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Original Research Article

ASSOCIATION BETWEEN CYP2E1 GENETIC VARIATIONS AND RISK OF POLYCYSTIC OVARY SYNDROME IN NORTH INDIAN WOMEN

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ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is a common endocrine disorder with a strong genetic and metabolic basis. Cytochrome P450 2E1 (CYP2E1) is an oxidative stress generating enzyme, and its genetic polymorphisms may influence susceptibility to PCOS. The objective is to evaluate CYP2E1 gene polymorphism in women with PCOS from North India.
Materials and Methods: A cross-sectional observational study was conducted on 139 women aged 18-40 years with diagnosed PCOS. Clinical assessment, anthropometric measurements, and biochemical evaluation of hormonal parameters and fasting insulin were performed. Insulin resistance was assessed using standard indices. CYP2E1 gene polymorphism was analyzed by polymerase chain reaction.
Results: The mean age of participants was 26.8 + 4.9 years, and 71.9% had a body mass index ≥25 kg/m2. Insulin resistance was present in 58.3% of subjects. Genotypic analysis showed wild- type CYP2E1 in 56.8%, heterozygous polymorphism in 30.2%, and homozygous polymorphism in 13.0% of participants. A substantial proportion of women carried variant alleles, suggesting a potential role in PCOS-related metabolic and hormonal disturbances.
Conclusion: CYP2E1 gene polymorphism was common among North Indian women with PCOS and may contribute to disease pathophysiology through oxidative stress-mediated mechanisms. Further large-scale studies are needed to confirm these findings and establish clinical relevance.
Keywords: CYP2E1, Genetic Variations, Polycystic Ovary Syndrome.

INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is one of the most prevalent endocrine disorders affecting women of reproductive age, with a global prevalence estimated between 6% and 15%, depending on diagnostic criteria and ethnicity.[1] It remains a leading cause of menstrual irregularity, infertility, and metabolic dysfunction among women of childbearing potential.The prevalence of PCOS varies significantly across regions, ranging from 2% to 25% world wide. Indian data indicate higher prevalence rates between 8% and 20% especially in urban populations.[2,3]

The clinical manifestations of PCOS are diverse, including menstrual irregularities, hirsutism, acne, alopecia, and infertility due to chronic anovulation.[4] Beyond reproductive symptoms, PCOS is linked with insulin resistance (IR), obesity, dyslipidemia, and impaired glucose tolerance, leading to an increased risk of type 2 diabetes mellitus (T2DM), nonalcoholic fatty liver disease (NAFLD), and cardiovascular disorders.[5,6]

The cytochrome P450 (CYP) superfamily of enzymes is central to steroid hormone synthesis, drug metabolism, and oxidative detoxification.[7] Among these, CYP2E1 plays a key role in metabolizing low

molecular weight substrates (ethanol, acetone, anesthetics) and in ROS generation.[8]

CYP2E1 constitutes about 21% of hepatic CYP enzymes and is crucial in maintaining oxidative balance. Polymorphisms in the CYP2E1 gene can influence enzyme activity, affecting susceptibility to oxidative stress-related diseases including cancers, liver injury, and metabolic disorders.[9,10]

In PCOS, oxidative stress interacts with hormonal and genetic factors to perpetuate insulin resistance and hyperandrogenism. CYP2E1 polymorphisms may upregulate ROS production, disrupting ovarian redox homeostasis and leading to thecal cell proliferation, follicular atresia, and enhanced androgen synthesis.[11]

Considering the above evidence, the present study was undertaken to examine the association between CYP2E1 genetic polymorphisms and PCOS risk among North Indian women. Understanding these associations may elucidate the contribution of oxidative stress-related genetic factors to PCOS pathophysiology.

1. To determine genotype and allele frequencies of selected CYP2E1 polymorphisms in PCOS patients and controls.
2. To correlate CYP2E1 genotypes with clinical, hormonal, and metabolic parameters (hyperandrogenism, BMI, insulin resistance).
3. To explore gene-environment interactions influencing PCOS risk and severity.

MATERIALS AND METHODS

The present study was conducted as a cross-sectional observational study to evaluate the association between cytochrome P450 2E1 (CYP2EI) gene polymorphism and polycystic ovary syndrome (PCOS). The study was carried out in the Department of Biochemistry, in collaboration with the Department of Obstetrics and Gynaecology, Santosh Hospital, Ghaziabad

d. The study was conducted over a defined study period after obtaining approval from the Institutional Ethics Committee.

Study Population: Women with a confirmed diagnosis of polycystic ovary syndrome attending the Outpatient Department (OPD) of Obstetrics and Gynaecology, Santosh Hospital, Ghaziabad, were included in the study.

Sample Size: A total of 139 patients diagnosed with PCOS were enrolled in the study.

Inclusion Criteria

Participants were included in the study if they fulfilled the following criteria:

- Women aged 18-40 years with a previously confirmed diagnosis of PCOS
- Women residing in North India for more than 20 years, to ensure ethnic homogeneity
- Participants who provided written informed consent for participation in the study

Exclusion Criteria

Participants were excluded from the study if they had:

- Pregnancy
- Hypothyroidism
- History of oral contraceptive use within the preceding six months
- Current or previous hormonal therapy
- Diabetes mellitus
- Any other ovarian disorder
- Any malignant disease

Methodology

Clinical Evaluation: All participants underwent a detailed clinical evaluation, which included a comprehensive medical history and physical examination. Anthropometric measurements such as height and weight were recorded, and body mass index (BMI was calculated using standard formulae.

Sample Collection: Venous blood samples were collected from all participants under aseptic precautions. Blood samples were divided appropriately for biochemical analysis and genetic evaluation. Samples for DNA extraction were stored under recommended conditions until further processing.

Hormonal and Metabolic Assessment: Serum levels of the following hormones were estimated using standard laboratory techniques

- Luteinizing hormone (LH)
- Follicle-stimulating hormone (FSH)
- Serum estrogen
- Serum androgen

Insulin resistance was assessed using biochemical indices based on fasting insulin and glucose measurements.

Genetic Analysis: Genomic DNA was extracted from peripheral blood leukocytes using standard extraction protocols. CYP2E1 gene polymorphism was analysed using the polymerase chain reaction (PCR) technique. Genotyping was performed following amplification of target gene regions, and polymorphic variants were identified according to established protocols.

Statistical Analysis: The statistical analysis in this study was carried out using SPSS 25. Continuous variables were summarized as mean + standard deviation for normally distributed data and as median with interquartile range for skewed distributions, while categorical variables were expressed as frequencies and percentages. Comparisons between two independent groups were performed using the independent t-test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. Associations between categorical variables, including genotype distribution, insulin resistance status, BMI categories, LH/FSH ratio, and hyperandrogenism, were assessed using the Chi-square test. Correlations between hormonal parameters, BMI, and insulin resistance were evaluated using Spearman's rank correlation coefficient. To identify independent predictors of insulin resistance, multivariate logistic regression

analysis was performed, and results were reported as adjusted odds ratios with 95% confidence intervals. A p value of less than 0.05 was considered statistically significant throughout the analysis.

Outcome Measures: The primary outcome of the study was the association between CYP2E1 gene polymorphism and PCOS. Secondary outcomes included the relationship of CYP2E1 polymorphism with hormonal parameters (FSH, LH, estrogen, androgen) and insulin resistance among PCOS subjects.

RESULTS

Out of 139 participants, the majority belonged to the 21-30 years age group, accounting for 91 individuals (65.5%), followed by 32 participants (23.0 %) in the 31-40 years group. A smaller proportion, 16 participants (11.5%), were aged between 18-20 years. The mean age of the study population was 26.8 + 4.9 years, with a median age of 26 years (IQR: 23-30 years). This indicates that most participants were concentrated in the midreproductive age group. The narrow interquartile range suggests relatively low age variability within the study.

Anthropometric Profile of Study Population: The mean height and weight of the study population were 158.6 + 5.4 cm and 66.2 + 9.1 kg, respectively. The mean BMI was 26.4 ÷ 3.8 kg/m2, with a median BMI of 26.1 (IQR: 23.8-28.9), indicating a tendency toward overweight status. Based on BMI classification, 62 participants (44.6%) were overweight, 38 (27.3%) were obese, and only 39 (28.1%) had a normal BMI. Overall, 100 participants (71.9%) had BMI ≥25 kg/m2. This reflects a high prevalence of excess body weight in the study population.

Hormonal Profile of Study Population: The mean serum LH level was 11.8 + 4.6 IU/L, while the mean FSH level was comparatively lower at 5.4 + 2.1 IU/L. This resulted in an elevated mean LH/FSH ratio of 2.1 + 1.2, with a median value of 2.1 (IQR: 1.7- 2.6). Serum estrogen levels showed a mean of 186.3 + 52.7 pg/mL, and serum androgen levels averaged 78.6 + 21.4 ng/dL. Median values closely mirrored the mean, suggesting a relatively symmetric distribution. These findings indicate significant hormonal imbalance among the participants.

Table 1: Hormonal Profile of Study Population

Parameter	Mean ± SD	Median (IQR)
Serum LH (IU/L)	11.8 ± 4.6	12.0 (9.0–15.0)
Serum FSH (IU/L)	5.4 ± 2.1	5.2 (4.1–6.8)
LH/FSH Ratio	2.1 ± 1.2	2.1 (1.7–2.6)
Serum Estrogen (pg/mL)	186.3 ± 52.7	178 (150–215)
Serum Androgen (ng/dL)	78.6 ± 21.4	76 (63–92)

Insulin Resistance Profile of Study Population: The mean fasting insulin level was 18.9 + 6.7 µIU/mL, with a median value of 17.6 µIU/mL (IQR: 14.222.1). Insulin resistance was identified in 81 out of 139 participants, corresponding to 58.3% of the study population. This indicates that more than half of the participants had impaired insulin sensitivity. The elevated fasting insulin values further support the presence of underlying metabolic dysfunction. These results highlight the strong association between the study condition and insulin resistance.

Distribution of CYP2E1 Gene Polymorphism: Genotypic analysis revealed that the wild-type CYP2E1 genotype was present in 79 participants (56.8%). The heterozygous polymorphic genotype was observed in 42 participants (30.2%), while 18 participants (13.0%) had the homozygous polymorphic genotype. Overall, 60 participants (43.2%) carried at least one variant allele. This substantial prevalence of polymorphism suggests a possible genetic predisposition within the study population. These findings provide a foundation for evaluating associations between CYP2E1 polymorphism and hormonal or metabolic parameters.

Association Between CYP2E1 Polymorphism and Hormonal/Metabolic Parameters: Subjects carrying the polymorphic variant of the CYP2E1 gene (n = 60) showed significantly higher mean serum LH levels compared to the wild-type group (13.2 + 5.2 IU/L vs 10.5 + 3.7 IU/L; p = 0.02). Serum FSH levels were also significantly higher in the variant group (5.9 + 2.4 IU/L) than in wild-type subjects (5.0 - 1.8 IU/L; P = 0.03). Consequently, the LH/FSH ratio was significantly elevated in the polymorphic group (2.3 + 1.4 vs 2.0 = 1.1; p = 0.02). Serum androgen levels were significantly higher among variant genotype carriers (87.2 + 24.3 ng/dL) compared to wildtype individuals (72.6 + 18.9 ng/dL; p = 0.01). Although serum estrogen levels were higher in the polymorphic group (193.8 + 55.1 pg/mL), this difference did not reach statistical significance (p = 0.08). Insulin resistance was observed in 64.5% (51/79) of wildtype subjects and 50.0% (30/60) of variant genotype carriers, with a statistically significant association (P= 0.01).

Insulin Resistance Status in PCOS Subjects: Insulin resistance was present in 81 out of 139 participants, accounting for 58.3% of the study population, while 58 participants (41.7%) were insulin sensitive. The mean fasting insulin level was 18.9 + 6.7 µIU/mL, with a median value of 17.6 µIU/mL (IQR: 14.222.1). These elevated insulin levels indicate impaired insulin sensitivity in a substantial proportion of subjects. The high prevalence of insulin resistance underscores the

metabolic burden associated with PCOS. This finding highlights the importance of metabolic evaluation in these patients.

Between CYP2E1 Polymorphism and Hormonal Parameters: Comparison between genotypes demonstrated significantly higher serum LH levels in variant genotype carriers (13.2 + 5.2 IU/L) compared to wild type subjects (10.5 + 3.7 IU/L; p = 0.02, independent t test). Serum FSH levels were also significantly increased in the variant group (5.9 + 2.4 IU/L vs 5.0 + 1.8 IU/L; P = 0.03). The LH/FSH ratio showed a significant elevation in variant genotypes (2.3 + 1.4 vs 2.0 + 1.1; p = 0.02, MannWhitney U test). Serum and androgen levels were significantly higher among variant genotype carriers (87.2 + 24.3 ng/dL) compared to wildtype individuals (72.6 + 18.9 ng/dL; p = 0.01). No statistically significant difference was observed for serum estrogen levels between the two groups (p = 0.08).

Association Between CYP2E1 Polymorphism and Insulin Resistance: Among wildtype genotype carriers (n = 79), insulin resistance was present in 51 subjects (64.6%), whereas 28 subjects (35.4%) were insulin sensitive. In contrast, among variant genotype carriers (n = 60), insulin resistance was observed in 30 subjects (50.0%), with an equal proportion being insulin sensitive. The association between CYP2E1 genotype and insulin resistance was statistically significant (p = 0.01, Chi-square test). This suggests a meaningful relationship between CYP2E1 genetic variation and metabolic dysfunction. The findings support a genotype-specific influence on insulin sensitivity.

Table 2: Association Between CYP2E1 Polymorphism and Insulin Resistance

CYP2E1 Genotype	Insulin Resistance Present n (%)	Insulin Resistance Absent n (%)	P-value	Statistical Test
Wild-type (n=79)	51 (64.6)	28 (35.4)	0.01	Chi-square test
Variant genotype (n=60)	30 (50.0)	30 (50.0)		
Total	81 (58.3)	58 (41.7)		

Association of BMI Categories with CYP2E1 Genotype: Normal BMI was observed in 28 wildtype subjects (35.4%) compared to 11 variant genotype carriers (18.3%). Overweight status was similarly distributed between wild-types (34/79; 43. 0%) and variant genotypes (28/60; 46.7%). Obesity was more frequent among variant genotype carriers, affecting 21 subjects (35.0%) compared to 17 wildtype subjects (21.6%). The overall association between BMI category and CYP2E1 genotype was statistically significant (p = 0.03). These findings indicate a higher prevalence of obesity among individuals carrying the CYP2E1 variant genotype.

Table 3: Association of BMI Categories with CYP2E1 Genotype

BMI Category (kg/m²)	Wild-type (n=79) n (%)	Variant Genotype (n=60) n (%)	Total n (%)	P-value	Statistical Test
Normal (18.5–24.9)	28 (35.4)	11 (18.3)	39 (28.1)	0.03	Chi-square test
Overweight (25–29.9)	34 (43.0)	28 (46.7)	62 (44.6)		
Obese (≥30)	17 (21.6)	21 (35.0)	38 (27.3)		
Total	79 (100)	60 (100)	139 (100)		

Association of LH/FSH Ratio with CYP2E1 Polymorphism: An LH/FSH ratio >2 was observed in 48 wildtype subjects (60.8%) and 48 variant genotype carriers (80.0%). Conversely, a normal LH/FSH ratio (≤2) was more common in the wild-type group (31/79; 39.2%) than in the variant group (12/60; 20.0%). The association between elevated LH/FSH ratio and CYP2E1 polymorphism was statistically significant (p = 0.02). This suggests that CYP2E1 variant genotypes are associated with greater gonadotropin imbalance in PCOS subjects.

Table 4: Association of LH/FSH Ratio with CYP2E1 Polymorphism

LH/FSH Ratio	Wild-type (n=79) n (%)	Variant Genotype (n=60) n (%)	Total n (%)	P-value	Statistical Test
≤ 2.0	31 (39.2)	12 (20.0)	43 (30.9)	0.02	Chi-square test
> 2.0	48 (60.8)	48 (80.0)	96 (69.1)		
Total	79 (100)	60 (100)	139 (100)		

Association of Hyperandrogenism with CYP2E1 Polymorphism: Hyperandrogenism was present in 43 wildtype subjects (54.4%) and 46 variant genotype car riers (76.7%). Normal serum androgen levels were more frequently observed in the wild-type group (36/79; 45.6%) compared to the variant group (14/60; 23.3%). The association between elevated androgen levels and CYP2E1 polymorphism was statistically significant (p =0.01). These findings indicate a strong link between CYP2E1 variant genotypes and hypera ndrogenic phenotype in PCOS.

Table 5: Association of Hyperandrogenism with CYP2E1 Polymorphism

Serum Androgen Status	Wild-type (n=79) n (%)	Variant Genotype (n=60) n (%)	Total n (%)	P-value	Statistical Test
Normal	36 (45.6)	14 (23.3)	50 (36.0)	0.01	Chi-square test
Elevated	43 (54.4)	46 (76.7)	89 (64.0)		
Total	79 (100)	60 (100)	139 (100)		

Severity of Insulin Resistance by CYP2E1 Genotype: Normal insulin sensitivity was observed in 28 wild type subjects (35.4%) and 30 variant genotype carriers (50.0%). Mild insulin resistance was more common in the wildtype group (34/79; 43.0%) compared to the variant group (18/60; 30.0%). Moderate-severe insulin resistance was seen in 17 wild type subjects (21.6%) and 12 variant genotype carriers (20.0%). The overall association between insulin resistance severity and CYP2E1 genotype was statistically significant (p = 0.01), indicating genotype-specific differences in metabolic status.

Table 6: Severity of Insulin Resistance by CYP2E1 Genotype

Insulin Resistance Status	Wild-type (n=79) n (%)	Variant Genotype (n=60) n (%)	Total n (%)	P-value	Statistical Test
Normal	28 (35.4)	30 (50.0)	58 (41.7)	0.01	Chi-square test
Mild IR	34 (43.0)	18 (30.0)	52 (37.4)		
Moderate–Severe IR	17 (21.6)	12 (20.0)	29 (20.9)		
Total	79 (100)	60 (100)	139 (100)		

Comparison of Anthropometric and Biochemical Parameters by CYP2E1 Genotype: The mean age was comparable between wildtype (26.2 + 4.6 years) and variant genotype groups (27.6 + 5.2 years; p = 0.08). Variant genotype carriers had significantly higher mean BMI (27.3 = 4.1 kg/m2) compared to wildtype subjects (25.7 - 3.4 kg/m2; p = 0.02). Mean LH and FSH levels were significantly elevated in the variant group (LH: 13.2 + 5.2 vs 10.5 + 3.7IU/L; FSH: 5.9 + 2.4 vs 5.0 + 1.8 IU/L). Serum androgen and fasting insulin levels were also significantly higher in variant genotype carriers (p = 0.01 for both). No significant difference was observed in serum estrogen levels between the groups (p = 0.08).

Summary of Phenotypic Expression Across CYP2E1 Genotypes: Obesity was more prevalent among variant genotype carriers (35.0%) compared to wild-type subjects (21.6%) (P = 0.03). An LH/FSH ratio >2 was observed in 80.0% of variant genotypes versus 60.8% of wildtype subjects (p = 0.02). Hyperandrogenism was significantly higher in the variant group (76.7%) than in the wildtype group (54.4%) (p = 0.01). Insulin resistance was present in 64.6% of wildtype and 50.0% of variant genotype carriers (p = 0.01). Overall, variant genotypes demonstrated a more adverse endocrine and metabolic phenotype.

Correlation Between Hormonal Parameters and Insulin Resistance: A moderate positive correlation was observed between serum LH levels and insulin resistance (r = 0.42, p < 0.001). Serum androgen levels also showed a significant positive correlation with insulin resistance (r = 0.46, p < 0.001). BMI demonstrated the strongest correlation with insulin resistance (r = 0.51, p < 0.001). These findings indicate that increasing adiposity and hormonal derangements are closely associated with worsening insulin resistance in PCOS subjects.

Multivariate Logistic Regression Analysis for Predictors of Insulin Resistance in PCOS Subjects: Multivariate logistic regression analysis identified CYP2E1 variant genotype as an independent predictor of insulin resistance (AOR: 2.31; 95% CI: 1.184.52; p = 0.01). Each unit increase in BMI was associated with a 19% increase in the odds of insulin resistance (AOR: 1.19;95% CI: 1.071.32; p = 0.002). An LH/FSH ratio >2 was also significantly associated with insulin resistance (AOR: 1.87; P = 0.04). Elevated serum androgen levels showed the strongest association (AOR: 2.54; 95% CI: 1.294.99; p = 0.006), highlighting their key role in metabolic dysfunction.

DISCUSSION

In the present study, the age distribution showed a clear predominance of women in the 21-30 years age group, comprising 65.5% (n = 91) of the total 139 participants, followed by 23.0% (n = 32) in the 31-40 years group, while 11.5% (n = 16) were aged 1820 years. The mean age of 26.8 + 4.9 years and median age of 26 years (IQR: 23-30) indicate that the study population was largely concentrated within the midreproductive age range, with relatively low age variability. This pattern is epidemiologically expected, as clinical manifestations of polycystic ovary syndrome (PCOS) commonly become apparent during early and mid-reproductive life. These findings are consistent with the evidence reported by Kakoly NS et al. (2018),[12] who conducted a large meta-analysis of 40 high-quality studies evaluating metabolic abnormalities in women with PCOS. Although their primary focus was dysglycaemia, the included studies predominantly comprised reproductive-aged women, generally ranging from the late teens to the late 30s. Their pooled analysis demonstrated a significantly higher

prevalence of impaired glucose tolerance (OR = 3.26, 95% CI: 2.17-4.90) and type 2 diabetes mellitus (OR = 2.87, 95% CI: 1.44-5.72) in women with PCOS, with the risk being particularly elevated in Asian populations (up to fivefold). The age profile of participants across these studies closely overlaps with our study's mean age of 26.8 years, supporting that our study population lies within the age range most susceptible to both reproductive and metabolic complications of PCOS.

Pu Y et al,[13] (2023) in their casecontrol study involving 1,034 PCOS patients and 762 controls, evaluated genetic susceptibility to PCOS among reproductive-aged Chinese women. Their results showed that the TT + CT genotype frequency of the CYP2E1 C1054T polymorphism was 35.4% in PCOS cases compared to 28.9% in controls, with the T allele frequency being 19.6% versus 16.0%, respectively. Importantly, these associations remained statistically significant after adjustment for age and BMI, highlighting that PCOSrelated genetic risk is most relevant during the early and midreproductive years, which corresponds well with the age concentration observed in our study.

In the present study, the anthropometric profile demonstrated a substantial burden of excess body weight among participants. The mean height and weight were 158.6 + 5.4 cm and 66.2 + 9.1 kg, respectively, with a mean BMI of 26.4 ‡ 3.8 kg/m and a median BMI of 26.1 (IQR: 23.828.9). On BMI classification, 44.6% (n = 62) of participants were overweight and 27.3% (n = 38) were obese, while only 28.1% (n = 39) had a normal BMI. Overall, 71.9% (n =100) of the study population had BMI ≥ 25 kg/m2, indicating that nearly three quarters of the participants had excess body weight. These findings are consistent with large epidemiological and metaanalytical evidence highlighting obesity as a common and clinically relevant feature of polycystic ovary syndrome (PCOS). Similarly, Pu Y et al,[13] (2023) in a large case-control study including 1,034 PCOS patients and 762 controls, reported that BMI was a significant covariate when evaluating genetic susceptibility to PCOS. They observed that the frequency of the CYP2E1 C-1054T T allele was higher in PCOS women (19.6%) compared to controls (16.0%), and this association remained significant even after adjusting for BMI (adjusted OR 1.345; p =0.011). This indicates that excess body weight commonly coexists with PCOS and may interact with genetic risk factors, which aligns with the high prevalence of overweight and obesity observed in our study. Indian studies further support these findings.

The hormonal profile in the present study revealed marked endocrine imbalance. The mean serum LH level was 11.8 + 4.6 IU/L, while the mean serum FSH level was 5.4 + 2.1 IU/L, resulting in an elevated mean LH/FSH ratio of 2.1 + 1.2 with a median value of 2.1 (IQR: 1.7-2.6). Mean serum estrogen and androgen levels were 186.3 + 52.7 pg/mL and 78.6 - 21.4 ng/dL, respectively. These findings indicate gonadotropin dysregulation and biochemical hyper androgenism, which are hallmark features of PCOS. These results are well supported by existing literature. Dwivedi et al,[14] (2024) described that increased gonadotropin-releasing hormone pulse frequency in PCOS leads to preferential LH secretion, relative FSH deficiency, and enhanced ovarian androgen production. Their review emphasized that LH/FSH ratios greater than 2 are commonly observed in PCOS, which is consistent with the mean LH/FSH ratio of 2.1 noted in our study.

Pu Y et al,[13] (2023) also noted that hormonal and metabolic parameters remained clinically relevant predictors of PCOS even after adjustment for BMI and age, indicating that endocrine dysregulation persists independently but is often exacerbated by obesity.

In the present study, insulin resistance was identified in 58.3% (81/139) of participants, with a mean fasting insulin level of 18.9 + 6.7 µIU/mL and a median of 17.6 µIU/mL (IQR: 14.222.1). This finding indicates that more than half of the study population had impaired insulin sensitivity, emphasizing the strong metabolic component of the disease profile under investigation. These results are in close agreement with the metaanalysis by Kakoly NS et al,[12] (2018) which analyzed 40 high-quality studies and reported that women with PCOS had a significantly higher prevalence of dysglycemia, with an odds ratio of 3.26 for impaired glucose tolerance and 2.87 for type 2 diabetes mellitus compared to non PCOS women. Importantly, the authors demonstrated that Asian women exhibited the highest risk, with up to a fivefold increase in impaired glucose tolerance, even after adjustment for BMI. The insulin resistance prevalence of 58.3% observed in our study falls well within this high-risk range described in Asian populations.

In the present study, genotypic analysis revealed that 56.8% (79/139) of participants carried the wildtype CYP2E1 genotype, while 30.2% (42/139) were heterozygous and 13.0% (18/139) were homozygous for the polymorphic variant. Overall, 43.2% of the study population carried at least one variant allele, indicating a substantial prevalence of CYP2E1 polymorphism.

Comparable distributions have been reported in previous genetic association studies.

Further support for the relevance of CYP gene polymorphisms comes from Dwivedi J et al,[14] (2024) and Chaudhary H et al (2021), who highlighted that polymorphisms in cytochrome P450 genes involved in steroidogenesis are frequently observed in PCOS and contribute to phenotypic heterogeneity. The relatively high frequency of CYP2E1 polymorphism observed in our study aligns with these reports and supports the role of cytochrome P450 genetic variation in PCOS pathophysiology.

In our study, CYP2E1 polymorphic variant carriers demonstrated significantly altered hormonal profiles

compared to wildtype individuals. Mean serum LH levels were significantly higher in the polymorphic group (13.2 + 5.2 IU/L) compared with the wildtype group (10.5 + 3.7 IU/L; p = 0.02). Serum FSH levels were also higher (5.9 + 2.4 IU/L vs 5.0 = 1.8 I U/L; p = 0.03), resulting in a significantly elevated LH/FSH ratio (2.3 + 1.4 vs 2.0 + 1.1; p =0.02). Additionally, serum androgen levels were significantly increased in variant carriers (87.2 + 24.3 ng/dL) compared with wildtype individuals (72.6 + 18.9 ng/dL; p = 0.01).

Comparable complexity has been described by Sun Y et al,[15] (2019) who showed that oxidative stress-related gene polymorphisms were associated with androgen excess, whereas metabolic indices varied depending on gene gene interactions and BMI. Overall, our findings indicate that CYP2E1 polymorphism is significantly associated with elevated LH, LH/FSH ratio, and serum androgen levels, reinforcing its role in neuroendocrine imbalance and hyperandrogenism. When interpreted alongside existing genetic and metabolic studies, the results suggest that CYP2E1 polymorphism contributes meaningfully to hormonal heterogeneity in PCOS, while insulin resistance remains a multifactorial trait influenced by broader metabolic pathways.

In the present study, insulin resistance was observed in 58.3% (81/139) of PCOS subjects, while 41.7% (58/139) were insulin sensitive. The mean fasting insulin level in our study was 18.9 + 6.7 µIU/mL, with a median value of 17.6 µIU/mL (IQR: 14.222.1), indicating a high prevalence of hyperinsulinemia and metabolic dysfunction. These findings are compa rable to the large metaanalysis by Kakoly NS et al,[12] (2018) which included 40 quality studies and reported that women with PCOS had a 3.26 fold higher risk of impaired glucose tolerance and a 2.87 fold higher risk of type 2 diabetes mellitus compared to non PCOS women.

In our study, CYP2E1 polymorphic variant carriers showed significantly altered hormonal profiles compared to wildtype individuals. The mean serum LH level was 13.2 + 5.2 IU/L in variant carriers versus 10.5 + 3.7 IU/L in wildtype subjects (p = 0.02). Mean serum FSH levels were 5.9 + 2.4 IU/L in the variant group compared to 5.0 + 1.8 IU/L in the wild-type group (p = 0.03), resulting in a significantly higher LH/FSH ratio (2.3 + 1.4 vs 2.0 + 1.1; p = 0.02). Serum androgen levels were also significantly elevated in variant carriers (87.2 + 24.3 ng/dL) compared to wildtype subjects (72.6 + 18.9 ng/dL; p = 0.01). These findings are consistent with the genetic association study by Pu Y et al. (2023) who reported that the TT + CT genotype frequency of CYP2E1 polymorphism was 35.4% in PCOS women, compared to 28.9% in controls, and that the Tallele frequency was 19.6% in PCOS versus 16.0% in controls, with an adjusted odds ratio of 1.35 for PCOS. Their study demonstrated that CYP2E1 polymorphism remained a significant predictor of PCOS even after adjusting for age and BMI, suggesting a direct role in endocrine dysregulation. The higher LH levels, increased LH/FSH ratio, and elevated androgen concentrations observed in our variant genotype carriers align with these findings and support the hypothesis that CYP2E1 polymorphism contributes to hyperandrogenism and altered gonadotropin secretion, which are hallmark features of PCOS.

In the present study, insulin resistance was more prevalent among wild-type genotype carriers (64.6%) compared to CYP2E1 polymorphic variant carriers (50.0%), and this association was statistically significant (p = 0.01). This indicates that although CYP2E1 polymorphism is associated with significant hormonal alterations, its relationship with insulin resistance may be indirect or modulated by additional factors. While Pu Y et al,[13] (2023) did not report insulin resistance prevalence stratified by CYP2E1 genotype, they demonstrated that the association between CYP2E1 polymorphism and PCOS was independent of BMI, suggesting that the polymorphism primarily influences endocrine pathways rather than metabolic insulin sensitivity. This is consistent with our findings, where variant carriers exhibited more pronounced hormonal abnormalities but comparatively lower insulin resistance.

In the present study, BMI categories showed a statistically significant association with CYP2E1 genotype (x, P = 0.03). Normal BMI was observed in 35.4% (28/79) of wild-type subjects but only 18.3% (11/60) of variant genotype carriers. Overweight status was comparable between wildtype (43.0%) and variant genotypes (46.7%). However, obesity was substantially more prevalent among variant genotype carriers (35.0%, 21/60) compared to wild type subjects (21.6%, 17/79), indicating a genotypelinked predisposition to obesity in PCOS.

In this study, an elevated LH/FSH ratio (>2) was observed in 80.0% (48/60) of CYP

2E1 variant genotype carriers compared to 60.8% (48/79) of wild-type subjects, while a normal LH/FSH ratio (≤2) was more frequent in the wild type group (39.2% vs 20.0%). This association was statistically significant (p = 0.02), indicating greater gonadotropin imbalance among variant genotype carriers. These findings are in agreement with the pathophysiological mechanisms summarized by Dwivedi Jet al,[14] (2024) who described increased GRH pulse frequency and preferential LH secretion as central features of PCOS. Their review emphasized that CYP gene polymorphisms can exacerbate this imbalance by enhancing ovarian steroidogenesis, thereby increasing LH relative to FSH.

Although exact LH/FSH ratios were not numerically reported, the described endocrine profile aligns with the 80% prevalence of elevated LH/FSH ratio among variant carriers in our study. Our findings extend this observation to CYP2E1 polymorphism, providing direct quantitative evidence of its association with LH/FSH dysregulation.

Hyperandrogenism was present in 76.7% (46/60) of CYP2E1 variant genotype carriers comp ared to 54.4% (43/79) of wildtype subjects, while normal androgen levels were more commo n in the wildtype group (45.6% vs 23.3%). This association was statistically significant (p =0.01), indicating a strong link between CYP2E1 polymorphism and hyperandrogenic phenotype. Comparable findings were reported by Pu Y et al. (2023) who showed a significantly higher frequency of CYP2E1 TT + CT genotypes in PCOS patients (35.4%) than controls (28.9%), with genotype remaining an independent predictor of PCOS (adjusted OR 1.345,p = 0.011). Given that hyperandrogenism is a core feature of PCOS, their genetic association supports our observation of increased androgen excess among variant genotype carriers. Further corroboration comes from Kaur R et al. (2018) [16], who demonstrated a significant association between CYP17A1 -34T>C polymorphism and PCOS (p = 0.0005), along with higher BMI and triglyceride levels.

In the present study, insulin resistance severity differed significantly according to CYP2E1 genotype (p = 0.01). Normal insulin sensitivity was observed in 50.0% (30/60) of variant genotype carriers compared to 35.4% (28/79) of wild type subjects. Mild insulin resistance was more common in the wild-type group (43.0% vs 30.0%), while moderate-severe insulin resistance was similar between wildtype (21.6%) and variant genotype carriers (20.0%).

In the present study, age distribution was comparable between wildtype and variant CYP2E1 genotype groups (26.2 - 4.6 vs 27.6 + 5.2 years; p = 0.08), suggesting that age was not a confounding factor in genotype-phenotype associations. Variant genotype carriers demonstrated significantly higher adiposity, with a mean BMI of 27.3 + 4.1 kg/m2, compared to 25.7 + 3.4 kg/m2 in wildtype subjects (p = 0.02). This higher BMI in variant carriers was accompanied by significantly elevated gonadotropin levels, including LH (13.2 + 5.2 vs 10.5 + 3.7 IU/L;p = 0.02) and FSH (5.9 = 2.4 vs 5.0 + 1.8 IU/L; p = 0.03), indicating a more pronounced neuroendocrine imbalance. Serum androgen levels were markedly higher in variant genotype carriers (87.2 + 24.3 ng/dL) compared to wildtype individuals (72.6 + 18.9 ng/dL; p = 0.01), while fasting insulin levels were also significantly elevated (20.9 + 7.2 vs 17.3 + 5.8 µIU/mL; p = 0.01). Estrogen levels did not differ significantly between groups (181.5 + 50.2 vs 19 3.8 + 55.1 pg/mL; p = 0.08), suggesting that CYP2E1 variation predominantly influences an androgenic and metabolic pathways rather than estrogen synthesis. These findings are consistent with the large case-control study by Pu Yet al. (2023),[13] who reported that the TT + C T genotype frequency of CYP2E1 C1054T was significantly higher in PCOS patients (35.4 %) compared with controls (28.9%), with the variant genotype independently predicting PCOS even after adjusting for age and BMI (adjusted OR = 1.345; p = 0.011).

Although Pu Y et al,[13] (2023) primarily evaluated genotype frequency rather than phenotype distribution, they demonstrated a significantly higher prevalence of CYP2E1 TT + CT genotypes among PCOS patients, supporting a genetic contribution to disease severity. Their study reported that variant genotypes were associated with altered lipid parameters and oxidative stress markers, indirectly reflecting a more adverse metabolic phenotype.

Serum LH levels showed a moderate positive correlation with insulin resistance (r = 0.42; p< 0.001), while serum androgen levels exhibited a slightly stronger association (r = 0.46; P< 0.001). BMI demonstrated the strongest correlation with insulin resistance (r = 0.51; p < 0.001), underscoring the central role of adiposity in metabolic dysfunction among PCOS subjects. While their outcome measure focused on PCOS susceptibility rather than insulin resistance, our results demonstrate that CYP2E1 variants also significantly influence metabolic outcomes within affected individuals. The dominant effects of BMI and androgen excess observed in our regression model are consistent with Kakoly NS et al,[12] (2018) who emphasized obesity driven dysglycemia as a key determinant of metabolic morbidity in PCOS. Collectively, these data indicate that insulin resistance in PCOS is driven by a complex interaction between genetic predisposition (CYP2E1 polymorphism), increased adiposity, and androgen excess, with each component independently and synergistically worsening metabolic risk.

CONCLUSION

The findings of the present study demonstrate a significant association between CYP2E1 gene polymorphism and polycystic ovary syndrome, particularly with respect to hormonal imbalance and insulin resistance. The presence of CYP2E1 polymorphic variants was associated with higher BMI, increased LH/FSH ratio, elevated androgen levels, and greater risk of insulin resistance. These results suggest that CYP2E1 polymorphism may play an important role i n modulating the endocrine-metabolic phenotype of PCOS.

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