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Association between glycine levels and insulin resistance in women with polycystic ovary syndrome: A case-control study

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Abstract

Background and objective: Polycystic Ovary Syndrome (PCOS) is an endocrine disorder with multi-factorial origins characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology. Its pathogenesis is complex, but one of the leading contributors to hyperandrogenism is insulin resistance (IR) which leads to a greater likelihood of developing type 2 diabetes mellitus (T2DM). This study aims to analyze the association between PCOS and T2DM, with a focus on IR and the potential moderating role of glycine.

Methods: This case-control study included 100 women (50 PCOS and 50 controls) aged 18–35 years. Women with PCOS showed significantly higher glycated hemoglobin (HbA1c) (6.014% ± 0.042 vs. 4.372% ± 0.071), fasting blood glucose (FBG) (97.25 ± 0.285 vs. 85.48 ± 0.755 mg/dL), insulin levels (20.24 ± 0.581 vs. 4.624 ± 0.087 µU/mL), and HOMA-IR (4.929 ± 0.125 vs. 0.982 ± 0.026) compared to controls (all P <0.001). Glycine levels were significantly lower in PCOS (125.76 ± 1.868 vs. 294.28 ± 8.754 µmol/L, P <0.001).

Results: COS women also had significantly higher insulin, fasting glucose, homeostasis model assessment for (HOMA-IR), and HbA1c levels but lower glycine levels compared with controls. Glycine was negatively correlated with insulin and HOMA-IR, while there were significant positive correlations between insulin and HOMA-IR (P <0.001).

Conclusion: These findings demonstrate that IR is a key factor in the metabolic dysfunction associated with PCOS and the potential development of T2DM.

Keywords: Biomarkers, Glycine, Insulin Resistance, Polycystic Ovary Syndrome, Type 2 Diabetes.

Introduction

PCOS is a common endocrine disorder affecting females of reproductive age. It is characterized by hyperandrogenism (having raised male hormones), menstrual irregularities, and the

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existence of cysts structures inside the ovaries identifiable through the ultrasound imaging (1). Nonetheless, IR is one of the vital processes in the pathophysiology of PCOS, which relegates PCOS, mainly a metabolic condition as opposed to a reproductive condition (2).

Other prevailing effects of PCOS, which are manifested in the long-term outcomes, are diabetes mellitus, cardiovascular disorders, and other metabolic conditions (1, 2). IR is a condition whereby the body cells do not respond positively to the insulin, hence compensatory hyperinsulinemia and decreased glucose consumption occur (3). Notably, a huge percentage of women having PCOS experience IR despite the weight-level and this determines the intensity of the syndrome (4). This IR culminates into stimulation of ovarian androgen production, which worsens the clinical manifestations like hirsutism, acne, and anovulation (5). Thus, proper determination and awareness of metabolic risk in PCOS involves assessment of IR (4, 5).

HbA1c has risen as an indispensable biomarker of long-term glycemic control. In contrast to fasting glucose that is a one-time reflection of blood sugar level, HbA1c is an average blood sugar level within two to three months (6, 7). Although lean PCOS women without evident diabetes do not have elevated HbA1c, early metabolic disturbances and chronic hyperglycemia can be seen (8). In turn, HbA1c is also becoming an effective biomarker of IR and development of T2DM among women with PCOS (9).

The role of amino acids in metabolic health is also starting to be investigated as new research finds that some may improve insulin sensitivity, decrease oxidative stress, and help to regulate inflammation, especially glycine, a non-essential amino acid (10). Developing IR, obesity and T2DM have been linked to lower glycine plasma concentrations (11, 12). These results indicate that glycine should be considered as protective metabolic component, and its deficiency points to deteriorated metabolism (13).

Although they are encouraging results, the subject of glycine levels and their association with IR in PCOS women has not been fully determined (14). In examining this relationship together with HbA1c, a known metabolic indicator, this study will deepen the knowledge on the metabolic imbalance in PCOS and evaluate the possibility of the use of HbA1c and glycine as markers and therapeutic targets.

In particular, this study will hypothesize to compare IR, glycine, and HbA1c among women with PCOS. Evolution of reliable biomarkers glycine and HbA1c might allow more customized and precise treatment options, especially in women on higher risk of T2DM development (15). It is possible that

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early metabolic risk factor detection can be followed up by diet, pharmacotherapy, and life style changes to enhance insulin sensitivity and reproductive performance (16). Finally, investigating glycine levels allows us to open a new branch within the area of amino acid-based treatment (15, 16).

Glycine supplementation or following a diet rich in glycine may be considered a new and non-hazardous intervention of IR in such populations (16). Such an intervention would be useful primarily in settings where access to advanced medical technology is scarce and PCOS is prevalent (17). IR continues to be a core aspect regarding PCOS pathogenesis, whereas the functions of glycine and HbA1c as marker and regulators of metabolism have gained more attention (17, 18). The interrelations between the mentioned variables could become new areas of study and clinical tools to manage PCOS (18).

Therefore, this study aims to investigate the role of IR in the development of T2DM among women with PCOS and to assess the potential effectiveness of glycine in improving insulin sensitivity and reducing diabetes risk.

Materials and Methods

Study Design: A total of 100 participants were used in this case-control study. The case group consisted of 50 women with PCOS and the control group were 50 healthy women with no PCOS. All the participants were aged between 18 and 35. The analysis comprised the assessment of the following parameters: level of glycine in the blood serum, fasting insulin, IR, HbA1c, FBG.

Study Setting: The study was conducted at the Outpatient Clinic of the Maternity Teaching Hospital in Erbil, within the Kurdistan Region of Iraq, between October 2024 and February 2025.

Inclusion Criteria: Eligible participants included females aged 18 to 35 years, either married or single, who were clinically diagnosed with PCOS based on the Rotterdam criteria. None of the participants had a prior diagnosis of (T2DM).

Exclusion Criteria: Exclusion criteria included males, females under 18 years of age, and individuals with a confirmed diagnosis of T2DM or other chronic medical conditions known to affect metabolic health.

Data Collection and Biochemical Evaluation: Following informed consent and explanation of the study objectives, 5 mL of venous blood was collected from all participants after an overnight fast of 8–12 hours. The samples were centrifuged to separate the serum, which was stored at −20°C until analysis. Serum levels of insulin, glycine, and FBG were measured using the Cobas 6000 fully automated analyzer (Roche Diagnostics, Germany). Glycine was quantified using an enzymatic colorimetric assay according to the

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manufacturer's instructions. The assay was validated under standard laboratory protocols, and internal quality control procedures were applied. The reference range for serum glycine was 150–450 µmol/L (14). HbA1c was measured from whole blood using the same analyzer system, following the manufacturer's recommended protocol.

IR was calculated using the Homeostasis Model Assessment of IR (HOMA-IR) according to the following formula:

HOMA-IR = (Fasting Insulin [µU/mL] × Fasting Glucose [mg/dL]) / 405 (4).

Ethical Approval: The study protocol was approved by the Ethical Committee of the Hawler Directorate of Health and the Scientific Committee of the College of Health Sciences at Hawler Medical University (Approval Number: Sc.EC.11HI).

Statistical Analysis: Data analysis was carried out using the Statistical Package for the Social Sciences (SPSS, version 23.0). Descriptive statistics were expressed as mean ± standard error of the mean (SEM). The Shapiro-Wilk test was used to assess the normality of the data. Since the data were normally distributed, an independent sample t-test was employed to compare the mean values between the case (PCOS) and control groups. To evaluate relationships between variables, Pearson correlation analysis was used. A P-value less than 0.05 was considered statistically significant. Additionally, effect sizes (e.g., Pearson's r) and 95% confidence intervals (CIs) were reported where applicable to strengthen the interpretation of results.

Results

An independent t-test comparing biochemical and metabolic parameters between the control and PCOS groups revealed significant differences across all measured markers (Table 1). Women with PCOS had significantly higher levels of HbA1c, FBG, insulin, and IR (HOMA-IR) compared to healthy controls ($P < 0.001$ for all). Conversely, serum glycine levels were significantly lower in the PCOS group ($P < 0.001$).

Correlation results, as shown in Figure 1, insulin hormone levels exhibited a strong positive correlation with IR in the PCOS group ($r = 0.993$, $P < 0.001$). This indicates that elevated insulin levels are closely linked to increased IR. In contrast, Figure 2 demonstrates a strong negative correlation between glycine and HOMA-IR ($r = –0.986$, $P < 0.001$), suggesting that lower glycine levels are associated with greater IR.

Additionally, Figure 3 illustrates a strong inverse relationship between glycine and insulin hormone levels ($r = –0.994$, $P < 0.001$), further supporting the potential protective role of glycine in metabolic regulation. These correlations were weak and non-significant in the control group, reflecting stable

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metabolic control in the absence of PCOS.

Overall, the findings highlight significant metabolic disturbances in women with PCOS and support glycine's potential utility as an early biomarker for metabolic dysfunction in this population. Correlation results, as shown in Figure 1, insulin hormone levels exhibited a strong positive correlation with IR in the PCOS group (r = 0.993, P <0.001). This indicates that elevated insulin levels are closely linked to increased IR. In contrast, Figure 2 demonstrates a strong negative correlation between glycine and HOMA-IR (r = –0.986, P <0.001), suggesting that lower glycine levels are associated with greater IR.

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Table 1. Comparison of metabolic markers between women with PCOS (Case group) and healthy controls (Control group)

Parameters	Group 1	Group 2	P-value (t-test)
HbA1c (%)	4.372 ± 0.071	6.014 ± 0.042	<0.001
FBG (mg/dL)	85.48±0.755	97.25±0.285	<0.001
Insulin Hormone (µU/mL)	4.624± 0.087	20.24±0.581	<0.001
IR(HOMA-IR)	0.982±0.026	4.929±0.125	<0.001
Glycine (µmol/L)	294.28±8.754	125.76±1.868	<0.001

Values are expressed as mean ±SEM.

Difference considered statistically significant at P <0.05.

Abbreviations: PCOS = Polycystic Ovary Syndrome; HbA1c= Glycated Hemoglobin; FBG = Fasting Blood Glucose; IR = Insulin Resistance; SEM = Standard Error of the Mean.

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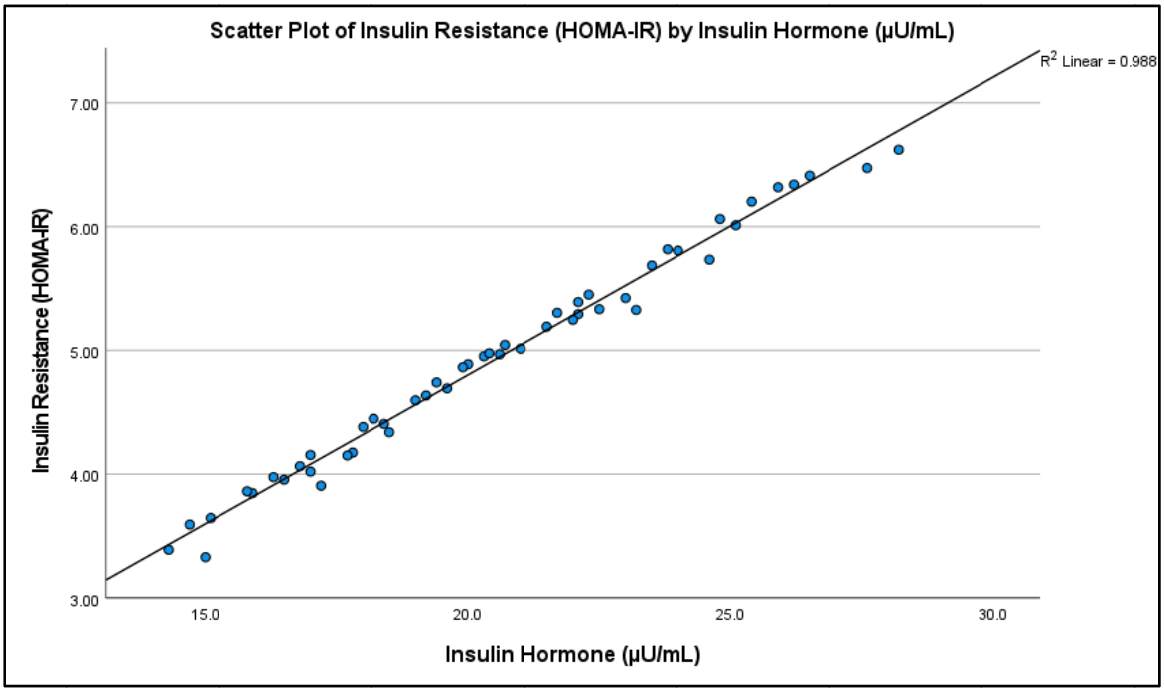

Figure 1. Scatter plot showing a strong positive correlation between insulin hormone levels (µU/mL) and IR (HOMA-IR) in the PCOS group (r = 0.993, P <0.001)

X-axis: Insulin Hormone (µU/mL); Y-axis: IR (HOMA-IR).

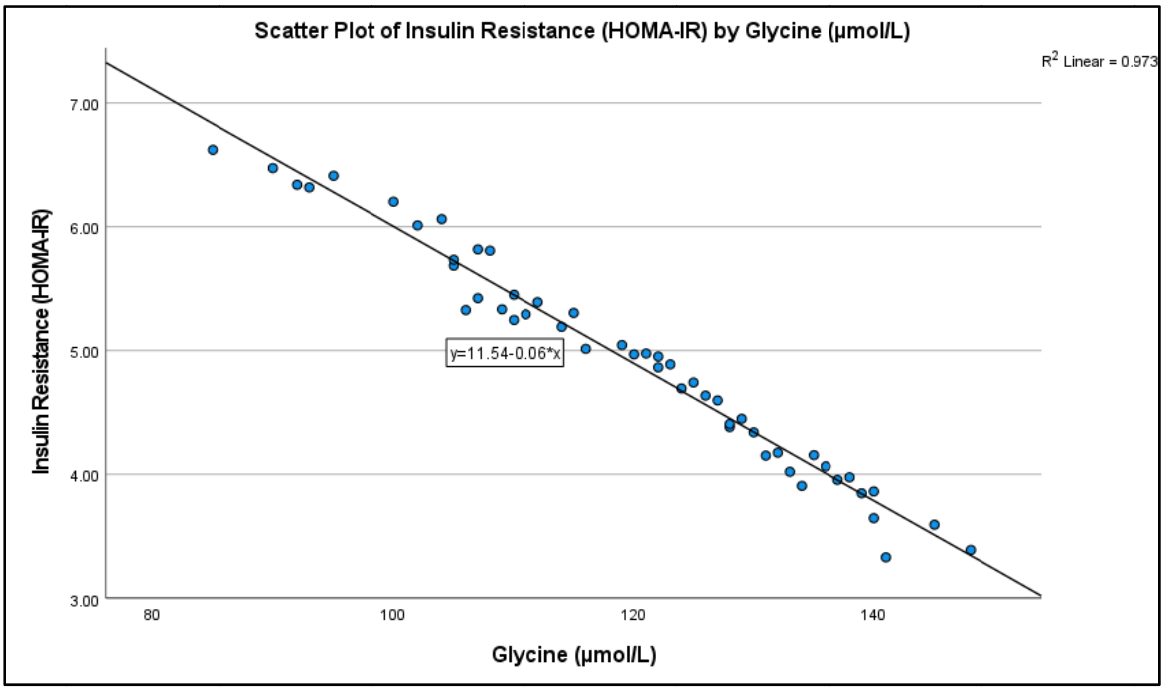

Figure 2. Scatter plot showing a strong negative correlation between glycine (µmol/L) and IR (HOMA-IR) in the PCOS group (r = –0.986, P <0.001)

X-axis: Glycine (µmol/L); Y-axis: IR (HOMA-IR).

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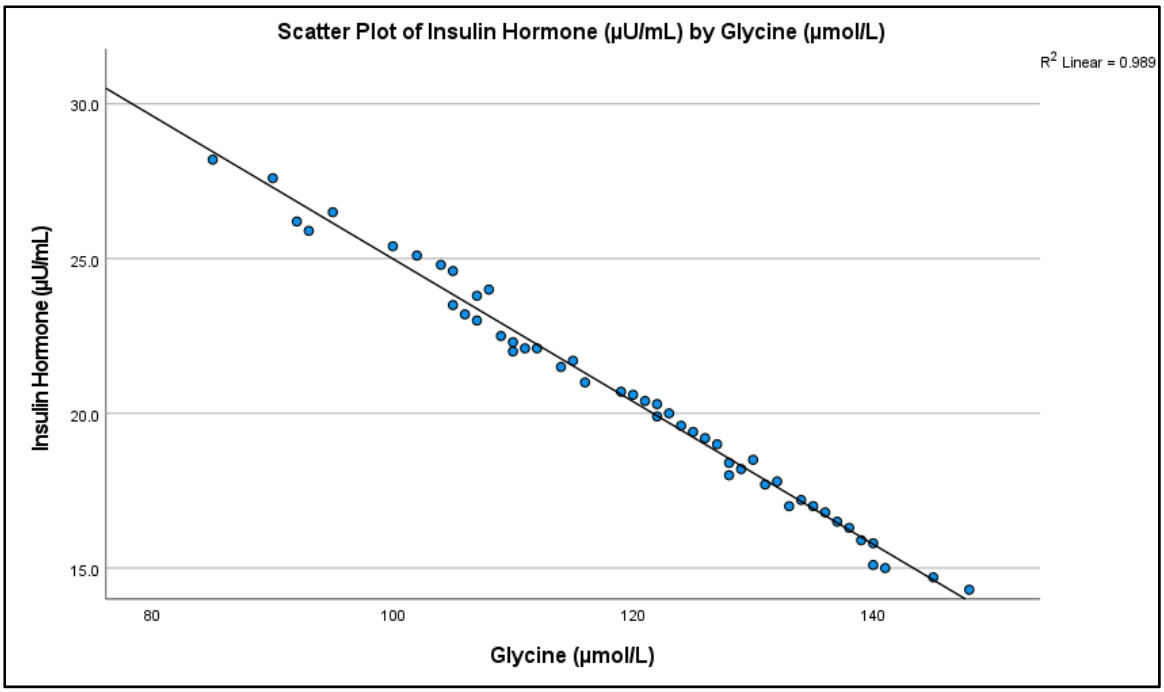

Figure 3. Scatter plot showing a strong negative correlation between glycine (µmol/L) and insulin hormone levels (µU/mL) in the PCOS group (r = –0.994, P <0.001)

X-axis: Glycine (µmol/L); Y-axis: Insulin Hormone (µU/mL).

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Discussion

This study measured glycine and IR levels in women with PCOS compared to healthy controls, while evaluating HbA1c as a long-term glycemic marker. Metabolic dysregulation was severe in the PCOS group with the accumulation of HbA1c levels, FBG, insulin levels, and HOMA-IR, as well as low glycine levels. These findings may confirm the assumption that IR can be considered one of the major characteristics of PCOS and that additional research in the field of glycine-related metabolic regulation can help to determine its importance. Besides, glycine and HbA1c may also be biomarkers of increased metabolic risk in PCOS at an early stage.

The elevated levels of insulin and HOMA- IR in PCOS patients concur with previous studies that appreciate that IR is the core of both the reproductive and metabolic abnormalities in PCOS irrespective of the body mass index (3-5). The result of close correlation between insulin and HOMA-IR that we have found in this population ($r = 0.993$, $P < 0.001$) once again proves the strong connection between hyperinsulinemia and IR (8). In addition, the significantly higher HbA1c levels in PCOS women compared to controls indicate long-term glycemic dysregulation even in the absence of overt diabetes. This is consistent with previous research linking elevated HbA1c in PCOS to increased risk of glucose intolerance and early metabolic disturbances (9). The correlation between FBG and HbA1c in our study reinforces the clinical utility of HbA1c as a marker for glycemic control and metabolic risk assessment in PCOS.

A novel and important finding in this study is the markedly lower glycine levels in women with PCOS. This observation is supported by earlier reports showing reduced circulating glycine in individuals with IR and type 2 diabetes (12, 13). the data demonstrated strong negative correlations between glycine and both HOMA-IR ($r = –0.986$, $P < 0.001$) and insulin levels ($r = –0.994$, $P < 0.001$), suggesting that decreased glycine may either contribute to or result from metabolic strain in PCOS. These findings highlight the potential regulatory role of glycine in insulin sensitivity and metabolic balance (12-14). Moreover, previous studies have reported improved insulin sensitivity and reduced oxidative stress following glycine supplementation in patients with metabolic syndrome (13). Our results corroborate these findings by showing an inverse relationship between glycine and IR, supporting glycine's protective effect in PCOS-related metabolic dysfunction (14). In contrast, the control group exhibited weaker, non-significant correlations among the studied variables, reflecting more stable metabolic regulation.

On the whole, all of these findings confirm the hypothesis that glycine acts

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as a sensor against IR and metabolic disturbance PCOS. The results underline the significance of the incorporation of glycine and HbA1c as easily skewed indicators of early assessment of metabolic risk. This is particularly applicable in resource-scarce environment where sophisticated diagnostics are not readily available to allow timely preventative measures which can include change in diet, physical activity, and possible glycine supplementation.

Clinical Application: Glycine may serve as a novel, accessible biomarker for early detection of IR in PCOS, supporting personalized metabolic interventions, especially in resource-limited settings.

Limitations: The sample size was relatively small and this study was performed at one center, which can also be the limitation of the findings generalizability. It is a case-control study, thus not able to prove the relationship as being causative between glycine levels and IR. Moreover, other confounders like diet and life style were not adjusted. Larger, prospective studies are required to confirm the role of glycine supplementation in improving insulin sensitivity and preventing metabolic complications in women with PCOS.

Conclusion

This study demonstrates that women with PCOS show significant metabolic disturbances, including elevated insulin, HOMA-IR, FBG, and HbA1c levels, along with reduced glycine concentrations. Routine assessment of glycine levels and HbA1c in PCOS patients may provide an early indication of metabolic risk and allow for timely interventions. Future research should explore the effectiveness of glycine supplementation in improving insulin sensitivity and preventing long-term metabolic complications in this population.

Competing interest

The authors declare that they have no competing interests.

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