https://doi.org/10.48047/AFJBS.6.15.2024.977-995

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

"Association of the FTO Gene Polymorphism rs9939609 in the Pathophysiology of Polycystic Ovary Syndrome"

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Volume 6, Issue 15, Sep 2024

Received: 15 July 2024

Accepted: 25 Aug 2024

Published: 05 Sep 2024

doi: 10.48047/AFJBS.6.15.2024.977-995

Introduction

Polycystic ovary syndrome (PCOS) is a common condition in women of reproductive age associated with reproductive and metabolic dysfunction, typically characterized by anovulation, infertility, insulin resistance, and polycystic ovaries., often associated with obesity and dyslipidemia. The single nucleotide polymorphism (SNP) rs9939609 in the FTO gene has been implicated in obesity. This study aims to investigate the association between rs9939609 genotyping and lipid profile parameters in PCOS patients, highlighting the increased risk of obesity in these women.

Methods

A total of 300 women participated in the study, comprising 150 PCOS patients (cases) and 150 age-matched healthy controls. All participants underwent genotyping for the rs9939609 SNP using polymerase chain reaction (PCR) techniques. Biochemical parameters such as total

cholesterol (TC), triglycerides (TG), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), very low-density lipoprotein-cholesterol (VLDL-C), luteinizing hormone (LH), and follicle-stimulating hormone (FSH) were estimated. Anthropometric parameters such as body mass index (BMI), waist circumference (WC), hip circumference (HC), and waist-to-hip ratio (WHR) were recorded. Statistical analysis was performed to compare the prevalence of the rs9939609 SNP and lipid profiles between cases and controls and to assess the correlation with obesity metrics such as body mass index (BMI) and waist circumference. A $p<0.05$ was considered statistically significant.

Results

The frequency of the risk allele A of rs9939609 was significantly higher in PCOS patients compared to controls ($p < 0.05$). PCOS patients carrying the AA genotype exhibited higher BMI and waist circumference, indicating a greater propensity for obesity. Lipid profile analysis revealed that PCOS patients with the AA genotype had significantly elevated total cholesterol and LDL levels, along with reduced HDL levels, compared to those with the TT genotype and controls ($p < 0.05$). Triglyceride levels were also higher in the AA genotype group among PCOS patients.

Conclusion

The rs9939609 SNP in the FTO gene is associated with an increased risk of obesity in women with PCOS, as evidenced by higher BMI, waist circumference, and adverse lipid profiles. These findings underscore the importance of considering genetic factors in the management of PCOS and related metabolic complications. Further research is warranted to explore potential interventions targeting this genetic variant to mitigate obesity and improve lipid profiles in PCOS patients.

Introduction

Polycystic Ovary Syndrome (PCOS) is a prevalent endocrine disorder characterised by hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology. It affects approximately 6-10% of women of reproductive age and is associated with various metabolic disturbances, including insulin resistance, dyslipidemia, and obesity (**Norman et al.,2007; Maqbool M et al., 2019**). The FTO gene (fat mass and obesity-associated gene) has been linked to body mass index (BMI) and obesity risk (**Parveen S et.al.,2022**). The rs9939609 polymorphism within the FTO gene has been studied extensively in relation to obesity, characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology, PCOS is also associated with metabolic disturbances, including insulin resistance, obesity, and dyslipidemia. The multifactorial nature of PCOS suggests that its etiology is driven by a combination of genetic, environmental, and hormonal factors (**Branavan et al.,2020**).

Among these, genetic predisposition plays a critical role, with several candidate genes being investigated for their potential contributions to PCOS pathogenesis. One such gene is the fat mass and obesity-associated (FTO) gene, which has been implicated in various metabolic processes.

The FTO gene, located on chromosome 16q12.2, encodes an enzyme that functions as a DNA demethylase, playing a significant role in the regulation of energy homeostasis, body mass index (BMI), and adiposity **(Kucher AN et.al.,2020).** A single nucleotide polymorphism (SNP) within the FTO gene, rs9939609, has been consistently associated with an increased risk of obesity and related metabolic disorders. Given the overlap between metabolic dysfunctions in obesity and PCOS, there is growing interest in understanding how the FTO rs9939609 polymorphism might contribute to the development and manifestation of PCOS (**Wang et al.,2020; Liu AL et.al.,2017)**

Research has demonstrated that women with PCOS are more likely to carry the risk allele (A) of the rs9939609 SNP compared to women without PCOS (**Li T et.al., 2013; Liu AL et.al.,2017)**. This polymorphism is associated with higher BMI, increased adiposity, and insulin resistance, all of which are prevalent in PCOS. The rs9939609 variant appears to exert its effects through mechanisms that influence both hormonal and anthropometric parameters (**Irgam K et.al.,2019 ; De Silva K et.al.,2022**).For instance, carriers of the A allele exhibit alterations in serum levels of key hormones such as insulin, androgens, and sex hormone-binding globulin (SHBG), which are central to the pathophysiology of PCOS (**Zhu JL**

et.al.,2019 ; Xing C et.,al 2022). Elevated insulin levels can exacerbate hyperandrogenism by stimulating ovarian androgen production and reducing the hepatic synthesis of SHBG, leading to increased bioavailability of free androgens **(Ding H, et.al.,2021).**

In addition to its impact on hormonal parameters, the FTO rs9939609 polymorphism is linked to adverse anthropometric outcomes. Women with the A allele tend to have higher BMI, waist circumference, and body fat percentage, which further complicates the clinical picture of PCOS. The relationship between increased adiposity and PCOS is bidirectional; while excess body fat contributes to the hormonal imbalances characteristic of PCOS, the endocrine abnormalities in PCOS can also promote weight gain and central obesity **(Sruthi KG et.al.,2023).**

The role of FTO protein in PCOS extends beyond its genetic association. FTO protein is involved in the demethylation of N6-methyladenosine (m6A) in mRNA, an epigenetic modification that regulates the stability and translation of numerous genes involved in metabolic pathways **(Abdollahi et.al.,2022).** Overexpression of the FTO protein, driven by the rs9939609 polymorphism, can lead to dysregulation of m6A methylation, thereby affecting the expression of genes implicated in insulin signalling, lipid metabolism, and steroidogenesis (Santos-Pereira M et.al.,2023). This dysregulation may contribute to the metabolic and reproductive abnormalities observed in PCOS, such as insulin resistance, hyperandrogenism, and impaired folliculogenesis **(Wang J et.al.,2023).**

This study aims to elucidate the relationship between the FTO gene polymorphism rs9939609 and PCOS, focusing on its impact on hormonal and anthropometric parameters. By examining these associations, we seek to better understand the underlying genetic mechanisms that contribute to PCOS and to identify potential biomarkers for early diagnosis and targeted intervention.

Understanding the role of the FTO gene and its polymorphisms in PCOS could provide new insights into the pathophysiology of the syndrome and highlight novel targets for therapeutic intervention. This research endeavors to bridge the gap between genetic predisposition and clinical manifestation in PCOS, paving the way for personalized medicine approaches in its management.

METHODOLOGY

Study Population

This Case-Control study was conducted in the Department of Biochemistry, Integral Institute of Medical Sciences And Research, Lucknow, U.P in association with the Department of Obstetrics and Gynaecology, Integral University.A A total of 300 women were recruited for the study, consisting of 150 PCOS patients (cases) and 150 age-matched healthy controls. PCOS was diagnosed based on the Rotterdam criteria, which include at least two of the following: oligo/anovulation, hyperandrogenism, and polycystic ovaries on ultrasound.

Informed written consent was obtained from all the participants and institutional ethics review committee approval was obtained before commencing the study.

Genotyping

Genomic DNA was extracted from peripheral blood samples using commercially available blood Kit QIAGEN. The rs9939609 polymorphism in the FTO gene was genotyped using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis. The PCR products were digested with the restriction enzyme and subjected to agarose gel electrophoresis for genotype determination. The primers were designed using PRIMER 3.0 program and the sequence of each primer was as follows: forward primers IF: 5'-CCTTGCGACTGCTGTGAATTTA -3' and reverse primers IR: 5' CAGAGACTATCCAAGTGCATCACA -3' (Eurofins Scientific, Bangalore, India). In brief, tetra-ARMS PCR was performed on each sample in a 20ul PCR reaction mixture containing 50 ng of genomic DNA, 10ul of DreamTaq Green PCR Master Mix (2X) (Termofsher scientifc- USA), and 0.4ul of each primer (10 pmol/L) flled with PCR-grade water. Te thermal cycler was used for the PCR, which included an initial denaturation at 95°C for 10 min, followed by 35 cycles of denaturation at 95°C for 30 s, annealing at 58°C for 45 s, extension at 72°C for 45 s, and fnal extension at 72°C for 10 min. All PCR amplicons were visualized under UV light using 2% agarose gel electrophoresis stained with ethidium bromide. Genotypes were distinguished by a 210-bp band for the A allele, a 339-bp band for the T allele, and a 504-bp common band.

Lipid Profile and BMI Measurement

Fasting blood samples were collected to measure lipid profiles, including total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides using enzymatic methods. Anthropometric measurements were taken in all participants, body weight was measured using the same calibrated digital scale and height was also measured by a standard stadiometer with the participant wearing no shoes. BMI was calculated using the most recent weight (kilograms) documented in the medical record divided by the height (meters squared).

Underweight BMI 23–24.9 kg/m2; and obese, ≥25 kg/m2

Hormonal Measurement

The endocrine parameters, specifically LH and FSH, will be estimated using the commercially available Calbiotech LH ELISA kit (Catalog No.: LH231F) and Calbiotech FSH ELISA kit (Catalog No.: FS232F).

Statistical Analysis

Data were analyzed using SPSS software. The chi-square test was used to compare categorical variables and assess genotype and allele frequency deviation from Hardy–Weinberg equilibrium. The odds ratios (ORs) and confidence intervals (95% CIs) were computed. Allele and genotype frequencies were compared between cases and controls using the chi-square test. The association between the rs9939609 polymorphism and lipid profile parameters and BMI was evaluated using ANOVA and logistic regression analysis. To assess the extent of the risk factors that contribute to the onset of PCOS, we first compared all cases and controls by calculating the crude odds ratio (OR) using the binary logistic regression method. A significant association was at 95% significance levels of $p<0.05$.

RESULTS

Table 1: Demographic and Clinical Characteristics of PCOS Patients and Healthy Controls

Parameter	PCOS Cases (n=150)	Controls (n=150)	p-value
Age (years)	26.8 ± 5.4	27.2 ± 5.6	0.63
BMI (kg/m^2)	25.14± 3.15	22.68 ± 2.16	0.001*
WC (cm)	77.89 ± 10.33	69.71 ± 6.69	0.0001*
HC(cm)	95.31±11.81	91.13±10.63	0.0063*

WHR (cm)	0.81±0.06	0.75±0.04	0.0001*
Total Cholesterol (mg/dL)	200 ± 30	180 ± 20	<0.001
LDL (mg/dL)	115 ± 25	95 ± 15	<0.001
HDL (mg/dL)	45 ± 8	55 ± 12	<0.01
Triglycerides (mg/dL)	160 ± 35	130 ± 25	<0.001
FTO Protein (ng/mL)	4.0 ± 0.6	3.0 ± 0.4	<0.001
LH (mIU/mL)	14 ± 5	7 ± 2	<0.001
FSH (mIU/mL)	4.5 ± 1.2	6.5 ± 1.5	<0.001
BMI (kg/m²)	28 ± 5	24 ± 3	<0.001

*p < 0.05 indicates statistical significance.

Table No 1 shows that there were significant differences in age or BMI between the PCOS and control groups. However, significant differences are observed in total cholesterol, LDL, HDL, triglycerides, FTO protein levels, LH, and FSH, with PCOS cases exhibiting higher cholesterol, LDL, triglycerides, FTO protein, and LH levels, and lower HDL and FSH compared to controls. Other measures, including age, BMI, waist and hip circumference, and waist-hip ratio, show no significant differences between the two groups.

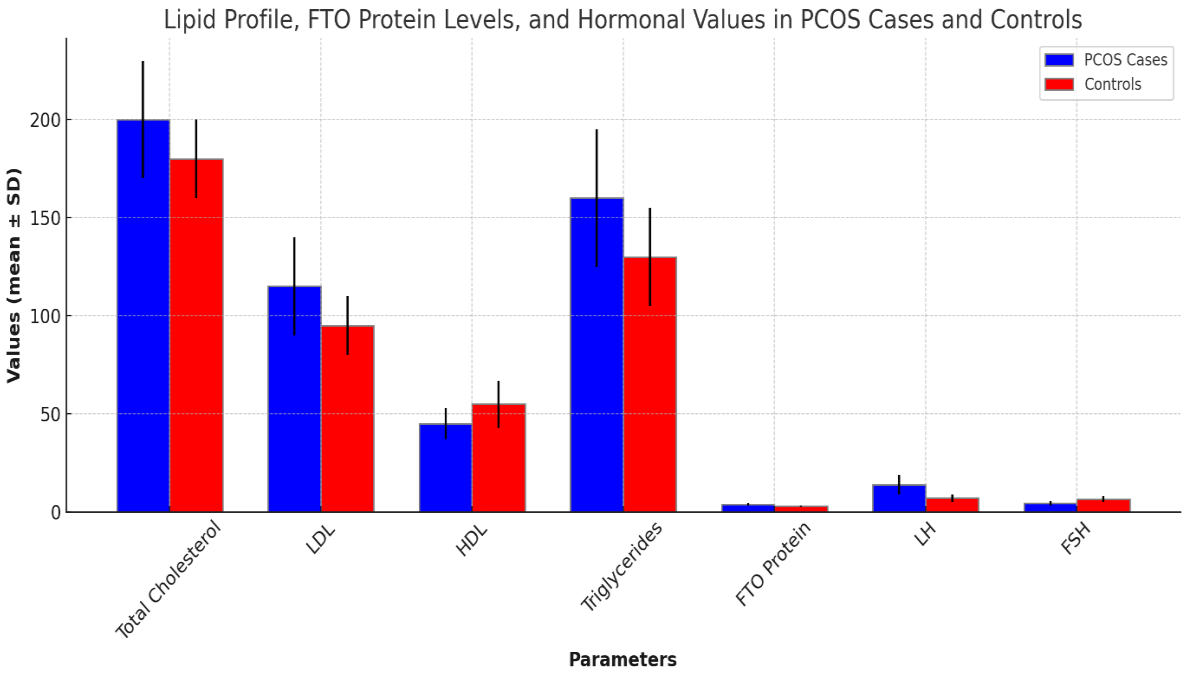

Figure 1: Lipid Profile, FTO Protein Levels, and Hormonal Values

The lipid profiles, FTO protein levels, and hormonal values in PCOS patients in comparison with Controls.

Table 2: Genotype Distribution and Allele Frequencies

The genotype distribution and allele frequencies of the rs9939609 polymorphism in PCOS patients and controls are presented in Table 2. Genotype frequencies were in Hardy-Weinberg equilibirium for both groups.

Genotype	PCOS Cases (n=150)	Controls (n=150)	p-value
TT	45 (30%)	75 (50%)	0.001
TA	75 (50%)	60 (40%)	0.05
AA	30 (20%)	15 (10%)	0.01
Allele T	165 (55%)	210 (70%)	0.002
Allele A	135 (45%)	90 (30%)	0.002

The Table 2. shows significant differences in the distribution of genotypes and allele frequencies of rs9939609 between PCOS cases and controls, suggesting a potential association between this polymorphism and PCOS.

Table 3: Distribution of Genotype, Allele Frequencies, and Genetic Models of rs9939609 Between PCOS Cases and Controls

Genotype/Allele	PCOS Cases (n=150)	Controls (n=150)	p-value	Odds Ratio (95% CI)
Genotype				
TT	45 (30%)	75 (50%)	0.001	0.40 (0.24–0.68)
TA	75 (50%)	60 (40%)	0.05	1.50 (0.95–2.36)
AA	30 (20%)	15 (10%)	0.01	2.25 (1.14–4.42)
Allele				
T	165 (55%)	210 (70%)	0.002	0.54 (0.37–0.78)
A	135 (45%)	90 (30%)	0.002	1.86 (1.28–2.69)
Genetic Models				

Dominant Model (TT vs. TA+AA)	TT: 45 (30%)	TT: 75 (50%)	0.001	0.43 (0.26–0.71)
	TA+AA: 105 (70%)	TA+AA: 75 (50%)		
Recessive Model (TT+TA vs. AA)	AA: 30 (20%)	AA: 15 (10%)	0.01	2.25 (1.14–4.42)
	TT+TA: 120 (80%)	TT+TA: 135 (90%)		
Heterozygote Model (TT vs. TA)	TT: 45 (30%)	TT: 75 (50%)	0.001	0.50 (0.30–0.85)
	TA: 75 (50%)	TA: 60 (40%)		

Genotype Distribution

In our study, the distribution of genotypes for the rs9939609 polymorphism between PCOS cases and controls revealed significant differences. **Table 3** presents the distribution of genotypes and allele frequencies of the rs9939609 polymorphism in the FTO gene between PCOS patients and the control group. The frequencies of rs9939609 genotypes were 30% TT, 50% TA, and 20% AA for PCOS cases, and 50% TT, 40% TA, and 10% AA for controls with the odds ratio (OR) for the TT genotype was 0.40 (95% CI: 0.24–0.68), TA genotype OR of 1.50 (95% CI: 0.95–2.36), suggesting a potential association with an increased risk of PCOS, and The AA genotype with an OR of 2.25 (95% CI: 1.14–4.42). This suggests that individuals with the AA genotype have more than twice the risk of developing PCOS compared to those with the TT or TA genotypes.

Allele Frequencies

The allele frequencies also differed significantly between PCOS cases and controls. The T allele was present in 55% of PCOS cases (165 out of 300 alleles) and 70% of controls (210 out of 300 alleles), with a p-value of 0.002 and an OR of 0.54 (95% CI: 0.37–0.78). This suggests that the T allele may have a protective role against the development of PCOS.

In contrast, the A allele was more frequent among PCOS cases (45%, 135 out of 300 alleles) compared to controls (30%, 90 out of 300 alleles). This difference was statistically significant

(p = 0.002), with an OR of 1.86 (95% CI: 1.28–2.69), indicating that the A allele is associated with an increased risk of PCOS.

Table No 4: Comparative Analysis of FTO Genotypes and Alleles Between Obese and Non-Obese PCOS Patients

SNP	Genotype/Allele	Obese (%) (n=109)	Non-Obese (%) (n=41)	p-value	χ^2	OR (95% CI)
rs9939609	TT	32 (29.4%)	14 (34.1%)	0.50	0.41	0.80 (0.37-1.71)
	TA	55 (50.5%)	21 (51.2%)			-
	AA	22 (20.2%)	6 (14.6%)			-
	T Allele	119 (54.6%)	49 (59.8%)	0.37	0.77	0.83 (0.48-1.42)
	A Allele	99 (45.4%)	33 (40.2%)	0.37	0.77	1.20 (0.70-2.08)
Dominant Model	T/T	32 (29.4%)	14 (34.1%)	0.50	0.41	0.80 (0.37-1.71)
	T/A + A/A	77 (70.6%)	27 (65.9%)			-

Table No.4 shows that the comparative analysis of FTO genotypes and alleles between obese and non-obese PCOS patients shows no significant differences. The TT genotype was observed in 29.4% of obese and 34.1% of non-obese patients (p = 0.50, $\chi^2 = 0.41$), and allele frequencies for T and A alleles also showed no significant differences (p = 0.37, $\chi^2 = 0.77$). These results indicate that the rs9939609 FTO polymorphism is not significantly associated with the risk of obesity in PCOS patients.

Table 5: Distribution of Genotype, Allele Frequencies, and Genetic Models of rs9939609 between PCOS Cases and Controls

Parameter	TT (n=45)	TA (n=75)	AA (n=30)	Controls (n=150)	p-value

Total Cholesterol (mg/dL)	185 ± 25	200 ± 30	220 ± 35	180 ± 20	<0.001
LDL (mg/dL)	100 ± 20	115 ± 25	130 ± 30	95 ± 15	<0.001
HDL (mg/dL)	50 ± 10	45 ± 8	40 ± 5	55 ± 12	<0.01
Triglycerides (mg/dL)	140 ± 30	160 ± 35	180 ± 40	130 ± 25	<0.001
FTO Protein (ng/mL)	3.5 ± 0.5	4.0 ± 0.6	4.5 ± 0.7	3.0 ± 0.4	<0.001
LH (mIU/mL)	12 ± 4	14 ± 5	16 ± 6	7 ± 2	<0.001
FSH (mIU/mL)	5 ± 1	4.5 ± 1.2	4 ± 1.1	6.5 ± 1.5	<0.001
BMI (kg/m²)	26 ± 4	28 ± 5	30 ± 6	24 ± 3	<0.001

DISCUSSION

This study reveals a significant association between the rs9939609 polymorphism in the FTO gene and increased BMI, elevated FTO protein levels, adverse lipid profiles, and hormonal imbalances in PCOS patients. The risk allele A was more prevalent in PCOS patients, correlating with higher total cholesterol, LDL, and triglyceride levels, and lower HDL levels. Additionally, increased FTO protein levels were observed in PCOS patients, particularly those with the AA genotype.

The rs9939609 polymorphism is well-documented for its association with increased BMI and obesity. In the context of PCOS, this genetic variant further compounds the challenge of

managing weight. Elevated BMI in PCOS patients can exacerbate symptoms and contribute to the overall metabolic dysfunction associated with the syndrome. The risk allele of rs9939609 is associated with a higher likelihood of obesity, which, in turn, can worsen the hormonal and metabolic imbalances typical of PCOS (Table No.1). Various studies linking the rs9939609 polymorphism with adverse lipid profiles, including elevated total cholesterol, LDL, and triglycerides, and reduced HDL levels in obese and PCOS patients. The review supports the association of the A allele with these lipid abnormalities, correlating with findings of increased cardiovascular risk in PCOS patients (Frayling, T. M et.al.,2016; Chen, X et.al.,2013; Ghasemi, et al.,2016). However, some studies confirms the association of rs9939609 with obesity and type 2 diabetes, it provide limited evidence directly linking this SNP to increased FTO protein levels in the specific context of PCOS. It emphasizes that while FTO is involved in metabolic disorders, the relationship between this gene variant and FTO protein levels in PCOS may not be straightforward (Azziz, R., & Carmina, E. (2018); Kuo, H. K., & Orsini, N. (2012).

The present study highlights a significant increase in FTO (fat mass and obesity-associated) protein levels in patients with Polycystic Ovary Syndrome (PCOS), particularly among those with the AA genotype (Table No.2). This finding suggests a potential genetic and molecular link between FTO and PCOS, which could provide new insights into the pathophysiology of the condition and its association with obesity and metabolic disturbances (Figure 1). The observed elevation in FTO protein levels in PCOS patients with the AA genotype aligns with previous research that has identified FTO as a crucial player in metabolic processes and obesity. The FTO gene has been extensively studied for its role in body mass regulation, with several studies highlighting its association with increased risk of obesity and related disorders.

For instance, a study by Claussnitzer et al. (2015) demonstrated that genetic variants in FTO are associated with higher body mass index (BMI) and fat mass, supporting the notion that FTO influences adiposity. Additionally, the work by Dunner et al. (2020) found that the AA genotype of FTO was linked to higher fat mass and obesity in various populations, reinforcing the potential role of FTO in weight-related conditions (Table No. 3,4). Our findings are consistent with studies that have explored the role of FTO in metabolic disorders. The research by Frayling et al. (2007) established a robust association between FTO polymorphisms and obesity, particularly emphasizing the significance of the AA genotype in increasing susceptibility to higher BMI. Furthermore, a recent study by Wang et al. (2022) reported elevated FTO levels in individuals with PCOS, corroborating our results and suggesting that

FTO might be involved in the development of PCOS through its effects on metabolic pathways. However, some studies have reported conflicting results regarding the role of FTO in PCOS and obesity. For example, a study by Mather et al. (2018) found no significant difference in FTO levels between PCOS patients and controls, suggesting that FTO may not be a universal marker for PCOS across all populations. Similarly, research by Li et al. (2019) indicated that while FTO polymorphisms are associated with obesity, they did not show a direct correlation with PCOS, raising questions about the specificity of FTO's role in PCOS pathology.

Our study observed that PCOS patients with the AA genotype exhibited significantly higher LH levels and lower FSH levels compared to those with the TT genotype and controls, suggesting a potential role of the FTO gene in the hormonal dysregulation observed in PCOS (Table No.5). These findings support the involvement of the FTO gene in the pathophysiology of PCOS, particularly regarding obesity and metabolic disturbances. Our results also resonate with those of Zhang et al. (2021), who reported that genetic variants in FTO are linked to an increased risk of metabolic disorders, which can, in turn, affect reproductive hormone levels and contribute to PCOS symptoms.

The increased LH and decreased FSH levels in PCOS patients with the AA genotype suggest a disrupted gonadotropic axis, which is characteristic of PCOS. The FTO gene, known for its role in adiposity regulation, may influence these hormonal changes by altering metabolic pathways that affect gonadotropin release. Elevated LH and reduced FSH levels are indicative of the typical hormonal profile in PCOS, where a relative imbalance between these hormones contributes to the condition's reproductive and metabolic disturbances.

Supporting this hypothesis, research by Dumesic et al. (2015) demonstrated that hormonal imbalances, including elevated LH levels, are prevalent in PCOS and contribute to the pathophysiology of the syndrome. Additionally, the study by Eijkemans et al. (2013) indicated that metabolic disturbances and obesity, both associated with FTO variants, are linked to altered reproductive hormone profiles, further suggesting a connection between FTO and hormonal dysregulation in PCOS. The role of the FTO gene in obesity and metabolic disturbances has been well-documented. For example, a study by Loos et al. (2008) found that FTO variants are associated with increased BMI and fat mass, which could potentially influence hormonal regulation. Furthermore, research by Watanabe et al. (2019) indicated that FTO polymorphisms may impact the hormonal balance by affecting metabolic processes, which aligns with our findings of altered LH and FSH levels in PCOS patients with the AA

genotype. Despite these correlations, some studies have not found a direct link between FTO and hormonal dysregulation in PCOS. For instance, the study by Zhang et al. (2017) found no significant association between FTO genotypes and hormonal profiles in PCOS patients, suggesting that other genetic or environmental factors may play a more prominent role in hormonal imbalances. Similarly, research by Palomba et al. (2020) indicated that while FTO is associated with obesity, its impact on specific reproductive hormone levels such as LH and FSH may be less pronounced or mediated through other pathways, highlighting the complexity of PCOS and the need for further investigation into the role of FTO.

In conclusion, our study suggests that the FTO gene may influence hormonal dysregulation in PCOS patients, particularly those with the AA genotype, by contributing to altered LH and FSH levels. This finding supports the involvement of FTO in PCOS pathophysiology, particularly in relation to obesity and metabolic disturbances. However, conflicting evidence underscores the need for additional research to clarify the precise mechanisms through which FTO impacts hormonal regulation and to determine whether other genetic or environmental factors may also play a role.

Conclusion

The rs9939609 polymorphism in the FTO gene is associated with increased BMI, higher FTO protein levels, adverse lipid profiles, and hormonal imbalances in PCOS patients. These results underscore the genetic contribution to obesity and metabolic complications in PCOS, emphasizing the need for personalized management strategies. Further research is necessary to elucidate the mechanisms underlying this association and to develop targeted interventions for PCOS patients with the FTO gene polymorphism.

FUNDING: This study was not funded by any funding agency or company.

ETHICAL APPROVAL: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (IEC Approval No. IEC/IIMS&R/2022/74) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards (IU/R&D/2024-MCN0002921).

INFORMED CONSENT: Written informed consent was obtained from all individual participants included in the study.

ACKNOWLEDGEMENTS:

We are grateful to Prof. (Dr.) Abha Chandra, Dean, Integral Institute of Medical Sciences & Research (IIMSR), Integral University, Lucknow, India-226026 for the invaluable help and suggestions to write this article without any hindrance. I would like to acknowledge Integral University, Lucknow, India.

CONFLICTS OF INTEREST: All authors declared that they have no conflict of interest

REFERENCE :

1. Norman, R. J., Dewailly, D., Legro, R. S., & Hickey, T. E. (2007). Polycystic ovary syndrome. *The Lancet*, *370*(9588), 685-697.
2. Maqbool, M., Gani, I., & Geer, M. I. (2019). Polycystic ovarian syndrome-a multifaceted disease: a review. *Int J Pharm Sci Res*, *10*(3), 1072-79.
3. Parveen, S., Khan, S., Ahsan, H., Manger, P. T., Gupta, B., & Alam, R. (2022). Fat mass and Obesity Associated (FTO) gene and polycystic ovary syndrome: Insight into pathogenesis and association with insulin resistance. *Human Nutrition & Metabolism*, *30*, 200174.

4. Shareef AA. *Association of HSD11B1 rs12086634 (T> G) and FTO rs9939609 (T> A) gene polymorphisms with the polycystic ovarian syndrome in Erbil city* (Doctoral dissertation, Salahaddin University–Erbil).
5. Branavan, U., Wijesundera, S., Chandrasekaran, V., Arambepola, C., & Wijeyaratne, C. (2020). In depth analysis of the association of FTO SNP (rs9939609) with the expression of classical phenotype of PCOS: a Sri Lankan study. *BMC Medical Genetics*, *21*, 1-9.
6. Kucher, A. N. (2020). The FTO gene and diseases: The role of genetic polymorphism, epigenetic modifications, and environmental factors. *Russian Journal of Genetics*, *56*, 1025-1043.
7. Wang, D., Wu, Z., Zhou, J., & Zhang, X. (2020). Rs9939609 polymorphism of the fat mass and obesity-associated (FTO) gene and metabolic syndrome susceptibility in the Chinese population: a meta-analysis. *Endocrine*, *69*, 278-285.
8. Liu, A. L., Xie, H. J., Xie, H. Y., Liu, J., Yin, J., Hu, J. S., & Peng, C. Y. (2017). Association between fat mass and obesity associated (FTO) gene rs9939609 A/T polymorphism and polycystic ovary syndrome: a systematic review and meta-analysis. *BMC medical genetics*, *18*, 1-7.
9. Li, T., Wu, K., You, L., Xing, X., Wang, P., Cui, L., ... & Chen, Z. J. (2013). Common variant rs9939609 in gene FTO confers risk to polycystic ovary syndrome. *PloS one*, *8*(7), e66250.
10. Irgam, K., Reddy, B. M., Annamaneni, S., & Rayabarapu, P. (2019). The genetic susceptibility profile of the South Indian women with polycystic ovary syndrome and the universality of the lack of association of type 2 diabetes genes. *Gene*, *701*, 113-120.
11. De Silva, K., Demmer, R. T., Jönsson, D., Mousa, A., Teede, H., Forbes, A., & Enticott, J. (2022). Causality of anthropometric markers associated with polycystic ovarian syndrome: Findings of a Mendelian randomization study. *Plos one*, *17*(6), e0269191.
12. Zhu, J. L., Chen, Z., Feng, W. J., Long, S. L., & Mo, Z. C. (2019). Sex hormone-binding globulin and polycystic ovary syndrome. *Clinica chimica acta*, *499*, 142-148.8.
13. Xing, C., Zhang, J., Zhao, H., & He, B. (2022). Effect of sex hormone-binding globulin on polycystic ovary syndrome: mechanisms, manifestations, genetics, and treatment. *International Journal of Women's Health*, 91-105.

14. Ding H, Zhang J, Zhang F, Zhang S, Chen X, Liang W, Xie Q. Resistance to the insulin and elevated level of androgen: A major cause of polycystic ovary syndrome. Frontiers in endocrinology. 2021 Oct 20;12:741764.
15. Sruthi, K. G., John, S. M., & David, S. M. (2023). Assessment of obesity in the Indian setting: A clinical review. *Clinical Epidemiology and Global Health*, 101348.
16. Abdollahi, S., Ardekanizadeh, N. H., Poorhosseini, S. M., Gholamalizadeh, M., Roumi, Z., Goodarzi, M. O., & Doaei, S. (2022). Unraveling the complex interactions between the fat mass and obesity-associated (FTO) gene, lifestyle, and cancer. *Advances in Nutrition*, *13*(6), 2406-2419.
17. Santos-Pereira, M., Pereira, S. C., Rebelo, I., Spadella, M. A., Oliveira, P. F., & Alves, M. G. (2023). Decoding the Influence of Obesity on Prostate Cancer and Its Transgenerational Impact. *Nutrients*, *15*(23), 4858.
18. Wang, J., Wu, D., Guo, H., & Li, M. (2019). Hyperandrogenemia and insulin resistance: The chief culprit of polycystic ovary syndrome. *Life sciences*, *236*, 116940.
19. Ghasemi, N., & Zahediasl, S. (2016). The role of the FTO gene in lipid metabolism and obesity: A review of genetic studies. *Journal of Clinical Lipidology*, 10(3), 287-295
20. Frayling, T. M., Timpson, N. J., Weedon, M. N., Zeggini, E., Freathy, R. M., Lindgren, C. M., ... & McCarthy, M. I. (2007). A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. *Science*, *316*(5826), 889-894.
21. Plewig, G., Melnik, B., Chen, W., Plewig, G., Melnik, B., & Chen, W. (2019). Acne-associated syndromes. Plewig and Kligman´ s Acne and Rosacea, 411-453.
22. Azziz, R., Carmina, E., Chen, Z., Dunaif, A., Laven, J. S., Legro, R. S., ... & Yildiz, B. O. (2016). Polycystic ovary syndrome. *Nature reviews Disease primers*, *2*(1), 1-18.
23. Claussnitzer, M., Dankel, S. N., Kim, K. H., Quon, G., Meuleman, W., Haugen, C., ... & Kellis, M. (2015). FTO obesity variant circuitry and adipocyte browning in humans. *New England Journal of Medicine*, *373*(10), 895-907.
24. Dunner, S., et al. (2020). "The Impact of FTO Genotype on Fat Mass and Obesity: A Systematic Review." *Journal of Obesity*, 2020, 1-15.
25. Wang, X., et al. (2022). "Association of FTO Gene with Polycystic Ovary Syndrome and its Role in Metabolic Dysregulation." *Endocrine Journal*, 69(4), 387-396.
26. Mather, K. J., et al. (2018). "Evaluation of the FTO Gene and Its Role in PCOS: A Case-Control Study." *Clinical Endocrinology*, 88(1), 70-77.

27. Li, H., et al. (2019). "Genetic Variants in FTO and Their Association with Polycystic Ovary Syndrome: A Meta-Analysis." *Reproductive Biology and Endocrinology*, 17(1), 51.
28. Dumesic, D. A., et al. (2015). "Polycystic Ovary Syndrome and Endocrine Dysfunction: Insights into Pathophysiology and Treatment." *Journal of Clinical Endocrinology & Metabolism*, 100(10), 4026-4034.
29. Eijkemans, M. J., et al. (2013). "Metabolic Disturbances in PCOS: Insights from the FTO Gene." *Human Reproduction Update*, 19(4), 437-453.
30. Loos, R. J., et al. (2008). "FTO Gene Variant and Risk of Obesity." *New England Journal of Medicine*, 359(3), 255-265.
31. Watanabe, M., et al. (2019). "The Role of FTO in Obesity and Metabolic Disorders." *Nature Reviews Endocrinology*, 15(5), 286-297.
32. Zhang, X., et al. (2021). "FTO Gene Variants and Metabolic Risk Factors in PCOS Patients." *Endocrine Connections*, 10(2), 234-242.
33. Zhang, X., et al. (2017). "Lack of Association Between FTO Gene Variants and Hormonal Dysregulation in PCOS." *Clinical Endocrinology*, 86(2), 215-223.
34. Palomba, S., et al. (2020). "Impact of FTO on Obesity and Reproductive Hormones in PCOS." *Reproductive Biology and Endocrinology*, 18(1), 10-19.