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High Fat Mass Index is Associated with Endometrial Hyperplasia in Polycystic Ovary Syndrome Patients: A Retrospective Study

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Aim: To assess body composition, glucolipid metabolism, and uric acid levels in PCOS (Polycystic Ovary Syndrome) patients to determine their relationship with the risk of endometrial hyperplasia (EH).

Methods: A total of 232 patients were included and divided into groups according to whether they had PCOS and endometrial pathology (Group A: non-PCOS and normal endometrium; Group B: PCOS and normal endometrium; Group C: non-PCOS and EH; Group D: PCOS and EH). Body composition differences between groups and correlations between body composition, glucolipid metabolism, and uric acid levels were analyzed.

Results: In Group D, the patient's PSM (Percent Skeletal Muscle) of Trunk, PBF (Percent Body Fat) of Arm, free mass index, FMI (Fat Mass Index), and appendicular skeletal muscle mass index were significantly higher than in Groups A, B, and C. Waist-hip rate, PBF, PBF of Trunk, PSM of Leg, skeletal muscle mass index and visceral fat level were significantly higher than in Groups A and B. FMI was an independent risk factor for EH in PCOS patients, the AUC for FMI prediction of endometrial hyperplasia in PCOS patients was 0.82. FMI had significant positive correlations with fasting glucose, fasting insulin, HOMA-IR (Homeostatic Model Assessment for Insulin Resistance), total cholesterol, triglyceride, low-density lipoprotein, triglyceride/high-density lipoprotein, and uric acid levels. FMI was correlated with HOMA-IR and uric acid at 0.602 and 0.649 respectively in PCOS patients.

Conclusion: Increased FMI and altered glucolipid metabolism as key factors associated with a higher risk of EH in patients with PCOS. Monitoring body composition and metabolic health in PCOS patients could help identify those at greater risk of EH, guiding preventive interventions.

Keywords: polycystic ovary syndrome, endometrial hyperplasia, body composition, glycolipid metabolism, metabolic syndrome

Introduction

Polycystic ovary syndrome (PCOS) is a common reproductive endocrine and chronic metabolic disorder characterized by persistent ovulatory dysfunction, clinical or biochemical hyperandrogenism, and polycystic ovarian changes.[1] PCOS can be as common as 6% to 10% of women of childbearing age.[2] PCOS is a serious threat to young women's reproductive health, with 70–80% of PCOS patients experiencing varying degrees of infertility.[3]

As a result of chronic anovulation, the endometrium of PCOS patients is stimulated by long-term estrogen without progesterone antagonism, which can lead to abnormal endometrial hyperplasia (EH) that can result in EH and even endometrial cancer (EC). About 30% of women with PCOS have EH. The incidence of EC is 3 to 10 times higher than in the normal population.[4,5] Previous studies showed that the incidence of PCOS gradually increased with increasing degree of EH.[6] EH seriously threatens the health of young women, where atypical endometrial hyperplasia (AH) is a precursor to EC

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and is more likely to progress to cancer. The endometrium of EH patients lacks periodic morphological changes and dysregulation of molecular events, resulting in decreased endometrial receptivity, decreased implantation rate, decreased live birth rate, increased abortion rate, and other clinical signs of significantly reduced fertility.

Insulin resistance, resulting in multiple defects in the regulation of carbohydrate, fat, and purine metabolism, is considered an important pathophysiological feature in developing PCOS.[7] Body Mass Index (BMI) is a classic measure of obesity but does not distinguish between body fat and muscle mass. Previous study[8] has shown that PCOS patients with normal weight and central obesity have a higher risk of insulin resistance and dyslipidemia than those with non-central obesity. This suggests that the distribution of muscle and fat may also influence metabolic dysfunction in PCOS. Metabolic disorders are also one of the independent risk factors for the development of endometrial hyperplasia. Therefore, it is unclear whether the changes in the distribution of human body components in PCOS patients affect the endometrium by affecting the metabolism of PCOS patients.

This study analyzed body composition, glycolipid metabolism, and uric acid levels in normal controls, PCOS patients with normal endometrial, non-PCOS patients with EH, and PCOS patients with EH. We hope to be able to assess the risk of endometrial hyperplasia in patients with PCOS and to contribute to the protection of fertility in young women with PCOS.

Material and Method

Study Design and Patients

This is a retrospective study that had approval from the ethics committee of Tianjin Medical University General Hospital. We collected patients from June 1, 2021, to March 1,2024.

Inclusion Criteria

(1) Patients' pathological diagnoses were EH without atypia, AH, secretory or proliferative phases of the endometrium, (2) Patients undergoing body composition analysis in our hospital, (3) Patients who have had fasting blood glucose, fasting insulin, blood lipids and uric acid tested in our hospital, (4) Patients without malignant tumors, (5) Patients without other system comorbidities.

Exclusion Criteria

(1) Patients were being treated with hormone therapy, (2) Patients' clinical and pathological data were missing.

Calculation of the Sample Size

This is a retrospective case-control study, the main outcome of this study was to determine the relationship between polycystic ovary syndrome and endometrial hyperplasia. For this aim, we used the following formula to calculate the minimal sample size for this type of study:

$$n = \frac{\left(Z_{1-\frac{\alpha}{2}}\sqrt{2P(1-P)} + Z_{\beta}\sqrt{P1(1-P1)+P0(1-P0)}\right)^2}{(\mathrm{P1}-\mathrm{P0})^2} = \frac{\left(1.96\sqrt{2*0.2*0.8} + 1.28\sqrt{0.3*0.7+0.1*0.9}\right)^2}{(0.2)^2} = 73.10 \approx 74$$

(ie the minimal sample size should be 74. P0 is the probability of endometrial hyperplasia in premenopausal women, which is 10%, P1 is the probability of endometrial hyperplasia in the PCOS population, which is about 30%,[9,10] and P is the average of P0 and P1. The statistical significance level was 5% ($\alpha = 0.05$) using a two-sided test $\beta = 0.1$).

Relevant Definitions and Standards

Diagnostic Criteria for PCOS

(1) Rare ovulation or anovulation (often accompanied by abnormal menstruation), (2) Clinical symptoms of hyperandrogenism and/or hyperandrogenism, (3) Polycystic ovarian changes on ultrasound: ≥12 follicles with a diameter of 2–9mm in one or both ovaries and/or ovarian volume ≥10mL.[11] Any two of the above three factors were met, and other diseases causing hyperandrogenism were excluded.

Parameters' Calculation method

BMI (Body Mass Index, kg/m^2) = Weight (kg)/Height^2 (m).

FFMI (Free Mass Index, kg/m^2) = Free Mass (kg)/Height^2 (m).
FMI (Fat Mass Index, kg/m^2) = Fat Mass (kg)/Height^2 (m).
SMI (Skeletal Muscle Mass Index, kg/m^2) = Skeletal Muscle Mass (kg)/Height^2 (m).
ASMI (Appendicular Skeletal Muscle Mass Index, kg/m^2) = Appendicular Skeletal Muscle Mass (kg)/Height^2 (m).
SVR = SMI/ Visceral Fat Area (Visceral Fat Level*10, cm^2).
HOMA-IR (Homeostatic Model Assessment for Insulin Resistance) = [fasting insulin (μIU/mL) × fasting blood glucose (mmol/L)]/22.5.

Data Collection

General Clinical Data

The data included age, menstrual cycle history, and measurements from vaginal or abdominal color Doppler ultrasounds (such as uterine size, endometrial thickness, bilateral ovarian size, and the number of 2–9 mm follicles).

Anthropometric Characteristics

The height, waist circumference, and hip circumference of both PCOS patients and controls were measured in centimeters. The body composition of all subjects was analyzed using the In Body 270 body composition analyzer. The following parameters were obtained: body weight, BMI, fat mass, skeletal muscle mass, PBF, VFL, and PSM. The percentage of muscle or fat mass in each site is referred to as the proportion of muscle or fat in that site relative to body weight.

Laboratory Measurements

Peripheral venous blood (5 mL) was collected on days 2 to 4 of the menstrual cycle from all subjects with regular menstruation and those with amenorrhoea for more than 1 month. The blood was centrifuged at 4000 rpm for 10 minutes after being allowed to stand at room temperature for approximately 40 minutes. The supernatant was collected for analysis. Fasting blood glucose, fasting insulin, blood lipids (total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and uric acid (UA)) were measured by electrochemiluminescence.

Pathological Diagnoses

Two experienced gynaecologists from the Pathology Department of Tianjin Medical University General Hospital diagnosed the endometrial pathology. In case of disagreement, a third gynaecological pathologist is consulted to finalise the pathological diagnosis report to ensure consistency of pathological diagnosis. The most severe pathological diagnosis was considered to be the final diagnosis for the study. Patients were divided into normal endometrium, SH (simple EH), CH (complex EH), and AH based on the results of the pathological diagnoses. A pathological diagnosis of secretory and proliferative phases of the endometrium was defined as normal endometrium.

Statistical Methods

Statistical analysis was performed using SPSS 26.0 software for Windows (IBM Inc)., the R programming language and environment (v.4.1.1; http://www.r-project.org/), and GraphPad Prism 8.0 for Windows (GraphPad Software Inc). One-way ANOVA tests were used for continuous variables and results were expressed as mean ± standard deviation. Scheffe's test was used to compare multiple groups. Stepwise forward regression was performed using significant multivariate logistic regression variables. The Spearman correlation test was used for correlation analysis. The level of significance was set at $P < 0.05$.

Results

The study included 232 patients based on the inclusion and exclusion criteria. Of these, 118 patients were non-PCOS and normal endometrial (Group A), 34 patients were PCOS and normal endometrial (Group B), 38 patients were non-PCOS and EH (Group C), and 42 patients were PCOS and EH (Group D).

Demographic Baseline Characteristics in Four Groups

Baseline demographic characteristics in Groups A, B, C, and D are shown in Table 1. In Group D, the patient's weight and BMI levels were significantly higher than in Groups A, B, and C. In Group C, the patient's weight and BMI levels were markedly higher than in Group A (Table 1).

Differences in Body Composition Among the Four Groups

In Group D, the patient's PSM of Trunk, PBF of Arm, FFMI, FMI, and ASMI were significantly higher than in Groups A, B, and C (Table 2 and Figure 1). In Group D, the patient's WHR, PBF, PBF of Trunk, PSM of Leg, SMI and VFL were significantly higher than in Groups A and B (Table 2). In Group D, the patient's PSM, PBF of Leg, and SVR were significantly higher than in Group A (Table 2).

In Group C, the patient's WHR, PBF, PSM, PSM of Trunk, Fat mass of Trunk, PBF of Trunk, PBF of Arm, PSM of Leg, PBF of Leg, FFMI, FMI, ASMI, VFL, and SVR were significantly higher than in Group A (Table 2).

Multivariate Regression Analysis of EH Risk Factors in PCOS Patients

Stepwise forward regression was performed using the significant variables in Table 1 and Table 2 in the multivariate logistic regression equation. The results showed that FMI was an independent risk factor for EH in PCOS patients, with groups A and B as reference groups. Increased FMI was an independent risk factor for endometrial hyperplasia in PCOS patients, while increased age was a protective factor, using C as the reference group (Table 3). The AUC for FMI prediction of EH in PCOS patients was 0.82 (Figure 2).

Correlation Between FMI and Glucose Metabolism in Patients with PCOS

Correlation analysis of FMI and glucose metabolic indices in PCOS patients showed significant positive correlations with fasting glucose, fasting insulin, and HOMA-IR. The correlation coefficient between FMI and HOMA-IR was 0.602 (Figure 3).

Table 1 Demographic Baseline Characteristics in Four Groups

	Group A (n=118)	Group B (n=34)	Group C (n=38)	Group D (n=42)	F	P value
Age (years)						
Mean ± SD	33.12±6.82	32.06±5.12^{C}	36.24±5.20^{B}	33.05±5.62	3.36	0.020
Median (IQR)	33 (26, 39)	30 (31, 41)	36 (28, 36)	33 (30, 37)		
Min-Max	21–45	23–45	28–45	18–44		
Height (cm)						
Mean ± SD	161.86±5.54^{D}	160.59±5.01	162.45±4.55	162.80±5.97	1.18	0.317
Median (IQR)	161.00 (158.00, 165.25)	160.00 (158.00–164.00)	162.00 (160.00–166.25)	162.00 (159.75, 167.00)		
Min-Max	145.00–178.00	147.00–173.00	151.00–173.00	148.00–174.00		
Weight (kg)						
Mean ± SD	60.74±11.42^{CD}	66.49±12.62^{D}	73.78±15.35^{AD}	85.10±21.40^{ABC}	31.40	<0.0001
Median (IQR)	58.30 (53.28, 64.45)	65.55 (55.78, 74.68)	73.70 (61.75, 82.53)	84.85 (72.10, 90.80)		
Min-Max	41.70–108.30	47.60–94.10	47.30–111.50	46.30–151.40		
Body Mass Index (kg/m^2)						
Mean ± SD	23.15±3.85^{BCD}	25.85±5.16^{AD}	27.90±5.32^{AD}	31.86±6.51 ^{ABC}	35.78	<0.0001
Median (IQR)	22.61 (20.46, 24.74)	25.95 (21.61, 29.84)	27.66 (23.56, 31.11)	31.13 (28.43, 34.40)		
Min-Max	17.30–37.47	18.68–39.17	18.79–39.01	18.09–50.59		
Pathological Diagnosis						
	Normal endometrium	Normal endometrium	SH (16/38) CH (12/38) AH (10/38)	SH (16/42) CH (17/42) AH (9/42)		

Notes: Group A: non-PCOS and normal endometrium; Group B: PCOS and normal endometrium; Group C: non-PCOS and EH; Group D: PCOS and EH. ^{A} compared to Group A, $p < 0.05$; ^{B} compared to Group B, $p < 0.05$; ^{C} compared to Group C, $p < 0.05$; ^{D} compared to Group D, $p < 0.05$;
Abbreviations: SH, Simple endometrial hyperplasia; CH, Complex endometrial hyperplasia; AH, Atypical endometrial hyperplasia; SD, Standard deviation; IQR: Interquartile range.

Table 2 Differences in Body Composition Among the Four Groups

	Group A (n=118)	Group B (n=34)	Group C (n=38)	Group D (n=42)	F	P value
WHR (%)	87.56±6.43^{CD}	89.12±6.55^{D}	93.11±6.33^{A}	95.64±6.31^{AB}	19.68	<0.0001
PBF (%)	32.15±6.22^{CD}	35.49±7.20^{D}	37.60±6.14^{A}	41.34±5.87^{AB}	24.40	<0.0001
PSM (%)	37.80±6.85^{CD}	35.76±4.84	34.13±3.19 ^{A}	32.28±3.15 ^{A}	11.82	<0.0001
PSM of Trunk (%)	29.70±2.23 ^{CD}	28.50±2.50^{D}	28.21±2.61 ^{AD}	26.65±2.58 ^{ABC}	17.62	<0.0001
PBF of Trunk (%)	15.72±3.54 ^{CD}	17.46±3.76^{D}	18.77±2.92 ^{A}	20.26±2.29 ^{AB}	22.97	<0.0001
PSM of Arm (%)	6.32±0.59	6.28±0.56	6.43±0.58	6.29±0.70	0.47	0.706
PBF of Arm (%)	4.61±1.29 ^{CD}	5.32±1.62^{D}	5.95±1.95 ^{AD}	7.32±2.64 ^{ABC}	25.81	<0.0001
PSM of Leg (%)	20.94±2.22 ^{CD}	19.87±2.43^{D}	19.21±2.06 ^{A}	17.96±1.90 ^{AB}	21.31	<0.0001
PBF of Leg (%)	10.06±1.77 ^{CD}	10.89±2.54	11.18±1.71 ^{A}	12.11±1.73 ^{A}	13.22	<0.0001
FFMI (kg/m^2)	15.51±5.34^{CD}	16.35±1.76^{D}	17.13±1.95^{AD}	18.40±2.41^{ABC}	29.05	<0.0001
FMI (kg/m^2)	7.64±2.70^{CD}	9.50±3.72^{D}	10.77±3.69^{D}	13.47±4.51^{ABC}	32.51	<0.0001
SMI (kg/m^2)	8.63±1.46^{D}	9.38±1.19 ^{D}	9.14±1.89	10.15±1.48^{AB}	11.27	<0.0001
ASMI (kg/m^2)	6.25±0.74^{CD}	7.06±0.95 ^{D}	6.67±0.97 ^{AD}	7.63±1.17 ^{ABC}	27.07	<0.0001
VFL	8.80±3.94 ^{CD}	10.82±4.33^{D}	12.58±4.35 ^{A}	14.31±3.91 ^{AB}	22.37	<0.0001
SVR	0.22±0.09^{CD}	0.18±0.07	0.16±0.05 ^{A}	0.19±0.08 ^{A}	12.34	<0.0001

Notes: Group A: non-PCOS and normal endometrium; Group B: PCOS and normal endometrium; Group C: non-PCOS and EH; Group D: PCOS and EH; ^{A} compared to Group A, $p < 0.05$; ^{B} compared to Group B, $p < 0.05$; ^{C} compared to Group C, $p < 0.05$; ^{D} compared to Group D, $p < 0.05$;
Abbreviations: WHR, waist hip rate; PSM, Percent Skeletal Muscle; PBF, Percent Body Fat; FFMI, Free Mass Index; FMI, Fat Mass Index; SMI, Skeletal Muscle Mass Index; ASMI, Appendicular Skeletal Muscle Mass Index; VFL, Visceral Fat Level; SVR, Skeletal Muscle Mass Index/ Visceral Fat Area.

Correlation Between FMI and Lipid Metabolism/Uric Acid in Patients with PCOS

Correlation analysis of FMI and lipid metabolic indices/uric acid in PCOS patients showed significant positive correlations with TC, TG, LDL, TG/HDL, and uric acid. FMI has significant negative correlations with HDL. The correlation coefficient between FMI and uric acid was 0.649 (Figure 4).

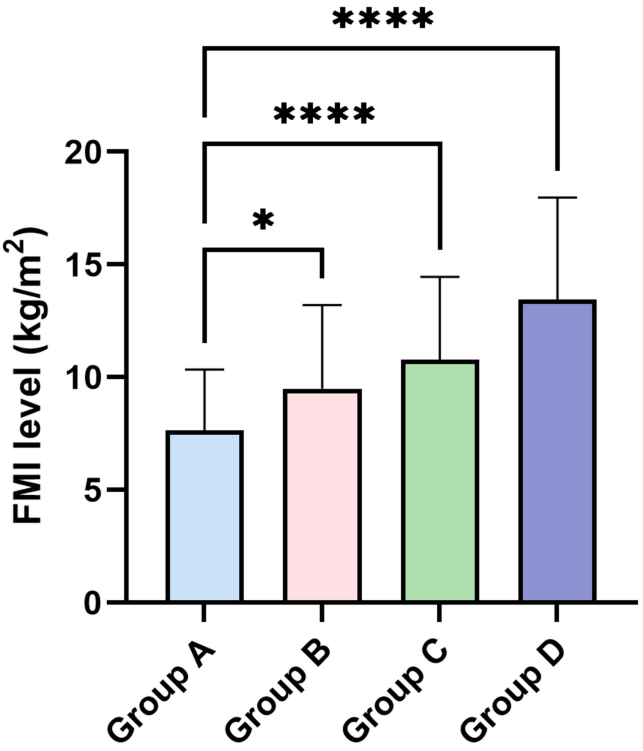

Figure 1 FMI levels in the Four Groups. Group (A) non-PCOS and normal endometrium; Group (B) PCOS and normal endometrium; Group (C) non-PCOS and EH; Group (D) PCOS and EH.
Abbreviation: FMI, Fat mass index.

Table 3 Multivariate Regression Analysis of EH Risk Factors in PCOS Patients

Reference Group			B	OR	OR 95% CI	P value
Group A	**Group D**	**Age (years)**	−0.039	0.962	0.897–1.031	0.276
		FMI (kg/m^2)	0.465	1.592	1.394–1.819	<0.0001
Group B	**Group D**	**Age (years)**	0.011	1.011	0.932–1.096	0.797
		FMI (kg/m^2)	0.231	1.260	1.104–1.437	0.001
Group C	**Group D**	**Age (years)**	−0.093	0.911	0.842–0.985	0.02
		FMI (kg/m^2)	0.161	1.174	1.042–1.324	0.009

Notes: Group A: non-PCOS and normal endometrium; Group B: PCOS and normal endometrium; Group C: non-PCOS and EH; Group D: PCOS and EH.
Abbreviations: PCOS, Polycystic Ovary Syndrome; EH, Endometrial Hyperplasia; FMI, Fat Mass Index.

Further group analysis of the PCOS population showed that FMI was more strongly associated with TG, TG/HDL, HDL, and uric acid levels in PCOS patients with hyperplastic endometrium compared to PCOS patients with normal endometrium (Figure 4).

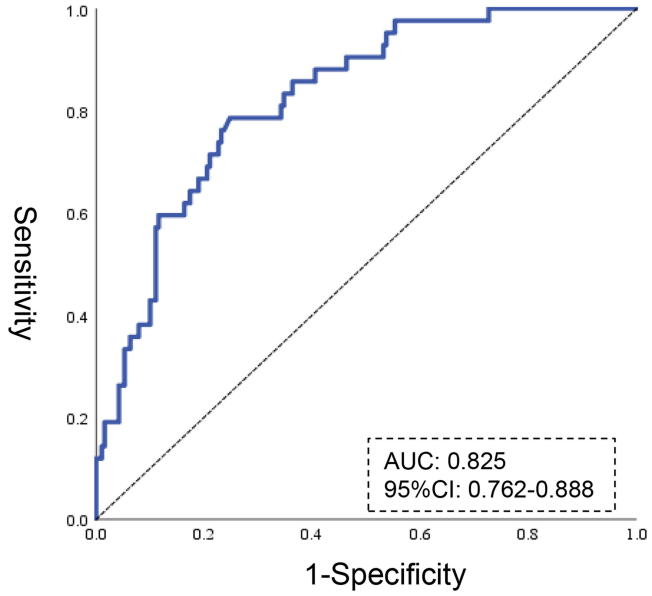

Figure 2 ROC curve of FMI for prediction of endometrial hyperplasia in patients with PCOS.
Abbreviations: AUC, Area under the ROC curve; CI, Confidence Interval.

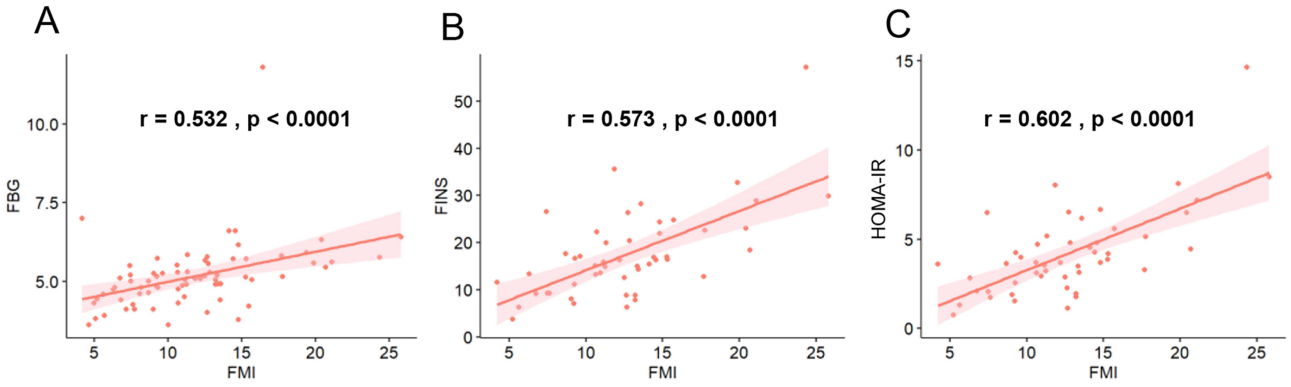

Figure 3 Correlation between FMI and glucose metabolism in patients with PCOS. (**A**) Correlation between FMI and FBG level in patients with PCOS; (**B**) Correlation between FMI and FINS level in patients with PCOS; (**C**) Correlation between FMI and HOMA-IR in patients with PCOS.
Abbreviations FMI, Fat mass index; EH, Endometrial Hyperplasia; EC, Endometrioid Adenocarcinoma; FBG: fasting blood glucose; FINS: fasting insulin; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance.

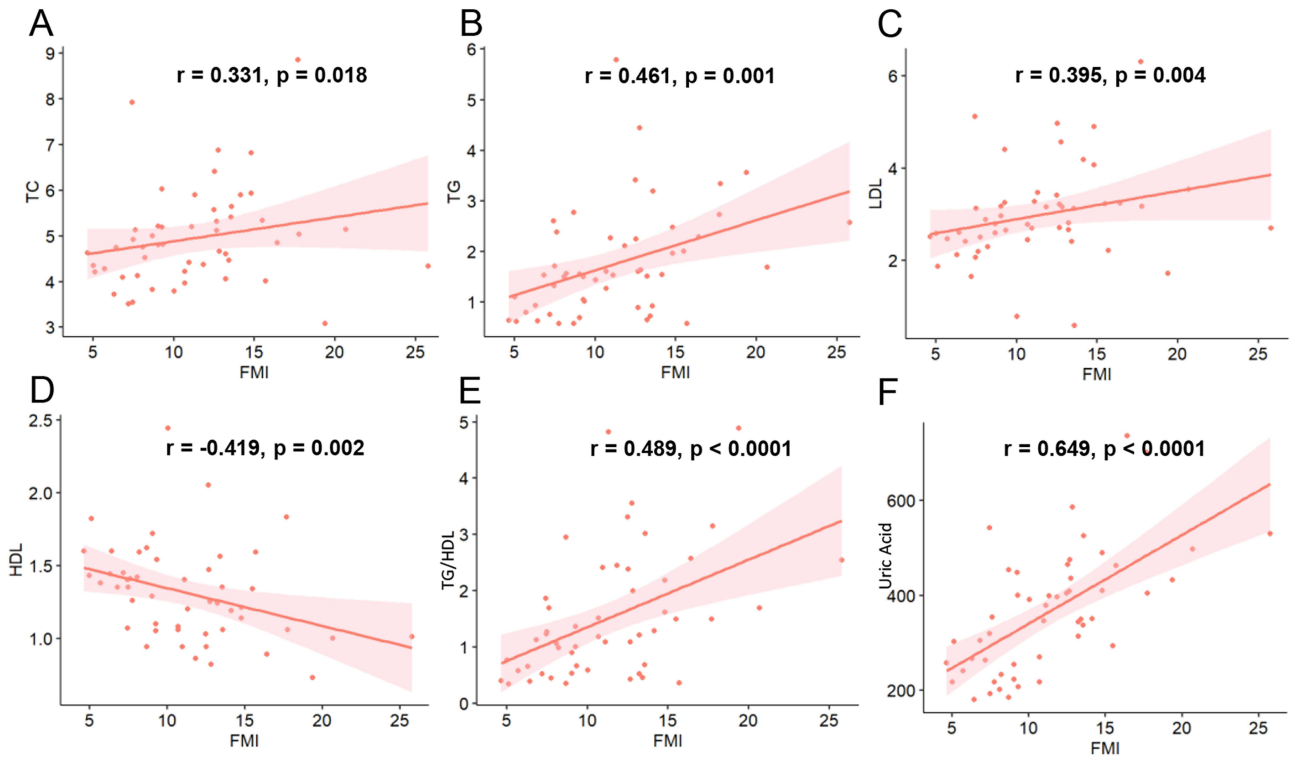

Figure 4 Correlation between FMI and lipid metabolism/Uric Acid in patients with PCOS. (**A**) Correlation between FMI and TC level in patients with PCOS; (**B**) Correlation between FMI and TG level in patients with PCOS; (**C**) Correlation between FMI and LDL level in patients with PCOS; (**D**) Correlation between FMI and HDL level in patients with PCOS; (**E**) Correlation between FMI and TG/HDL level in patients with PCOS; (**F**) Correlation between FMI and Uric Acid level in patients with PCOS.
Abbreviations: FMI, Fat mass index; EH, Endometrial Hyperplasia; EC, Endometrioid Adenocarcinoma; TC, Total Cholesterol; TG, Triglyceride; LDL, Low density lipoprotein; HDL, High density lipoprotein.

Discussion

The prevalence of EH ranges from 1% to 48.8% in patients with PCOS.[12] A meta-analysis study[13] showed that the prevalence of PCOS was 17.23%, 10.26%, 9.13%, and 2.22% in people aged 21–30, 10–20, 31–40, and over 40 years respectively. PCOS mainly affects the reproductive function of women of childbearing age. A Korean study[14] of nearly 70,000 patients found a 14.1% annual increase in the incidence of PCOS in recent years. Further analysis of PCOS in 1,806 patients with EH and 335,440 PCOS patients with normal endometrium showed that the combination of T2D (diabetes mellitus type 2, OR=1.17 [95% CI 1.00–1.38, P=0.050]), obesity (OR=1.34 [95% CI: 1.10–1.64, P=0.004]), HT (Hypertension, OR=1.49 [95% CI: 1.31–1.68, P<0.001]), HL (Hyperlipidemia, OR=2.17 [95% CI: 1.55–3.02, P<0.001]), and infertility (OR=1.24 [95% CI: 1.10–1.39, P<0.001]) increased the risk of EH in PCOS patients. In our study, the BMI level of EH patients was significantly higher than that of non-EH patients, regardless of whether PCOS was combined. The BMI level of EH patients with PCOS was significantly higher than that of EH patients without PCOS, which is consistent with previous research.

BMI does not reflect the distribution of body fat and muscle, although it is a commonly used indicator of obesity. However, PCOS patients with a normal BMI have a significantly higher level of body fat than healthy women, and the fat is mainly distributed in the upper limbs and around the trunk.[15] PCOS patients with normal BMI have a higher prevalence of dysglycaemia and dysglycaemia than healthy women of similar age and BMI.[16] Metabolic changes may be responsible for the increase in body fat volume and distribution. Specifically, body fat distribution, particularly abdominal subcutaneous and visceral fat, reflects these changes better than overall adiposity.[17] In the development of PCOS, obesity and specific fat distribution patterns may play an important role. Previous studies analyzed the body composition of PCOS patients and normal healthy women and found that the percentage of body fat, the percentage of fat in both upper limbs, the percentage of fat in both lower limbs and the percentage of trunk fat were significantly higher in PCOS patients than in normal healthy women, while the percentage of muscle in both lower limbs and the percentage of trunk muscle were significantly lower than in normal healthy women, suggesting that changes in fat and muscle distribution are significantly altered in PCOS patients. This study is

the first to further subdivide PCOS and non-PCOS patients according to the presence or absence of EH and to analyse their body composition. PCOS patients with EH had increased WHR, increased PBF, increased FFMI, increased FMI, increased VFL, increased PBF in the trunk and upper limbs, and decreased PSM in the trunk and lower limbs compared to PCOS patients with normal endometrium. Compared with non-PCOS women with normal endometrium, non-PCOS women with EH also showed similar changes in fat and muscle distribution. The distribution of fat and muscle in patients with EH was altered, with fat being deposited mainly in the upper extremities and trunk, manifesting as central obesity. Further multivariate regression analysis showed that FMI was an independent risk factor for EH in patients with PCOS compared with non-PCOS /PCOS patients with normal endometrium. Patients with PCOS developed EH at an earlier age compared with non-PCOS patients with EH, suggesting that PCOS accelerates the progression of endometrial lesions.

Increased FMI indicates increased body fat in PCOS. Adipose tissue, which has a hormonal function, uses aromatase to transform androgens produced by non-ovarian tissues into estrone. Increased adiposity increases the conversion of androstenedione to estrone.[18] This is because estrone does not fluctuate periodically like the estrogens secreted by the follicles. As a result, the pituitary gland cannot stimulate the release of large amounts of LH and FSH, and the serum LH/FSH peak is difficult to form, leading to obstructed follicular development or ejection and oligomenorrhoea or amenorrhoea. Ovulation disorders result in prolonged exposure of the endometrium to the effects of estrogen without the antagonism of progesterone, with the resultant abnormal endometrial hyperplasia.[19] The imbalance between pro-inflammatory and anti-inflammatory adipokines accelerates the development of obesity-related diseases, which are not only closely associated with diabetes, inflammation and cardiovascular disease, but also play a crucial role in the development of malignant tumours.[20] Adipokines may be directly involved in the development of EH/EC, but may also interact with oestrogen to indirectly promote its development. Changes in the levels of various adipokines can also cause insulin resistance, directly promote the proliferation of tumour cells and inhibit cell apoptosis through PI3K/Akt and Ras/MAPK signalling pathways, and participate in the pathogenesis of EC.[21]

Studies have shown that PCOS has a positive association with EH, T1D, and T2D in obese patients after adjustment for BMI.[22,23] Duleba's study[24] has shown that both normal-weight and obese women with PCOS have elevated circulating insulin levels/serum glucose levels compared to healthy women of normal weight and obese women. Conway's study[25] indicated that normal-weight women with PCOS demonstrate hepatic insulin resistance only, whereas obese women demonstrate whole-body insulin resistance. This means that the occurrence of metabolic abnormalities in people with PCOS is not always dependent on their BMI. Hyperinsulinemia has been shown to play an important role in the pathophysiology of PCOS. Insulin resistance is associated with hyperinsulinemia. In this study, further analysis of PCOS patients showed that FMI levels were significantly correlated with glucose and lipid metabolism and uric acid levels. The correlation coefficient between FMI and HOMA-IR was 0.602, the correlation coefficient between FMI and HDL was −0.419, and the correlation coefficient between FMI and TG/HDL was 0.481. The correlation coefficient between FMI and uric acid was 0.649.

Hyperinsulinemia increases plasma levels of free androgens by reducing the production of sex hormone-binding globulin. Endometrial cell differentiation can be affected by high plasma levels of androgens and insulin.[26] This further increases the concentration of bioavailable circulating androgens, which dysregulates the production of follicles and leads to a series of pathological events in patients with PCOS.[27] Qi's research[28] has shown that compared to PCOS patients without PCOS and PCOS patients without IR, the implantation rate of PCOS patients with IR is relatively low, and endometrial biopsies from PCOS patients with IR show increased cortisol levels, decreased 11β-hydroxysteroid dehydrogenases expression, and defects in the endometrial insulin signaling pathway. In addition, by inhibiting Akt phosphorylation and glucose transporter type 4 translocation (through induction of phosphatase and tensin cognate deletion (PTEN) on chromosome 10), cortisol attenuates insulin-stimulated glucose uptake in endometrial epithelial cells. Endometrial sterol regulatory element binding protein-1 gene expression was significantly increased in patients with PCOS and endometrial cancer compared with controls and was positively associated with serum triglycerides in patients with PCOS and endometrial cancer.[29] Metformin and sorafenib promote apoptosis through synergistic regulation of autophagy and reduce endometrial hyperplasia in patients with PCOS.[30]

The TG/HDL ratio is considered a predictive marker of IR and β cell dysfunction. Elevated levels of TG are an early manifestation of insulin resistance. High TG is often associated with intra-abdominal fat accumulation, increased lipoprotein lipase activity, and lipolysis to non-esterified fatty acids, which interfere with the binding of insulin to the

appropriate receptors in the surrounding tissues, thus reducing the biological effect of insulin. Furthermore, elevated TGs lead to increased free fatty acids (FFA), and prolonged exposure to TG-induced FFA may reduce AMP-activated kinase protein activity and increase TG accumulation, leading to altered pancreatic α-cell insulin signaling and glucagon over-secretion.[31,32] Insulin resistance promotes the synthesis of very low-density lipoprotein in the liver and inhibits the breakdown of TG by the lipoprotein enzyme, thereby increasing the amount of TG in the circulation. Low HDL-C exacerbates β cell dysfunction, and HDL protects beta cells from cytokine- or glucose-induced apoptosis through two components, including apoA1 (the major protein component of HDL) and S1P, exacerbating insulin resistance and thus glucose intolerance.[33,34]

We also found that FMI levels were significantly positively correlated with serum uric acid levels in PCOS patients, in addition to the close relationship between blood glucose and dyslipidemia. Studies[35,36] have shown that for every 1mg/dL increase in serum UA, the risk of developing T2DM increases by approximately 6% to 17%. High levels of UA are associated with insulin resistance and beta-cell dysfunction, two defects that are central to the pathophysiology of T2DM.[37,38] Serum UA levels have been reported to correlate positively with indicators of insulin resistance in healthy individuals with normal serum UA concentrations.[39] In normal healthy people, other studies have shown that acute hyperinsulinemia inhibits renal uric acid excretion.[40] Benzbromarone is a urinary excretion inhibitor of fatty acid-binding protein 4 that improves glucose tolerance in mice with type 2 diabetes.[41] A retrospective cohort study[41] showed that gout patients treated with benzbromarone had a reduced incidence of new-onset diabetes compared to those not treated with benzbromarone.

In conclusion, this study uniquely examined the interaction between metabolic dysfunction and endometrial health in patients with PCOS, confirmed FMI as a predictive marker and explored additional metabolic markers associated with EH risk in patients with PCOS. In patients with PCOS, attention should be paid to the quality and distribution of fat when assessing; some patients have a low BMI level, but increased abdominal fat is still detrimental to health. Some patients have a low body mass index, but increased abdominal fat is still detrimental to health. Pay attention to glucose, lipid and purine metabolism, prevent related complications and endometrial changes through early intervention, and improve reproductive function in PCOS patients. The results of this study will also help to develop targeted interventions, such as reminding PCOS patients with normal weight or normal BMI if their FMI level is elevated, to improve their diet structure or type, improve their lifestyle and increase moderate exercise to help reduce the risk of EH and protect fertility in young women.

Limitations

This is a retrospective single-center study. To reduce the selection bias, three gynecology experts and one statistics expert were invited to strictly define the inclusion and exclusion criteria. The completeness of medical history and auxiliary examination data was determined one by one. For partial data or data missing in the medical records, the patients were followed up to complete the medical data as much as possible. As many participants as possible were included in the study to reduce bias. However, the selection bias cannot be completely controlled by these measures. In the future, multicenter hospitals (local hospitals, hospitals at all levels) should be included with more participants to reduce the selection bias as much as possible.

Data Sharing Statement

Data can be obtained by corresponding authors if necessary.

Ethics Approval

This study adheres to the principles outlined in the Declaration of Helsinki, ensuring the protection of patient privacy and confidentiality. The studies involving human participants were reviewed and approved by The Committee for Medical Research Ethics at Tianjin Medical University General Hospital (Ethical No. IRB2024-YX-222-01). The patients provided their written informed consent to participate in this study. Written informed consent was obtained from the individuals for the publication of any potentially identifiable images or data included in this article.

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Author Contributions

All authors made a significant contribution to the reported work from its conception, designing, execution, data acquisition, analysis, and interpretation; all authors participated in drafting, revising, or critically reviewing the article; and gave their final approval of the version to be published; have agreed on the journal to which the article has been submitted; agree to be accountable for all aspects of the work.

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Disclosure

The authors have no conflict of interest to disclose.

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