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Homocysteine and Insulin Resistance among Women with Polycystic Ovary Syndrome

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Abstract. General Background: Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in women of reproductive age, often associated with obesity, insulin resistance (IR), and metabolic dysfunction. Specific Background: Emerging evidence suggests that hyperhomocysteinemia (HHcy) may contribute to the metabolic and cardiovascular complications of PCOS, yet its relationship with IR and β-cell function remains unclear. Knowledge Gap: While previous studies have linked homocysteine (Hcy) to insulin sensitivity, limited data exist regarding its direct correlation with β-cell activity in PCOS patients. Aim: This study aimed to evaluate the correlation of Hcy levels with IR and β-cell function among women diagnosed with PCOS. Results: In a case-control design including 100 PCOS patients and 100 controls, women with PCOS exhibited significantly higher Hcy, fasting glucose, insulin, HOMA-IR, HOMA-B, testosterone, and HbA1c levels. Hcy correlated positively with HOMA-IR, fasting glucose, insulin, HbA1c, and testosterone, but showed no significant association with β-cell function. Novelty: This study highlights Hcy as a strong metabolic marker linked to IR and glycemic dysregulation, independent of β-cell activity in PCOS. Implications: These findings suggest that elevated Hcy may exacerbate the risk of type 2 diabetes, metabolic syndrome, and cardiovascular disease in women with PCOS, underscoring the need for early metabolic monitoring and intervention.

Highlights:

1. Strong correlation found between homocysteine and insulin resistance in PCOS women.
2. Elevated insulin and glycaemic markers increase risk of T2D and related disorders.
3. No significant correlation between homocysteine and β-cell function.

Keywords: Polycystic Ovarian Syndrome, Homocysteine, Insulin Resistance, β-cell Function, Cardiovascular Disease

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Introduction

PCOS, the most prevalent endocrinopathy in women, affects between 7% and 12% of women globally who are of reproductive age [1]. Numerous clinical signs, including obesity, insulin resistance (IR), and elevated testosterone, might be indicative of PCOS [2]. The National Institutes of Health (NIH) established oligo-anovulation and hyperandrogenism as diagnostic findings in 1990, laying the foundation for the PCOS diagnostic criteria [3]. The 2003 Rotterdam criteria were based on three diagnostic features: polycystic ovaries, hyperandrogenism (clinical and/or biochemical), and oligo-anovulation. At least two of the three criteria have to be met for PCOS to be diagnosed [4]. The Rotterdam criteria were used to create four phenotypes. Patients with polycystic ovaries, hyperandrogenism, and persistent anovulation—the three hallmarks of PCOS—were shown to have phenotype A PCOS. Women with chronic anovulation and polycystic ovaries but normal androgen status (no hirsutism or excess androgens in the bloodstream) were found to have phenotype D PCOS, while patients with hyperandrogenism and no polycystic ovaries were found to have phenotype B PCOS, and those with hyperandrogenism and polycystic ovaries but ovulatory cycles to have phenotype C PCOS [5]. However, women with PCOS have been observed having Hyperhomocysteinemia (HHcy) [6]. One amino acid that contains sulphur and is a part of the methionine cycle is homocysteine (Hcy) [7]. It has been demonstrated that Hcy levels are correlated with insulin resistance (IR), body mass index (BMI) and blood pressure (BP). As PCOS is commonly associated with hypertension, obesity, and hyperinsulinemia, it makes sense to consider that high Hcy levels might also be a characteristic of PCOS [8]. This study aimed to evaluate the association between ß-cell function and IR and Hcy levels in PCOS-affected women.

Patients and Methods:

This is case-control study conducted from January, 2024 throughout April, 2024 and included 100 patients with PCOS, 17-44 years of age and 100 control women, 16-40 years of age. Menstrual, reproductive, familial, and medication histories are among the many medical details collected from PCOS and control women. The 2003 Rotterdam criteria, which call for the presence of two of the following: polycystic ovaries, clinical and/or biochemical hyperandrogenism, and oligo-ovulation or anovulation, were used to confirm the diagnosis of PCOS.

Systolic and diastolic blood pressure (SBP and DBP), as well as each participant's waist circumference (WC) and body mass index (BMI), were assessed. Following an 8-hour fast, biochemical tests were performed. Total L-Hcy in human blood or plasma may be quantitatively measured using the one-step immunoassay known as the ARCHITECT Hcy test. It makes use of chemiluminescent micro particle immunoassay, a fully automated diagnostic technology, and Chemiflex, a configurable assay methodology. Dithiothreitol (DTT) lowers bound or dimerised homocysteine (oxidised form) to free homocysteine, which is then converted to free homocysteine by the recombinant enzyme S-adenosyl homocysteine hydrolase (rSAHHase) when sufficient adenosine is present. Then, for particle-bound monoclonal antibody, the SAH competes with S-adenosyl cysteine labelled with acridinium. Pre-trigger and trigger solutions are introduced to the reaction mixture after a wash step and magnetic separation, and the chemiluminescence that results is quantified in relative light units (RLUs). The quantity of Hcy in the sample and the RLUs found by the ARCHITECT immunoassay system optics are indirectly related.

Fasting blood glucose (FBG) determined by full automated Dri-Chem Fujifilm system

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(colorimetric assay). Chemiluminescent microparticle immunoassay (CMIA), a fully automated Abbott system method for quantifying human insulin in human serum or plasma, was used to test the amount of serum insulin. Using a fluorescence immunoassay (FIA) and a fully automated AFIAS system, glycated haemoglobin (HbA1c) was measured. The VIDAS system (Enzyme Linked fluorescence Assay), which combines an enzyme immunoassay competition approach with a final fluorescence detection (ELFA), was used to measure the amount of testosterone.

IR and ß-cell function were determined using the Homeostatic Model Assessment equations:

IR: **(HOMA-IR) = FBG × insulin/405**

Where, FBG in mg/dL, insulin in µIU/ml.

ß-cell function: **(HOMA-B) = 360 × insulin/FBG–63**

Where, FBG in mg/dL, insulin in µIU/ml.

The data were presented as mean± standard deviation and percentage using the Statistical Package for Social Science (SPSS) software, version 26. Use the independent T-test for comparing two groups. If the P-value was less than 0.05, it was deemed statistically significant.

Results

Table 1 lists the research groups' characteristics. BMI, WC, DBP, and SBP were significantly higher in PCOS patients than in control women (P<0.001). Nonetheless, P > 0.05 suggested that the patients' and controls' ages did not differ significantly [9], [10].

Table 2 shows that patients with PCOS had substantially higher levels of Hcy, FBG, insulin, HOMA-IR, HOMA-B, testosterone (P < 0.001), and HbA1c (P<0.01) than control women.

Significant positive connections between Hcy levels and HOMA-IR, FBG, Insulin, HbA1c, and testosterone were found (P<0.05) in Table 3, which showed correlation analysis of Hcy levels with the observed biochemical parameters [11]. However, there was no significant relationship (P>0.05) between Hcy and HOMA B.

Table 1. Characteristics of the study groups

Characteristic	PCOS group (n=100)	Control women (n=100)
Age (years)	28.21±7.6	28.46 ± 6.7
BMI (kg/m^2)	28.34 ±5.2**	22.25±2.3
WC (cm)	91.3±12.08**	77.27± 6.03
SBP (mmHg)	120.49 ± 9.7*	116.9 ± 6.9
DBP (mmHg)	79.2 ± 7.89**	75.6 ± 6.35

Data are expressed as mean ± SD

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*: P < 0.01 (Patients with PCOS vs control women)
**: P < 0.001 (Patients with PCOS vs control women)

Table 2. Biochemical parameters among Patients with PCOS and control women

Parameter	Patients group (n=100)	Control group (n=100)
Hcy (µmol/L)	13.85 ± 2.68**	5.58 ± 1.52
FBG (mg/ dL)	89.29 ±8.55**	83.03 ±7.212
Insulin (µU/mL)	16.47 ± 3.72**	8.55± 1.69
HbA1c (%)	5.212 ± 0.595*	5.03 ± 0.47
HOMA-IR	3.66 ±1.01**	1.76 ± 0.438
HOMA –B	248.8±100.5**	187.68±145.3
Testosterone (ng/ml)	1.006 ± 0.34**	0.47 ± 0.15

Data are expressed as mean ± SD
*: P < 0.01 (Patients with PCOS vs control women)
**: P < 0.001 (Patients with PCOS vs control women)

Table 3. Correlation of Hcy levels with the biochemical parameters

Parameter		**Hcy**
HOMA -IR	Pearson Correlation	.827**
	Sig. (2-tailed)	.000
HOMA -B	Pearson Correlation	.086
	Sig. (2-tailed)	.394
FBG	Pearson Correlation	.454**
	Sig. (2-tailed)	.000
Insuli n	Pearson Correlation	.840**
	Sig. (2-tailed)	.000
HbA1c	Pearson Correlation	.652**
	Sig. (2-tailed)	.000
T.T	Pearson Correlation	.504**
	Sig. (2-tailed)	.000

Discussion

Recent studies have demonstrated that PCOS is a multi-metabolic syndrome in addition to being the most prevalent reproductive illness. Therefore, T2D, hypertension, dyslipidemia, and CVD are more likely to occur in women with PCOS [12], [13]. Recent studies have concentrated on the local and systemic effects of IR as well as its secondary consequences, which include ovarian, metabolic, and systemic impacts. There is evidence that hyperinsulinemia and/or the IR in the general population may have a number of harmful metabolic implications, such as raising plasma Hcy [14]. The finding of high BMI and WC among women with PCOS in this study could be attributed to metabolic disorder. such as Hyperandrogenism, IR, dyslipidemia, and glucose intolerance, which has been

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linked to PCOS [15]. These results are in agreement with another study [16].

The present study reported significantly higher Hcy levels among women with PCOS, a result also confirmed by others [17], [18], [19]. This may be caused by PCOS women exhibiting diminished insulin sensitivity, potentially leading to excessive release of inflammatory agents and the promotion of IR; this, in turn, may precipitate hyperhomocysteinemia [20]. Additionally, obesity increases visceral adipose tissue, which disrupts certain hepatic functions through the porta and changes the normal action of enzymes involved in the clearance of Hcy. [21]. In addition, this study found significantly elevated insulin and FBS concentrations in PCOS. This finding may be is due to higher frequencies of overweight and obesity among patients with PCOS [22]. Excess fat has been shown to activate protein kinase, which in turn decreases glucose absorption and causes compensatory hyperinsulinemia. This can result in excessive fat storage by causing adipose cells to grow and proliferate in an environment with excess calories. In a vicious cycle, this is making IR worse by making people more obese [23]. This may be also related to decreased levels of GLUT4 levels in subcutaneous adipose tissue in with PCOS, resulting in insulin insensitivity [24].

HOMA-IR and HOMA-B values were found to be significantly higher among women with PCOS. This is similar to results of other studies [25],[26]. IR was the most important predictor of β-cell function in both normal and PCOS women. Compensatory hyperinsulinemia helps to keep plasma glucose levels within normal limits. The majority of women had appropriate β-cell activity as their FBG levels were normal. The study found that the most insulin-resistant PCOS women had extremely high amounts of β-cells secreting insulin. Nonetheless, these patients could be more susceptible to T2D development and β cell depletion [27].

Furthermore, the present study reported significantly higher testosterone levels in association with PCOS, a result comparable to the finding of others [28], [29]. This could be due to most of PCOS patients suffer from obesity. This increases functional ovarian hyperandrogenism and makes thecal cells more sensitive to luteinizing hormone (LH) activation [30]. Sex hormone-binding globulin (SHBG) in PCOS women is low as these patients have elevated androgen concentration with compensatory hyperandrogenemia and IR. Furthermore, androgens and insulin inhibit synthesis and hepatic SHBG secretion [31].

The present study revealed significant positive correlations of Hyc with HOMA-IR, FBG, insulin, HbA1c and Testosterone. There are several possible mechanisms that can explain these correlations. First, increased Hcy concentrations led to lipid buildup and changed lipids in organs. Second, endoplasmic reticulum stress caused by Hcy dysregulates the pathways involved in the manufacture of triglycerides and cholesterol, resulting in abnormal lipid metabolism. Third, obesity is thought to be a chronic inflammatory disease. In this context, it was discovered that higher Hcy levels were linked to inflammatory markers including fibrinogen and CRP [32]. VLDL C overproduction may be accompanied with IR. This results in smaller, denser LDL C, fewer HDL C particles, and more TG particles [33].

Conclusion

It has been found that significant positive correlation exists between HOMA-IR and serum Hcy level [34]. Additionally, the current investigation discovered favourable relationships between Hcy and IR and insulin. This result is consistent with what other people have seen [35], [36]. Mohammed et al [37] reported correlation between IR and Hcy. This may be due to the insulin that inhibits hepatic cystathionin beta synthase activity. Furthermore, testosterone showed positive correlations with Hcy, a result also observed in other study [38]. However, there was no discernible relationship between Hcy and ß-cell

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function in this investigation.

In summary, there is a strong association between Hcy and insulin, HOMA-IR, and other glycaemic indicators. As a result, women with PCOS are much more likely to develop T2D, MetS, and CVD, as well as the negative effects of these conditions.

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