

Correlation Between Hemoglobin Levels and Polycystic Ovary Syndrome Metabolic Disorder

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Objective: The purpose of this study was to explore the relationship between hemoglobin levels and metabolic disorders in patients with PCOS.

Methods: A total of 573 patients were selected, based on the hemoglobin level; 342 patients with PCOS were divided into two groups as follows: Group A (normal Hb group, n = 269) and Group B (high Hb group, n = 73); 231 non-PCOS patients were divided into two groups as follows: Group C (normal Hb group, n = 199), and Group D (high Hb group, n = 32). The general information, glucose and lipid metabolism indicators, and uric acid levels of all patients were compiled for data analysis.

Results: (1) Hb, HGB concentration in mean red blood cells and RDW in PCOS patients were higher than those in non-PCOS patients, and MCV was lower than that in non-PCOS patients ($P < 0.05$); (2) Compared with Group A, patients in Group B had higher BMI, Hb, 2-hPG, FINS, 2-hINS, HOMA-IR, LDL-C, and uric acid levels while the QUICKI was lower; in Group C, the age, FSH, HDL-C, and LDL-C were higher, and AMH, BMI, T, TG, and uric acid level were lower ($P < 0.05$); compared with Group D, AMH, BMI, FINS, HOMA-IR, TG, uric acid level increased, while age, FSH, and QUICKI decreased in Group B; and Hb and T decreased in Group C ($P < 0.05$); (3) Pearson's correlation analysis indicated that Hb in PCOS patients was positively correlated with BMI, FPG, 2-hPG, FINS, 2-hINS, and HOMA-IR, and negatively correlated with the QUICKI ($P < 0.05$); (4) Multi-factor logistic regression analysis suggested that the high Hb level in PCOS patients was an independent risk factor of IR ($P < 0.05$).

Conclusion: Hb level in patients with PCOS was associated with BMI and glucose metabolism indicators; a high Hb level may be an independent risk factor for IR.

Keywords: hemoglobin, insulin resistance, metabolic disorder, polycystic ovary syndrome

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine metabolic disorders affecting women of childbearing age.¹ It is characterized by hyperandrogenemia, scanty or amenorrhoeic menstruation, and infertility, as well as metabolic disorders such as obesity, insulin resistance, abnormal glucose tolerance, and lipid spectrum disorder, as well as long-term susceptibility to diabetes, cardiovascular disease, tumors, and so on.² A large-scale national epidemiological survey in China reported that the prevalence of metabolic syndrome in women with PCOS was significantly higher than that in non-PCOS women of childbearing age.³ As a result, detecting metabolic changes in PCOS patients at an early stage is crucial.

Hemoglobin (Hb) is an important transporter of oxygen in the body, and its level can be influenced by genes and the environment.⁴ A number of previous studies have demonstrated that a high Hb level is associated with the incidence of metabolic syndrome (MS), hyperuricemia (HUA), and nonalcoholic fatty liver disease (NAFLD), and it can be considered one of the predictors of MS.⁵⁻⁸ Hemoglobin can induce vasoconstriction by limiting nitric oxide in vascular smooth muscle cells, and induced hypertension.⁹ Several studies have shown associations of HCT, Hgb, RBC, and WBC

with insulin resistance.^{10,11} However, the relationship between Hb levels and metabolic disorders in patients with PCOS has not been reported. Therefore, in this study, we investigated the possible mechanisms of metabolic disorders in patients with PCOS by examining the relationship between Hb levels and metabolic indicators.

Materials and Method

Study Participants and Grouping

A total of 342 patients with PCOS undergoing treatment at the Reproductive Medicine Center of Ningxia Medical University from January 2020 to July 2022 were selected and included in the study groups; and 231 individuals who have regular menstrual cycles with male factor or tubal factor infertility were included in the control group. PCOS was diagnosed based on any two of the following three items based on the 2003 Rotterdam PCOS Diagnostic Criteria (excluding other conditions causing hyperandrogenemia):^{12–14} 1) Sporadic ovulation or anovulation; 2) Hyperandrogenemia suggested by clinical or biochemical tests; 3) Ovarian polycystic change indicated by ultrasonography: ≥ 12 small follicles of 2–9 mm diameter in at least one ovary, and/or ovarian volume $> 10 \text{ cm}^3$. For all patients, hematologic disorders such as leukemia, anemia, liver or kidney disease, hyperthyroidism or hypothyroidism, autoimmune disease, and acute or chronic infectious disease were excluded from the study.

The normal range of hemoglobin concentration in adult women in China is 110–150 g/L, and concentration $> 150 \text{ g/L}$ was defined as elevated hemoglobin concentration.¹⁵ Based on hemoglobin levels, the patients were divided into Group A (PCOS normal hemoglobin group, $n = 269$), Group B (PCOS high hemoglobin group, $n = 73$), Group C (non-PCOS normal hemoglobin group, $n = 199$), and Group D (non-PCOS high hemoglobin group, $n = 32$). The study was approved by the Ethics Committee of Ningxia Medical University General Hospital, and all patients signed the informed consent form.

Medical History and Physical Examination

The medical history of the study participants was collected based on a standardized questionnaire and the participants underwent a physical examination that included measurement of height, body mass, waist circumference, hip circumference, and calculation of body mass index: $\text{BMI} = \text{body mass (kg)}/\text{height}^2 (\text{m}^2)$ while they were fasting. Overweight or obese: $\text{BMI} \geq 25 \text{ kg/m}^2$.

Determination of Physiological and Chemical Indicators

Fasting venous blood was drawn from the participants in the early morning of the 2nd to 5th day of menstruation, to test follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), testosterone (T), prolactin (PRL), anti-Müllerian hormone (AMH) using the chemiluminescence method. Blood routine was tested using an automatic blood cell analyzer. Fasting insulin (FINS), fasting plasma glucose (FPG), 2-hours plasma glucose (2-hPG), 2-hours insulin (2-hINS), blood lipids, and liver and kidney functions were tested using a fully automatic biochemical analyzer. $\text{HOMA-IR} = (\text{FPG} \times \text{FINS})/22.5$, $\text{QUICKI} = 1/(\lg \text{FINS} + \lg \text{FPG})$.

Statistical Analysis

The data were analyzed using SPSS 24.0 software. We used the Shapiro–Wilk test to determine if the measurement data conformed to the normal distribution or not. Data conforming to a normal distribution were expressed as $(\bar{x} \pm s)$, *t*-test was used to compare two groups, and the comparison between multiple groups was conducted using one-way analysis of variance (ANOVA). Data failing to conform to a normal distribution were expressed using the median (interquartile range), and inter-group comparisons were performed using the non-parametric Kruskal–Wallis *H*-test. We used Pearson correlation analysis for correlation analysis, and multiple-factor analysis was performed using multivariate logistic regression analysis. The receiver operating characteristic (ROC) curve was used to analyze the predictive value of hemoglobin levels for metabolic disorders in patients with PCOS. $P < 0.05$ indicated that there was a statistically significant difference. GraphPad Prism 8.0 was used for plotting and graphing data.

Results

Comparison of the Red Blood Cell Parameters of Patients in the PCOS and Control Groups

In patients with PCOS, the hemoglobin level, HGB concentration in mean red blood cells, and RDW (CV) were higher when compared to non-PCOS patients, while the red blood cell distribution volume was lower than that in non-PCOS patients (both $P < 0.05$). There was no significant difference in the other indicators between the two groups ($P > 0.05$), as shown in Table 1.

Comparison of General Information of Patients in Different Groups

Compared with Group A, BMI and hemoglobin levels were higher in Group B, while in Group C, patient age and FSH levels were higher, but AMH, BMI, and T levels were lower. Compared with Group D, patient age and FSH level were lower, but BMI and AMH level were higher in Group B, while in Group C, hemoglobin level and T levels were lower, showing a statistically significant difference ($P < 0.05$). There was no significant difference in LH, E2, PRL, and P levels in patients between different groups ($P > 0.05$), as shown in Table 2.

Comparison of Metabolic Indicators Between Different Groups

Compared with Group A, 2-hPG, FINS, 2-hINS, HOMA-IR, LDL-C, and uric acid levels were higher but QUICKI levels were lower in Group B, while in Group C, TG and uric acid levels were lower but HDL-C and LDL-C were higher ($P < 0.05$). Compared with Group D, FINS, HOMA-IR, TG, and uric acid levels were higher in Group B, but QUICKI levels were lower, showing a statistically significant difference ($P < 0.05$). There was no significant difference in FPG, TC, apoA1, and apoB between the different groups ($P > 0.05$), as shown in Table 3.

Table 1 Comparison of Erythrocyte Parameters Between the PCOS Group and Control Group ($\bar{x} \pm s$)

Group	PCOS Group (n=342)	Control Group (n=231)	T	P
RBC ($10^{12}/L$)	4.75±0.37	4.69±0.34	1.915	0.056
Hb (g/L)	140.66±10.89	138.72±10.22	2.138	0.033
HCT (%)	42.06±2.90	42.35±2.77	-1.179	0.239
MCV (fL)	88.89±5.01	90.38±4.26	-3.689	< 0.001
Mean HGB content in red blood cells (pg)	29.64±2.08	29.66±1.97	-0.117	0.907
Mean HGB concentration in red blood cells (g/L)	331.39±26.08	326.73±21.43	2.246	0.025
Red blood cell distribution width (SD)(%)	41.06±3.57	40.83±3.03	0.769	0.442
Red blood cell distribution width (CV)(%)	12.88±2.21	12.40±1.02	3.054	0.002

Abbreviations: RBC, red blood cell; Hb, hemoglobin; HCT, hematocrit; MCV, Mean Corpuscular Volume.

Table 2 Comparison of General Information of Patients Between Groups [$(\bar{x} \pm s)$, M (P25, P75)]

Group	Group A (n=269)	Group B (n=73)	Group C (n=199)	Group D (n=32)
Age (years)	30.32±3.81	30.21±3.65 [#]	33.59±4.59*	33.34±5.26
Hb (g/L)	136.85±8.85	154.70±4.05 [#]	136.39±8.96 [#]	153.22±3.28
BMI (kg/m ²)	24.28±3.81	26.66±4.57*	22.68±2.80*	22.78±2.83
FSH (IU/L)	6.09±1.91	6.35±1.73 [#]	8.06±3.73*	8.73±2.99
LH (IU/L)	5.55 (3.24, 8.59)	5.33 (3.48, 7.52)	2.83 (1.28, 4.33)	2.22 (1.17, 4.59)
E2 (pg/mL)	45.69 (33.11, 65.22)	45.87 (33.48, 62.71)	54.25 (37.81, 117.52)	42.85 (34.39, 56.55)
PRL (IU/L)	10.87 (8.31, 15.80)	13.41 (8.55, 16.66)	11.07 (8.07, 20.10)	8.36 (7.75, 10.39)
T (ng/dL)	33.47±17.17	35.99±17.10	24.39±10.69 [#]	34.32±18.03
P (pmol/mL)	0.56 (0.42, 0.90)	0.47 (0.33, 0.77)	0.83 (0.49, 10.41)	0.47 (0.75, 4.04)
AMH (ng/mL)	7.13±4.02	6.17±3.70 [#]	2.62±1.07*	2.19±1.73

Notes: *Indicates $P < 0.05$ compared with Group A, [#]Indicates $P < 0.05$ compared with Group D.

Table 3 Comparison of Metabolic Indexes Between Groups ($\bar{x} \pm s$)

Group	Group A (n=269)	Group B (n=73)	Group C (n=199)	Group D (n=32)
FPG (mmol/L)	5.05±0.92	5.30±1.16	5.02±0.38	5.03±0.47
2-hPG (mmol/L)	6.39±1.68	7.47±3.48*	–	–
FINS (mU/L)	13.10±8.65	17.33±7.02*#	11.51±5.89	10.75±4.64
2-hINS (mU/L)	75.19±42.21	111.17±71.76*	–	–
HOMA-IR	2.98±2.18	4.09±2.23*#	2.55±1.34	2.52±1.29
QUICKI	0.60±0.12	0.53±0.07*#	0.61±0.11	0.60±0.10
TC (mmol/L)	4.49±0.91	4.77±1.03	4.58±0.77	4.67±0.99
TG (mmol/L)	1.58±1.02	1.77±0.78#	1.19±0.67*	1.25±0.68
HDL-C (mmol/L)	1.26±0.36	1.22±0.29	1.34±0.27*	1.31±0.26
LDL-C (mmol/L)	2.33±0.76	2.87±0.90*	2.71±0.65*	2.82±0.89
apoA1 (g/L)	1.43±0.25	1.51±0.29	1.38±0.24	1.50±0.223
apoB (g/L)	0.83±0.24	0.89±0.23	0.81±0.20	0.76±0.17
Uric acid (umol/L)	313.23±89.98	346.53±74.51*#	280.27±74.84*	284.03±92.64

Notes: *Indicates $P < 0.05$ compared with Group A, #Indicates $P < 0.05$ compared with Group D.

Correlation Between Hemoglobin Levels and Metabolic Indicators in PCOS Patients

In patients with PCOS, the hemoglobin level was positively correlated with BMI, FPG, 2-hPG, FINS, 2-hINS, and HOMA-IR, but was negatively correlated with the QUICKI index, indicating statistical significance ($P < 0.05$), as shown in Table 4 and Figure 1.

Relationship Between Hemoglobin Level and Metabolic Components

In our regression model, we took the hemoglobin group as the independent variable, and the metabolic components (obesity, hyperglycemia, insulin resistance, dyslipidemia, and hyperuricemia) were the dependent variables. The model results showed that hemoglobin level was an independent risk factor affecting insulin resistance, and the risk of insulin resistance increased with the rise of hemoglobin levels, as shown in Table 5.

Table 4 Correlation Between Hemoglobin and Metabolic Indicators in Patients with PCOS

Index	<i>r</i>	<i>P</i>
BMI (kg/m ²)	0.191	< 0.001
FPG (mmol/L)	0.123	0.049
2-hPG (mmol/L)	0.152	0.049
FINS (mU/L)	0.168	0.023
2-hINS (mU/L)	0.222	0.006
HOMA-IR	0.170	0.029
QUICKI Index	-0.210	0.007
TG (mmol/L)	0.028	0.636
TC (mmol/L)	0.053	0.368
HDL-C (mmol/L)	-0.086	0.156
LDL-C (mmol/L)	0.115	0.056
apoA1 (g/L)	0.082	0.235
apoB (g/L)	0.118	0.089
Uric acid (umol/L)	0.117	0.069

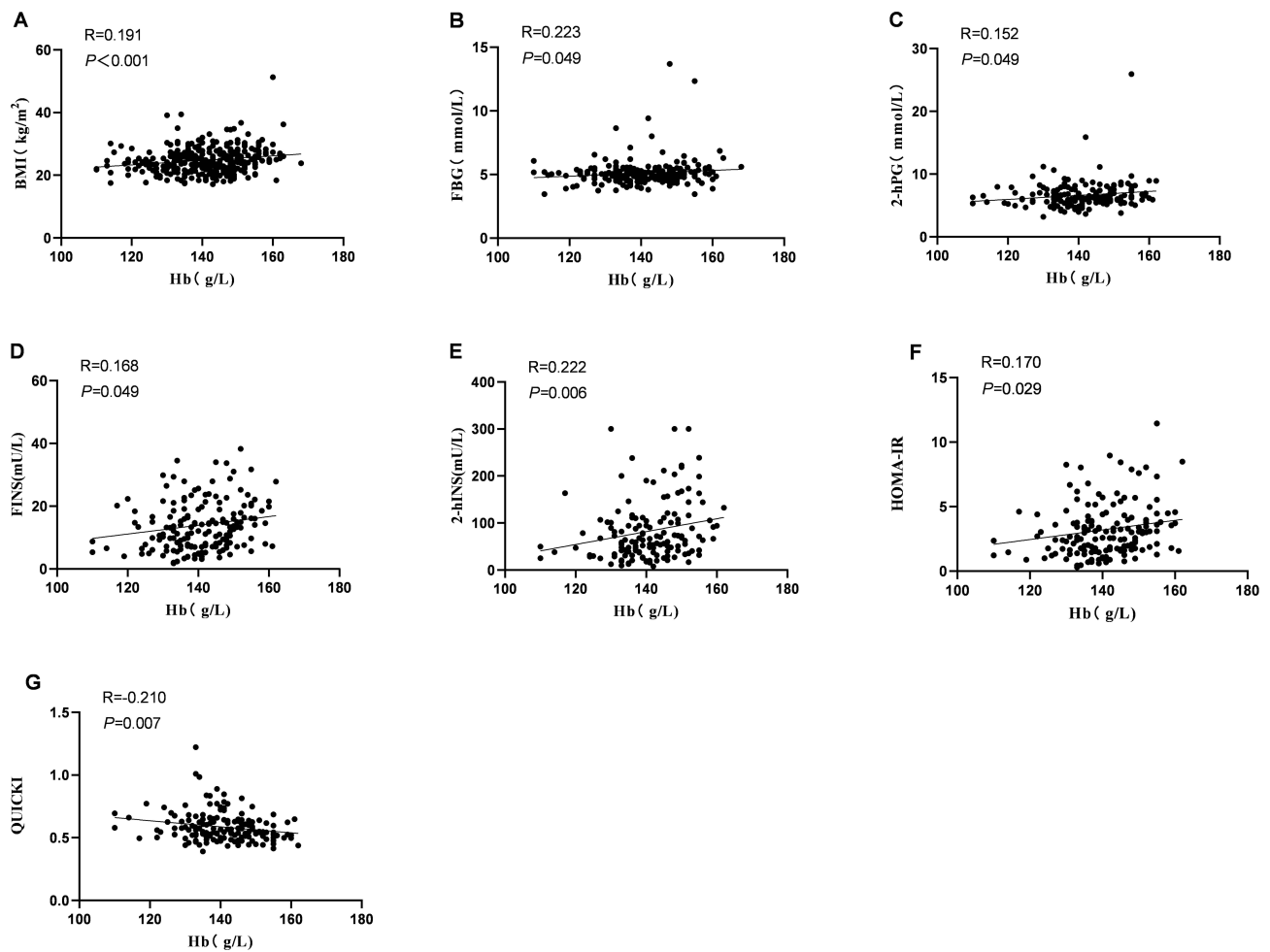


Figure 1 Relationship between hemoglobin levels and related metabolic indicators ((A) BMI, (B) FPG, (C) 2-hPG, (D) FINS, (E) 2-hINS, (F) HOMA-IR, (G) QUICKI) in patients with PCOS.

Prediction of IR in PCOS Patients Based on the Hemoglobin Level

ROC curve analysis was performed for predicting IR in patients with PCOS based on the hemoglobin level; based on the results, the area under the curve (AUC) was 0.801, $P < 0.001$, 95% CI (0.743, 0.850); when the hemoglobin level was 149.5 g/L, the sensitivity of IR in patients with PCOS was 0.718, and the specificity was 0.764, as shown in Figure 2.

Table 5 Correlation Between Metabolic Disorders and High Hemoglobin in Patients with PCOS

Components	B	SE	χ^2	P	OR	95% CI
Obesity	0.488	0.613	0.635	0.425	1.629	0.490–5.412
Dyslipidemia	0.267	0.594	0.203	0.653	0.766	0.239–2.450
Hyperglycemia	0.941	1.153	0.665	0.415	2.561	0.267–24.553
Insulin resistance	3.085	0.593	27.027	< 0.001	21.872	6.835–69.988
Hyperuricemia	0.017	0.631	0.001	0.979	0.983	0.285–3.390

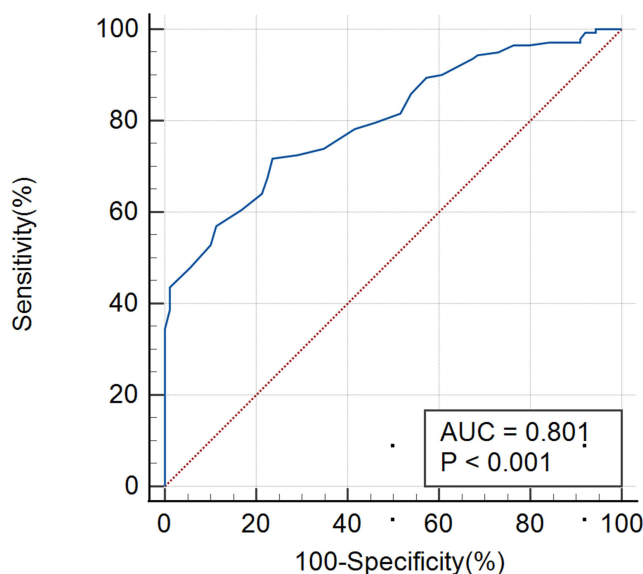


Figure 2 Prediction of IR in patients with PCOS based on hemoglobin levels based on the ROC curve.

Discussion

PCOS is a common reproductive endocrine metabolic disorder that can lead to ovulatory infertility as well as obesity and glucose and lipid metabolism disorders; as a result, it has gradually gained a lot of research attention. In the current study, we found that Hb levels, HGB concentration in mean red blood cells, and the red blood cell distribution width (RDW) in patients with PCOS were higher than those in non-PCOS patients, while the mean corpuscular volume (MCV) was lower than that in non-PCOS patients.

Hyperandrogenemia is an important pathophysiological feature of PCOS. In the current study, the T level in patients in the PCOS group and non-PCOS high hemoglobin group was significantly higher than that in the non-PCOS normal hemoglobin group, suggesting that testosterone may be involved in the elevation of Hb. Testosterone was found to induce erythropoiesis and increase Hb levels by affecting the bioavailability of iron and stimulating the differentiation of erythropoietin (EPO).^{16,17}

Multiple studies have shown that patients with PCOS are more prone to obstructive sleep apnea (OSA) than non-PCOS patients of childbearing age,^{18,19} and Hb levels were significantly higher in patients with OSA.²⁰ Persistent hypoxemia has been recognized to be involved in the pathological change process of OSA,²¹ and chronic hypoxia stimulates EPO synthesis, thus promoting an increase in Hb and RBC in the peripheral circulation.²² Therefore, it is necessary to screen for OSA in patients with PCOS presenting elevated hemoglobin levels.

Furthermore, other studies^{23,24} found that the RDW level was higher in patients with PCOS, which was consistent with the results of our study. Qiang et al²³ showed that the high RDW level in PCOS patients was positively correlated with hs-CRP, HOMA-IR, and BMI. PCOS is a chronic inflammatory disease²⁵ that can cause oxidative stress by stimulating immature red blood cells to release RDW and increasing the mean HGB concentration.²⁶ As a result, the increase in RDW and mean HGB concentration can be associated with chronic low-grade inflammation in patients with PCOS.

MS was found to be 2.5 times more common in patients with PCOS than in normal women.²⁷ Previous studies showed that PCOS patients had varying degrees of metabolic disorders.^{28,29} In the current study, BMI and uric acid levels in the PCOS high Hb level group were higher than those in other groups, suggesting that BMI could affect Hb levels in patients with PCOS. Our correlation analysis revealed a significant positive correlation between Hb levels and BMI in patients with PCOS, which was consistent with the result of Shimizu et al.³⁰ Obesity was seen in 30–70% of PCOS patients,³¹ and the decreased oxygenation of adipose tissue resulted in overexpression of erythropoietin transcription-stimulating factors such as hypoxia-inducible factor (HIF-1),³² thus stimulating the increase of hemoglobin synthesis.

Very high rates of OSA have been reported in women with obese PCOS,^{33,34} and obesity and OSA cooperate with each other to further promote elevated hemoglobin levels.

In addition, CD40L is a member of the tumor necrosis factor (TNF) family that has been linked to glucose and lipid metabolism disorders and the development of cardiovascular disease.³⁵ CD40L levels were significantly higher in patients with high Hb levels and patients with obesity^{36,37} while other studies found CD40L to be positively correlated with BMI and Hb levels^{37,38} and Hb to be an independent risk factor for elevated CD40L.³⁶ Therefore, we hypothesized that CD40L could have a potential link between hemoglobin and obesity.

Insulin resistance (IR) has been identified as the critical link in the development and progression of PCOS.³⁹ We found that 2-hPG, FINS, 2-hINS, and HOMA-IR were higher, but the QUICKI index was lower in the high Hb level group, and they were significantly correlated with the Hb level. Additional logistic regression revealed that the Hb level was an independent risk factor for the development of insulin resistance in patients with PCOS, which was consistent with the results of previous studies.^{40,41} Endothelial dysfunction has been found to be an important risk factor for insulin resistance; hemoglobin, as the carrier and buffer of nitric oxide (NO), can regulate vascular endothelial function via the L-arginine-NO pathway, and a high Hb level can lead to endothelial dysfunction, thus causing insulin resistance.^{42–44} Hemoglobin has been found to be closely related to HCT; elevated hemoglobin increases blood viscosity, reduces blood flow, and affects the supply of oxygen, glucose, and insulin in the tissues, thus promoting insulin resistance.⁴⁵ Furthermore, high Hb levels can cause oxidative stress in pancreatic β -cells, impair their functioning, and lower insulin sensitivity, thus leading to abnormal glucose metabolism.⁴⁶

Another study showed that insulin could also promote the proliferation of bone marrow and hematopoietic stem cells, and bind to receptors on red blood cells,⁴⁷ thus stimulating the proliferation of red blood cells and increasing the Hb level. Hyperinsulinemia might exert its effects in erythropoiesis through several different mechanisms. Insulin and its analogues, such as the IGF-1, have a synergistic effect with erythropoietin on stimulating the proliferation of erythroid colonies.^{48,49} Also, hyperinsulinemia has been associated with increased levels of the hypoxia-inducible factor-1 alpha (HIF-1 α), which promotes the synthesis of proteins, including the vascular endothelial growth factor and erythropoietin that stimulate erythropoiesis.^{50,51} As a result, hemoglobin and insulin resistance may be regulated in a two-way manner, with each influencing the other.

Conclusion

In conclusion, we found that hemoglobin levels in patients with PCOS were higher than in non-PCOS patients. High hemoglobin levels were an independent risk factor of IR in PCOS patients. Blood routine testing is a simple and low-cost testing method, and its use as an indicator for screening metabolic disorders in patients with PCOS should be further studied.

Data Sharing Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the Declaration of Helsinki (as was revised in 2013). The study was approved by Ethics Committee of the General Hospital of Ningxia Medical University (No.KYLL-2021-1073). Written informed consent was obtained from all participants.

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Disclosure

The authors declare that they have no competing interests in this work.

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