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Research Article

Association of Metabolic and Inflammatory Biomarkers with Endometrial Cancer in Women with Polycystic Ovary Syndrome

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Abstract

Background: Polycystic ovary syndrome (PCOS) is a common metabolic and endocrine disease marked by insulin resistance, obesity, hormonal disturbance and low-grade chronic inflammation. These changes can lead to an increased risk of endometrial abnormalities, including endometrial cancer. **Objective:** To evaluate hormonal, metabolic and inflammatory biomarkers in women with PCOS and women with endometrial cancer and a history of PCOS, paying particular attention to serum CA125, AMH, FBS, fasting insulin, HOMA-IR and IL-6. **Methods:** This comparative cross-sectional study was conducted on 90 women equally divided into 3 groups: women with endometrial cancer and PCOS history (n=30), women with PCOS (n=30), and healthy controls (n=30). Serum levels of CA125, AMH, fasting blood glucose, fasting insulin, HOMA-IR, and IL-6 were measured and compared between study groups. **Results:** For all the investigated biomarkers, significant differences between the three groups were observed ($p<0.001$). Women with endometrial cancer and a history of PCOS had the highest mean levels of CA125, fasting insulin, HOMA-IR and IL-6. AMH levels were highest in women with PCOS. The fasting blood glucose was significantly higher in both clinical groups than in healthy controls, with no significant difference between the endometrial cancer + PCOS and PCOS groups. BMI was positively correlated with HOMA-IR ($r=0.645$, $p<0.001$), and serum IL-6 was positively correlated with CA125 ($r=0.699$, $p<0.001$). **Conclusion:** Women with endometrial cancer and a previous history of PCOS had higher CA125, fasting insulin, HOMA-IR and IL-6 levels. AMH was highest in women with PCOS. The findings suggest a link between metabolic dysfunction, systemic inflammation and PCOS-associated endometrial cancer.

1. Introduction

Polycystic ovary syndrome (PCOS) is one of the most common hormonal disorder in women of reproductive age. Depending on the diagnostic standards, the number of women who have it can range from 6% to 20%. Obesity, insulin resistance, dyslipidaemia, chronic low-grade inflammation, hyperandrogenism, ovulatory dysfunction, menstrual irregularities and polycystic ovarian morphology are frequently seen in PCOS [1, 2]. Increasing evidence shows that PCOS is associated with endometrial abnormalities, especially endometrial hyperplasia and endometrial cancer. Chronic anovulation in the setting of inadequate progesterone levels can result in prolonged unopposed oestrogen stimulation of the endometrium, which can promote excessive endometrial proliferation and increase the risk for hyperplastic and malignant transformation [3, 4].

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Obesity and insulin resistance are central features in the pathophysiology of PCOS and may be involved in associated endometrial abnormalities. Increased adiposity results in an increased peripheral aromatisation of androgens to oestrogens, thereby increasing circulating levels of oestrogens. Hyperinsulinemia may also induce ovarian androgen secretion and activate insulin and insulin-like growth factor signalling pathways involved in aberrant cellular proliferation and carcinogenesis [5, 6].

Chronic low-grade inflammation has also been implicated in the pathophysiology of PCOS and might contribute to endometrial abnormalities. Pro-inflammatory cytokines, in particular interleukin-6 (IL-6), are implicated in oxidative stress, angiogenesis, tissue remodelling and abnormal cellular proliferation [7, 8]. Elevated levels of circulating IL-6 have been reported in women with PCOS and gynaecological malignancies, suggesting a possible link between systemic inflammatory activity and endometrial carcinogenesis [7, 8].

Cancer antigen 125 (CA125) is a tumour associated glycoprotein studied extensively in gynaecological malignancy and endometrial pathological conditions. Increased disease burden and pathological tissue change in endometrial cancer may be indicated by elevated serum CA125 level [9]. Conversely, anti-Müllerian hormone (AMH) is an important marker of ovarian reserve and follicular activity and is often increased in women with PCOS due to the increased number and activity of small antral follicles [10]. Hormonal and inflammatory biomarkers are not the only useful measures for providing information on the metabolic dysfunction associated with PCOS. Metabolic parameters such as fasting blood glucose, fasting insulin and the homeostatic model assessment of insulin resistance (HOMA-IR) are also helpful. Assessing these metabolic changes in conjunction with hormonal and inflammatory biomarkers could offer a more complete biological profile of PCOS and endometrial cancer.

Thus, the present study aimed to evaluate the serum levels of CA125 and AMH, fasting blood glucose, fasting insulin, HOMA-IR, and IL-6 in women with PCOS, women with endometrial cancer and previous history of PCOS, and healthy controls, and to investigate the associations among these hormonal, metabolic, and inflammatory biomarkers.

2. Methods

Study Design and Population

The present comparative cross sectional study was conducted at the Iraqi Center for Cancer and Medical Genetics Research from January to December 2025. A total of 90 women were recruited and divided into three equal groups:

Group I: Thirty patients (n=30) with histopathological confirmed endometrial cancer and prior confirmed diagnosis of polycystic ovary syndrome (PCOS). A specialist pathologist confirmed the diagnosis of endometrial cancer. Blood samples were collected prior to the initiation of chemotherapy, radiotherapy or any other anticancer treatment.

Group II: Women with PCOS (N=30) A specialist gynaecologist diagnosed PCOS based on the presence of at least two of the following features: oligo- or anovulation, clinical or biochemical evidence of hyperandrogenism, and polycystic ovarian morphology on ultrasonography, after ruling out other relevant endocrine disorders.

Group III: women who were apparently healthy with no history of endocrine or gynecological disorders (n=30).

Inclusion and Exclusion Criteria

Inclusion Criteria: Women aged 20–40 years, who met the diagnostic criteria for the assigned study group and gave consent to participate in the study.

Exclusion Criteria: Pregnant women. Women with autoimmune disease or chronic systemic disorders. Women receiving hormonal therapy during the study period. Patients with other malignancies. Participants with severe chronic diseases that may affect the investigated metabolic or inflammatory biomarkers.

Sample Collection

A 5 mL sample of venous blood was collected aseptically from each participant after an overnight fast. Blood samples were allowed to clot at room temperature and then centrifuged at 3000 rpm for 10 minutes. Separated serum was aliquoted and kept at-20°C until laboratory analysis.

Laboratory Investigations

Hormonal and Tumor Biomarkers

Serum anti-Müllerian hormone (AMH) levels were measured using Maglumi automated chemiluminescence immunoassay analyzer (Snibe Diagnostic, China). Serum cancer antigen 125 (CA125) levels were determined using CL-900i automated immunoassay analyzer according to the manufacturers' instructions.

Metabolic Parameters

Fasting blood glucose (FBS) levels were measured using Mindray BS-230 automated chemistry analyzer (Mindray, China). Serum insulin levels were determined using Abbott Architect immunoassay system (Abbott Laboratories, USA). Insulin-resistance was calculated by homeostatic model assessment for insulin-resistance (HOMA-IR) with the following formula:

$$HOMA-IR = \frac{\text{Fasting Insulin}(\mu IU/mL) \times \text{Fasting Glucose(mg/dL)}}{405}$$

Inflammatory Marker

Human IL-6 concentrations in serum were measured quantitatively using a commercial Human IL-6 ELISA Kit (MyBioSource, San Diego, CA, USA, Cat. No. MBS269986) following the manufacturer's protocol. Absorbance was measured at 450 nm using a microplate reader, and sample concentrations were estimated using a standard calibration curve.

Statical Analysis

Data analysis was performed using IBM SPSS Statistics, version 25.0. Continuous variables are presented as mean ± standard deviation (SD) and categorical variables as frequency and percentage. Normality of continuous variables was tested prior to analysis. Differences between the three study groups were evaluated using Welch's analysis of variance (Welch's ANOVA) due to unequal variances between groups, followed by Games–Howell post-hoc pairwise comparisons when the overall test was significant. Chi-square test was used for categorical variables. The relationships between BMI and HOMA-IR and between serum IL-6 and CA125 levels were assessed by Pearson correlation coefficient. Additionally, adjusted analyses were conducted to compare biomarker levels after controlling for age and BMI. $p < 0.05$ was considered statistically significant.

Ethical Clearance

The study was conducted according to the research plan approved for the year 2025 at the Iraqi Center for Cancer and Medical Genetics Research, Mustansiriyah University, after the approval of the Scientific Committee. Informed consent was obtained from all participants before enrolment.

3. Results

The study included a total of 90 women divided into three equal groups; women with endometrial cancer and previous history of PCOS (n=30), women with PCOS (n=30) and healthy controls (n=30). Table 1 presents the demographic and clinical characteristics. There was a statistically significant difference in age among the three groups (p=0.026). BMI also differed significantly among the three groups ($p<0.001$). Menstrual irregularities were significantly more frequent in the PCOS and endometrial cancer + PCOS groups compared with healthy controls ($p<0.001$).

Table 1: Demographic and clinical characteristics of study groups

Parameter	Endometrial cancer + PCOS (n=30)	PCOS (n=30)	Controls (n=30)	P-value
Age (years)	33.07 ± 3.68^a	30.07 ± 5.10^b	30.43 ± 4.90^b	0.026
BMI (kg/m²)	33.01 ± 3.72^a	31.26 ± 3.42^a	24.19 ± 2.46^b	<0.001
Irregular menstrual cycle (%)	24 (80.0%)	27 (90.0%)	3 (10.0%)	<0.001

Note that values are given as mean ± SD or n (%), depending on what is needed. Different superscript letters in the same row mean that the differences between the two groups are statistically significant ($p<0.05$).

Table 2 shows the serum levels of the biochemical, hormonal and inflammatory markers investigated. Significant differences were observed between three study groups for CA125, AMH, IL-6, FBS, fasting insulin, and HOMA-IR (all $p<0.001$). Women with endometrial cancer and previous history of PCOS had the highest mean levels of CA125, fasting insulin, HOMA-IR, and IL-6, and AMH levels were highest in the PCOS group. Fasting blood glucose levels were significantly higher in both clinical groups compared with healthy controls, with no significant difference between endometrial cancer + PCOS and PCOS groups.

Table 2: Biochemical, hormonal, and inflammatory markers among study groups

Parameter	Endometrial cancer + PCOS (n=30)	PCOS (n=30)	Controls (n=30)	P-value
CA125 (U/mL)	49.59 ± 10.52^a	24.29 ± 4.61^b	13.01 ± 4.03^c	<0.001
AMH (ng/mL)	3.38 ± 1.09^a	7.46 ± 1.42^b	2.54 ± 0.76^c	<0.001
FBS (mg/dL)	110.27 ± 15.36^a	103.40 ± 11.03^a	87.74 ± 7.09^b	<0.001
Fasting insulin (µIU/mL)	20.57 ± 4.67^a	16.48 ± 4.59^b	8.89 ± 2.64^c	<0.001
HOMA-IR	5.56 ± 1.28^a	4.21 ± 1.22^b	1.92 ± 0.59^c	<0.001
IL-6 (pg/mL)	10.89 ± 3.20^a	8.19 ± 2.99^b	3.57 ± 1.33^c	<0.001

Note that the values are represented as mean ± SD. Superscript letters in the same row indicate significant pairwise differences ($p<0.05$, Games-Howell post-hoc test).

Significant differences between the groups persisted after adjustment for age and BMI for CA125, AMH, fasting blood glucose, fasting insulin, HOMA-IR and IL-6 (all $p\leq0.001$)indicating that the differences in biomarkers were not only explained by variation in age or body mass index.

Serum IL-6 and CA125 levels also demonstrated a significant strong positive correlation ($r=0.699$, $p<0.001$). These findings suggest that higher BMI is associated with increased insulin resistance and higher IL-6 levels are associated with higher CA125 concentrations in the study population. Correlation analysis showed a significant positive correlation between BMI and HOMA-IR ($r=0.645$, $p<0.001$) and between serum IL-6 and CA125 ($r=0.699$, $p<0.001$). These correlations are shown in Figure 1.

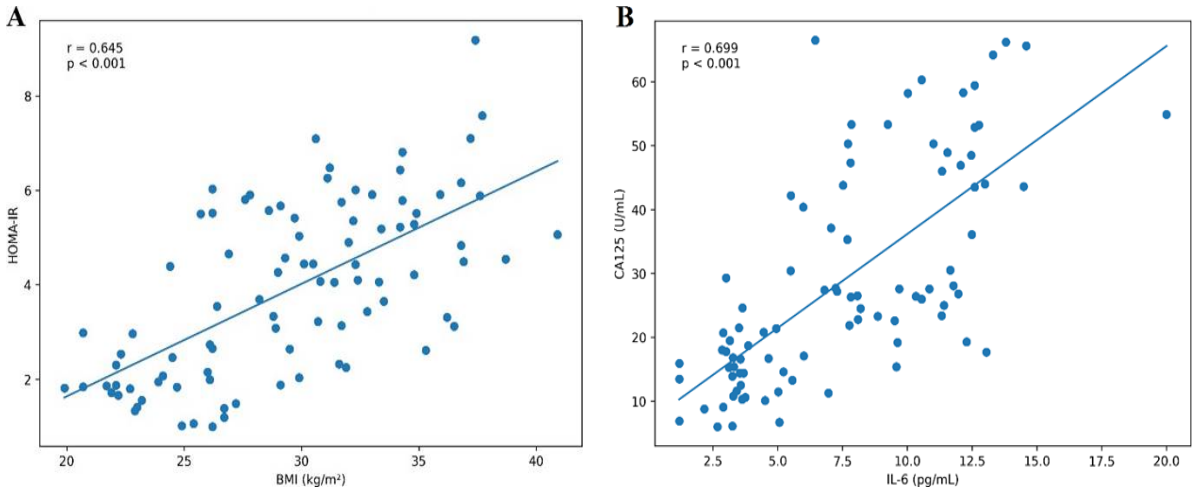

Figure 1: Correlation between metabolic and inflammatory biomarkers Association of BMI with HOMA-IR (A). (B) Correlation of serum IL-6 and CA125 levels.

4. Discussion

Polycystic ovary syndrome (PCOSis a complicated endocrine-metabolic disorder that affects hormones, metabolism, and inflammation. It may be linked to a higher chance of endometrial problems [3, 11]. This study looked at serum levels of HOMA-IR, IL-6, CA125, AMH, fasting blood glucose, fasting insulin, women with PCOS, women with endometrial cancer and a history of PCOS, and healthy women who had never had PCOS.

Serum CA125 levels were significantly elevated in women with endometrial cancer and previous history of PCOS as compared to women with PCOS alone and healthy controls. These findings are in agreement with previous reports showing higher CA125 levels in endometrial cancer and other pathological gynecological conditions [9, 12]. High levels of CA125 may reflect a higher disease burden and changes associated with endometrial malignancy. However, CA125 is a non-specific tumor-associated marker and therefore should be interpreted in context of clinical and histopathological findings and not as an independent diagnostic marker.

Conversely, women with PCOS showed the highest AMH concentrations, whereas women with endometrial cancer and a history of PCOS had lower concentrations. Increased AMH levels are frequently observed in PCOS and are associated with increased number and activity of small antral follicles and altered folliculogenesis [10].

The lower AMH concentration in the endometrial cancer + PCOS group may reflect, in part, the difference in age and ovarian function between the groups in the study and should therefore be interpreted with caution.

Significant differences in metabolic parameters between the study groups were also demonstrated in the present study. Women with endometrial cancer and a history of PCOS had the highest fasting insulin and HOMA-IR, followed by women with PCOS and healthy controls. These results are consistent with the well-established association of PCOS with insulin resistance [5, 6]. Hyperinsulinemia may increase ovarian androgen production and stimulate insulin and insulin like growth factor signalling pathways involved in cellular proliferation and endometrial growth. Fasting blood glucose was significantly different among the three groups, but was not significantly different between the endometrial cancer + PCOS and PCOS groups, suggesting that insulin-related parameters may better distinguish the metabolic changes between these two clinical groups.

Obesity may contribute to metabolic and endometrial abnormalities by increasing peripheral aromatization of androgens to estrogens in adipose tissue. Chronic ovulatory dysfunction in women, especially when associated with prolonged exposure of the endometrium to relatively unopposed estrogen, can lead to excessive endometrial proliferation and increased risk of hyperplastic and malignant changes [3, 4]. BMI was significantly different between the study groups and was positively correlated with HOMA-IR in the present study which supports the close relationship between adiposity and insulin resistance in this population.

Serum IL-6 levels were also significantly higher in the endometrial cancer + PCOS group compared with the PCOS group and healthy controls. IL-6 is a major pro-inflammatory cytokine involved in chronic inflammatory response, oxidative stress, angiogenesis and cellular proliferation. Increased circulating IL-6 levels have been associated in prior studies with the chronic low-grade inflammatory state characteristic of PCOS and may also be contributing to the inflammatory environment seen with endometrial pathological changes [7, 13]. The positive correlation between IL-6 and CA125 observed may reflect an association between increased systemic inflammatory activity and increased levels of a tumour-associated biomarker. This relation, however, should not be understood as evidence of a direct causal interaction.

Findings from the correlation analysis also showed a strong positive relationship between BMI and HOMA-IR. This meant that more fat was linked to more insulin resistance. Furthermore, serum IL-6 and CA125 concentrations were significantly positively correlated. These results suggest the presence of metabolic dysfunction and systemic inflammation along with alterations in tumour associated biomarkers in women with PCOS and PCOS-associated endometrial cancer. However, as these correlations were tested for the entire study population, they should be interpreted according to differences between the three study groups.

When figuring out what these results mean, there are a few things that should be kept in mind. The study only looked at one center and had a small sample size. Moreover, the study groups were not entirely matched for age and BMI, although these variables were considered in the statistical analysis. The cross-sectional design does not allow for establishing temporal or causal relationships of metabolic or inflammatory abnormalities with the development of endometrial cancer. Furthermore, detailed molecular and histopathological tumour characteristics were not included in the current analysis. The lack of a separate group of endometrial cancer patients without a history of PCOS further limits the ability to distinguish biomarkers specifically associated with PCOS-associated endometrial cancer from endometrial

cancer in general.

To summarize, the present results show distinct hormonal, metabolic and inflammatory profiles in women with PCOS, women with endometrial cancer and a prior history of PCOS, and healthy controls. Women with endometrial cancer and previous PCOS had particularly increased insulin resistance and inflammatory activity and higher concentrations of CA125. Further prospective studies with larger and well-matched populations and detailed tumour characterization are necessary to clarify the biological and clinical significance of these associations.

5. Conclusion

In the present study we showed significant differences in hormonal, metabolic and inflammatory biomarkers between women with PCOS, women with endometrial cancer and previous history of PCOS and healthy controls. Women with previous history of PCOS and endometrial cancer had higher levels of CA125, fasting insulin, HOMA-IR and IL-6; while AMH levels were highest in women with PCOS. The results suggest the association of insulin resistance and systemic inflammation with the metabolic and clinical profile of PCOS-related endometrial cancer. However, cause cannot be established as this was a cross-sectional study. Further clarification of these relationships requires larger prospective studies with well-matched groups and detailed tumour characterization.

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Ethical Approval: The study was reviewed and approved by Scientific and Ethics Committees of Iraqi Center for Cancer and Medical Genetics Research, Mustansiriyah University according to the approved scientific research plan for the year 2025.

Informed Consent: Informed consent was obtained from all participants before enrolment.

Conflict of Interest: The authors declare no conflict of interest.

Data Availability: The accompanying author can provide the data supporting the study's conclusions upon reasonable request.

Disclaimer (Artificial Intelligence): The author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.), and text-to-image generators have been used during writing or editing of manuscripts.

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