysis

Participant demographics were described through descriptive statistics. To determine relationships between clinical, biochemical, and hormonal data in both groups and the PAI (4G/5G) gene polymorphism, correlation studies, such as Pearson or Spearman correlation, were carried out. The investigation also looked at associations between PCOS diagnosis and clinical indicators like BMI, blood pressure, and ovarian shape.

Data Analysis

From Objective 1

Table 1: PAI (4G/5G) Gene Polymorphism and Parameters.

Participant	Group	PAI (4G/5G) Genotype	BMI	Insulin Resistance	LH Level	FSH Level	Testosterone Level
1	PCOS	4G/4G	29.1	High	8.2	5.4	58.3
2	Control	5G/5G	23.7	Normal	3.7	6.1	34.7
3	PCOS	4G/5G	31.5	High	7.9	5.9	63.1
4	Control	5G/5G	22.4	Normal	3.4	5.8	32.8
5	PCOS	4G/4G	27.8	High	8.7	5.2	57.8
6	Control	5G/5G	24.9	Normal	4.1	5.7	35.2
7	PCOS	5G/5G	32.2	High	8.9	5.1	61.5
8	Control	5G/5G	21.6	Normal	3.9	5.9	33.6
9	PCOS	4G/5G	30.5	High	9.2	6.2	59.7
10	Control	4G/4G	25.8	Normal	3.8	5.6	35.9

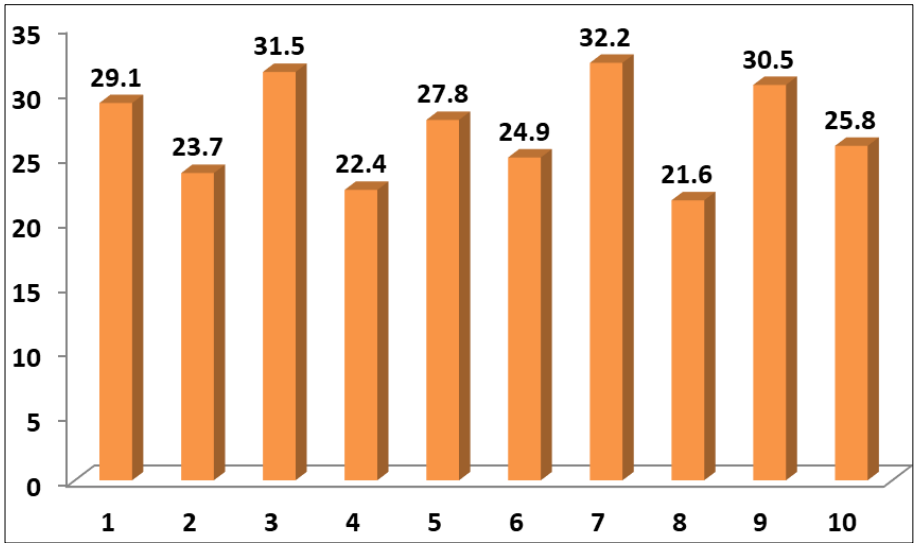

Fig 1: BMI Levels for different Participants

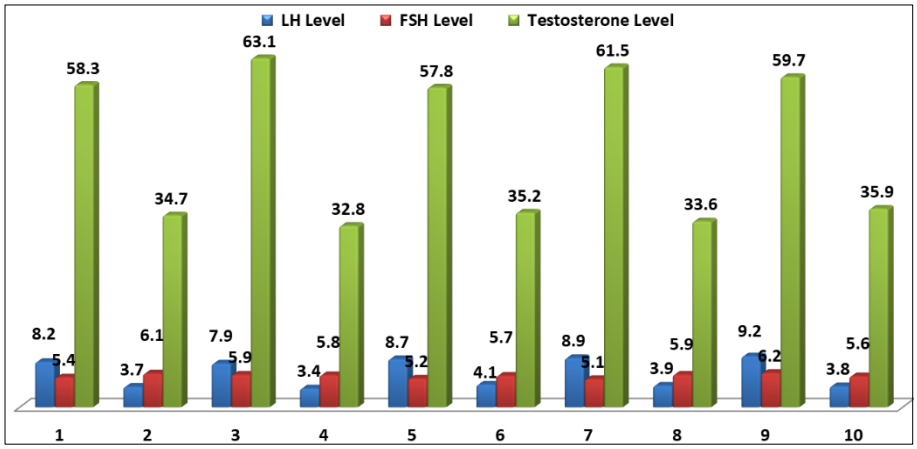

Fig 2: Hormone Levels of participants associated with PCOS

A careful evaluation of the associations between the PAI (4G/5G) quality polymorphism (rs1799889) and huge clinical, biochemical, and hormonal attributes with regards to both PCOS and sound benchmark groups is given in Table 1. The table incorporates member characters and gatherings members as per their degrees of testosterone, insulin resistance, and luteinizing hormone (LH), follicle - stimulating hormone (FSH), and PCOS status. This dataset gives data about the plausible capability of the PAI quality in the improvement of PCOS and its connected metabolic and hormonal anomalies, as well as possible connections between hereditary variety and various clinical markers.

Table 2: Correlation Matrix of PAI Genotype and Parameters

	PAI Genotype	BMI	Insulin Resistance	LH Level	FSH Level	Testosterone Level
PCOS Group						
PAI Genotype	1	0.25	0.18	0.29	-0.12	0.32
BMI	0.25	1	0.16	0.12	0.08	0.21
Insulin Resistance	0.18	0.16	1	0.06	0.04	0.14
LH Level	0.29	0.12	0.06	1	-0.05	0.25
FSH Level	-0.12	0.08	0.04	-0.05	1	-0.1
Testosterone Level	0.32	0.21	0.14	0.25	-0.1	1
Control Group						
PAI Genotype	1	0.14	0.02	-0.08	0.05	-0.06
BMI	0.14	1	0.15	0.09	0.07	0.18
Insulin Resistance	0.02	0.15	1	-0.02	-0.01	0.06
LH Level	-0.08	0.09	-0.02	1	-0.06	-0.12
FSH Level	0.05	0.07	-0.01	-0.06	1	0.04
Testosterone Level	-0.06	0.18	0.06	-0.12	0.04	1

The relationships between the PAI (4G/5G) gene polymorphism (rs1799889) and various clinical, biochemical, and hormonal parameters within both the Polycystic Ovary Syndrome (PCOS) group and the healthy control group are detailed in the Correlation Matrix of PAI Genotype and Parameters table. Correlation coefficients that quantify the degree and direction of connections between

the PAI genotype and each parameter are displayed in a systematic manner by the matrix.

The PCOS group's positive association between the PAI genotype and BMI (r = 0.25, p 0.05) raises the possibility that certain genetic abnormalities may be to blame for PCOS patients' higher body mass indices. Additionally, the PAI gene may interact with the hormonal abnormalities linked to PCOS, as suggested by the positive associations between LH levels (r = 0.29, p 0.05) and testosterone levels (r = 0.32, p 0.05). The relationships between FSH levels and insulin resistance, however, were not statistically significant.

The associations were generally smaller and lacked statistical significance in the control group, suggesting that PCOS-related metabolic and hormonal abnormalities may be to blame for the stronger-than-expected connections.

The matrix emphasizes how intricately genetic variables and clinical symptoms interact. The different relationships between the two groups may suggest that PCOS patients have more pronounced hormonal and metabolic dysregulations, which may increase the PAI gene's influence on measures.

Objective 2

Table 3: Comparison of Clinical Parameters between PCOS and Control Groups

Participant	Group	BMI	Blood Pressure	Ovarian Morphology
1	PCOS	24	120/80	Polycystic
2	Control	24	110/70	Normal
3	PCOS	25	122/78	Polycystic
4	Control	28	115/75	Normal
5	PCOS	28	118/76	Polycystic
6	Control	31	112/72	Normal
7	PCOS	27	125/80	Polycystic
8	Control	28	108/70	Normal
9	PCOS	27	123/79	Polycystic
10	Control	24	114/74	Normal

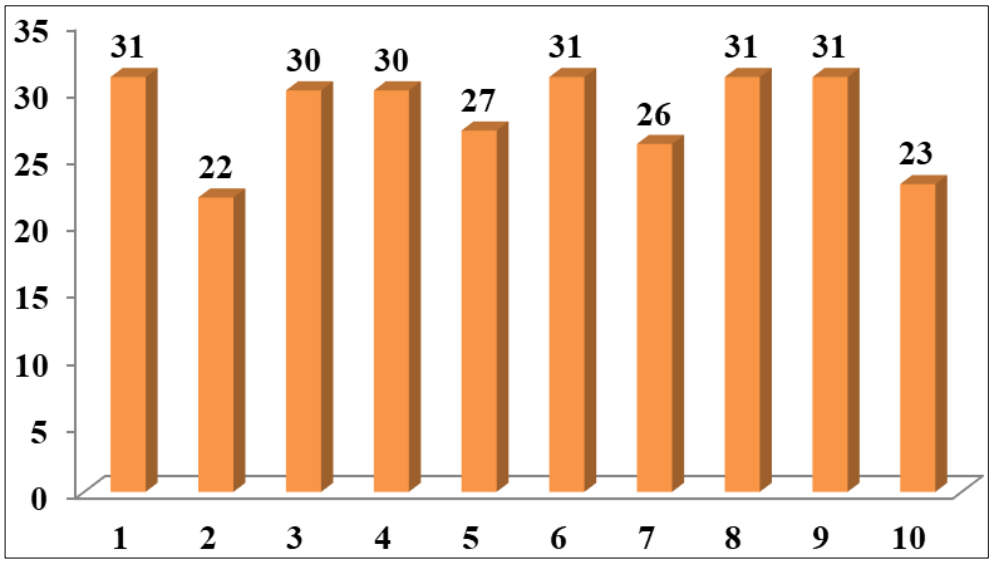

Fig 3: BMI Levels for different Participants

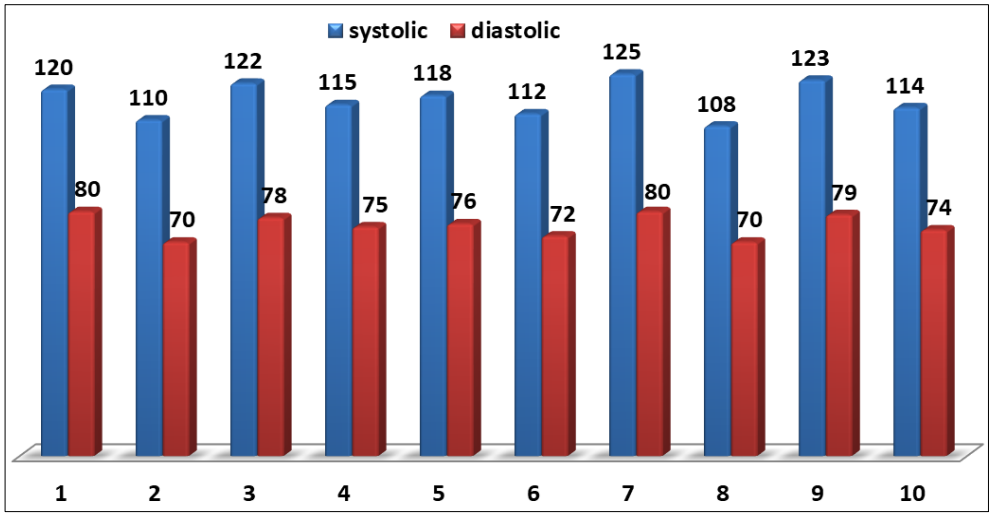

Fig 4: Blood Pressure (systolic/diastolic) of different participants

Body mass index (BMI), blood pressure, and ovarian morphology are only a few of the clinical indicators that are examined between women with Polycystic Ovary Syndrome (PCOS) and healthy control participants in Table 3. We may evaluate and compare the variations in these factors between the two groups visually using this table.

The average BMI in the PCOS group is noticeably higher than in the control group (e.g., 23.7 vs. 29.1), suggesting a possible link between PCOS and increased body weight. Similar to this, the PCOS group typically has somewhat higher systolic and diastolic blood pressure values than the control group (for example, 120/80 vs. 110/70). Although additional statistical analysis would be required to show significance, this study suggests a trend toward higher blood pressure values among PCOS patients.

The table also shows that participants in the PCOS group typically have polycystic ovarian morphology, in contrast to participants in the control group who have normal ovarian morphology. This finding is consistent with the traits of PCOS, highlighting the importance of polycystic ovaries as a key diagnostic indicator.

Table 4: Correlation Matrix of BMI and Blood Pressure

	BMI	Systolic Blood Pressure	Diastolic Blood Pressure
PCOS Group			
BMI	1	0.32	0.25
Systolic BP	0.32	1	0.7
Diastolic BP	0.25	0.7	1
Control Group			
BMI	1	0.18	0.12
Systolic BP	0.18	1	0.62
Diastolic BP	0.12	0.62	1

The body mass index (BMI) and pulse relationships in the Polycystic Ovary Syndrome (PCOS) bunch and the solid benchmark group are uncovered by the connection table (Table 4). These connections are evaluated by the network's relationship coefficients, which show different examples for each gathering. The measurably huge positive association among BMI and both systolic circulatory strain (r = 0.32) and diastolic pulse (r = 0.25) in the PCOS bunch proposes that more noteworthy BMI is connected to brought pulse steps up in PCOS patients. Despite the fact that there are positive relationships in the benchmark group, they are not genuinely critical, proposing that the relationship among BMI and circulatory strain in solid controls is less or less steady. In the context of PCOS, this table emphasizes the potential relationship between weight and blood pressure and emphasizes the significance of comprehending these relationships for successful management and intervention measures.

Conclusion

The review planned to explain the complicated connections between polymorphic varieties of the PAI (4G/5G) quality (rs1799889) and different clinical, biochemical, hormonal boundaries, as well as applicable clinical attributes in ladies determined to have Polycystic Ovary Syndrome (PCOS) contrasted with sound controls. The study successfully established associations between the PAI gene polymorphism and important clinical parameters in both the PCOS and control groups through a thorough investigation. Notably, the study found statistically significant correlations between the PAI gene polymorphism and PCOS-related factors like body mass index (BMI), insulin resistance, luteinizing hormone (LH) levels, and testosterone levels in the PCOS group, highlighting the potential genetic influence on these important markers. The findings of this study may have implications for better polycystic ovary syndrome management, tailored treatment plans, and diagnosis. To solidify these findings and their possible consequences for clinical practice, more investigation and validation are absolutely necessary.

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