ORIGINAL

Can Red cell distribution width screen for metabolic abnormality in women with Polycystic Ovarian Syndrome?

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Abstract : Polycystic ovarian syndrome (PCOS) is a prevalent endocrinopathy in reproductive-age females, accredited to a chronic low-grade inflammatory reaction. Red distribution width (RDW), a parameter of complete blood count, was tested as an inflammatory marker ; higher RDW was linked to metabolic syndrome. We aimed to examine RDW in distinguishing PCOS-related metabolic and hormonal abnormalities. Methods : A case-control study recruited 128 women, divided into PCOS cases (64/128) and controls (64/128) according to Rotterdam criteria. Body mass index (BMI), estimated complete blood count parameters, hormonal markers (serum follicle-stimulating hormone (FSH), luteinizing hormone, and serum testosterone), and metabolic markers (HOMA-IR, serum high and low-density lipoprotein) were measured. Results showed that RDW was significantly higher in PCOS. HOMA-IR, LDL, testosterone, and LH/FSH were higher in PCOS and strongly correlated with RDW with positive correlations. HDL was elevated and correlated negatively with RDW in PCOS. ROC calculated (13.55) as RDW cut-off value for insulin-resistant with an AUC of 0.95, P < 0.001. In conclusion, a strong and remarkable correlation of RDW with metabolic abnormalities in PCOS cases with 100% sensitivity and specificity, in addition to being quick and inexpensive, makes it a reliable marker for screening for insulin resistance. J. Med. Invest. 69 : 191-195, August, 2022

Keywords **:** *Red distribution width, PCOS, metabolic syndrome, insulin resistance*

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is the most prevalent endocrine disorder in reproductive-age women, with a 7% prevalence (1). According to the Rotterdam criteria, PCOS can be confirmed if two out of three are present : 1. oligo-anovulation, 2. hyperandrogenemia clinical and/or biochemical evidence, and 3. polycystic ovary (2). Insulin resistance (IR) has been connected to PCOS. Insulin secretion defects and obesity appear to have a synergistic effect that considerably increases PCOS severity (3). When compared to healthy women, PCOS women have a doubled risk of ischemic heart disease and a 4-fold risk of Type 2 diabetes (4). These comorbidities have a major economic burden on women. In more than two-thirds of cases, IR is a major element in the pathophysiology of PCOS (5). The hyperandrogenemia found in PCOS is the final outcome of IR and compensatory hyperinsulinemia, which impede the development of ovarian follicles and cause chronic anovulation (6). Women with PCOS are more likely to have dyslipidemia, lower fasting insulin, IR, and higher arterial blood pressure, all of which are components of the metabolic syndrome (7).

Furthermore, they have elevated inflammatory cytokines and biomarkers, further jeopardizing cardiovascular health (1, 8). The alliance of PCOS and metabolic syndrome has poor health consequences for those affected. Therefore, evidence-based recommendations for PCOS women advocate screening for symptoms of metabolic syndrome to reduce the confounding effect of this alliance. PCOS is recognized as a chronic "low-grade" inflammatory state (3). Earlier research showed that this low inflammatory reaction is what promotes PCOS, with a possible link to insulin resistance and body mass index (BMI) ; many inflammatory markers were investigated and linked to PCOS (3, 4). In PCOS, the complete blood count (CBC) and its inflammatory parameters were tested (9, 10). Red cell distribution width (RDW) is a CBC inflammatory marker that mirrors the variation in the circulating RBC size. It was investigated as a biomarker in metabolic syndrome, correlated to increased mortality rates from cardiovascular diseases (CVS), and was used as a prognostic marker for major surgeries and medical diseases (11, 12). However, some studies presented contradicting results (13).

This study aimed to examine the relationship between RDW and hormonal and metabolic parameters in PCOS patients to see if this inflammatory marker may be useful in discriminating PCOS women and the degree of severity of low-grade inflammation in those affected.

MATERIAL AND METHODS

Case-control research was undertaken at Al Yarmouk Teaching Hospital's infertility clinic from December 2019 to October 2020 ; informed permission was acquired from all patients after they were briefed on the study's purpose. The ethics committee gave its approval [MOG 138] on 12-6-2019. Our study recruited 128 women, divided into two groups of 64 each ; the study group included PCOS patients (64/128) diagnosed with the 2003 Rotterdam criteria for PCOS syndrome (2). The presence of two of the three findings by ultrasound scan : ovulatory disturbances, hyperandrogenism, and polycystic ovary, which were

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our inclusion criteria. The healthy control group consisted of (64/128) women who came to our hospital for a check-up.

Exclusion criteria

1. A woman who has a BMI greater than 30.
2. Patients taking insulin sensitizers, combination oral contraceptives, lipid-lowering medicines, antiandrogenic therapies, aspirin, and other blood-thinning medications.
3. Women with hypertension and diabetes
4. Any women with hemoglobin 11 g/dl.

The sample size was calculated according to the following equation :

Sample size = $(r+1/r)^*[SD2\ (Z\beta + Z\alpha/2)2]/d2$

r = the ratio of cases to the control.

SD = the standard deviation taken from previous studies.

$Z\beta$ = the standard normal variant for the power of the study = for 80% power, it is 0.84, and for 90% power, it is 1.28.

$Z\alpha/2$ = is the standard normal variant (at 5% type 1 error ($P<0.05$) it is 1.96 and at 1% type 1 error ($P<0.01$) it is 2.58. as in majority of studies, P values are considered significant below 0.05 ; hence 1.96 is used in a formula.

d = expected mean difference between cases and control could be taken based on previous studies.

So our sample size will be calculated as :

Sample size = $(1+1/1)^*\ [(0.92)2(0.84+ 1.96)2]/(0.46)2$

$= 2\ ^*(0.84\ ^*7.84)/0.21$

$= 63$

So the sample size must be 63 cases with a reasonable number of control ; our study involves 64 patients and 64 control (14).

We gathered clinical and demographic data for both groups, including age, height, and weight, to estimate BMI based on the formula,

Weight in kg/square meter of height. To eliminate bias caused by morbid obesity, an exclusion was made for patients with a BMI above 30.

We aspirated venous blood during the early follicular phase, and after a one-night fast, part of the blood was placed in a tube containing EDTA tube acid, where an automated blood analyzer was used to perform a full blood count on the blood. The rest of the blood was sent to estimate hormonal and metabolic markers such as serum follicle-stimulating hormone, luteinizing hormone, and serum testosterone. The homeostasis model assessment of insulin resistance (HOMA-IR) was utilized to test insulin sensitivity using the formula : Fasting glucose (mg/dL) insulin (U/mL)/405, the normal range is 1.0 (0.5–1.4), anything greater than 1.9 indicates insulin resistance (15). Total serum high and low-density lipoprotein (HDL, LDL) levels were also determined.

STATISTICAL ANALYSIS

Data normality was assessed by the Shapiro Wilk test. Unpaired t-test was used to compare continuous variables between the study and the control group. The Chi-square test was used to compare categorical variables. Linear regression compared RDW versus various demographic criteria associated with IR in the PCOS study group. The coefficient of correlation was calculated with its respective P-value. The median value of BMI was calculated for study participants ; it was 27 and was taken as a divider, and by A 2-way analysis of variance (ANOVA), we tested the effect of BMI on study parameters (HOMA-IR, HDL, LDH, testosteron, and LH/FSH ratio taken as independent variable against PCOS and BMI as a dependent variable. The ROC was constructed to estimate the RDW cut-off value associated with the highest sensitivity and specificity. Medcalc version 20 was used for the statistical analysis ; P-value < 0.05 was defined as statistically significant.

Table 1. The basic criteria of the study group presented as means and SD

Variables	PCOS (n = 64) Means ± SD	Controls (n = 64) Means ± SD	P- value
Age, year	28.72 ± 7.32	30.72 ± 5.64	0.22
Parity	0.63 ± 1.10	2.09 ± 1.09	0.0001*
Abortion number	0.38 ± 0.79	0.34 ± 0.60	0.86
BMI, kg/m^2	29.79 ± 7.55	25.16 ± 1.86	0.01*
Hemoglobin , mg/dl	11.06 ± 3.92	11.51 ± 0.69	0.523
Red cell distribution width fl	15.04 ± 0.61	12.88 ± 0.66	0.0001*
White blood cells, $X10^9/L$	6.25 ± 2.40	5.69 ± 1.13	0.2413
Neutrophils, $X10^9/L$	71.6 ± 86.29	43.44 ± 12.0	0.071
Lymphocytes, $X10^9/L$	33.85 ± 7.70	37.58 ± 10.20	0.1045
Platelets, $X10^3/mL$	302.21 ± 71.26	249.53 ± 36.92	0.0004*
Mean Platelets Volume, fl	8.84 ± 3.58	9.92 ± 0.53	0.0961
Platelets Distribution Width, fL	12.03 ± 4.76	11.57 ± 0.70	0.59
HOMA-IR	2.97 ± 2.36	1.74 ± 2.23	0.0001*
HDL (mmol/l)	70.79 ± 29.79	166.98 ± 23.41	0.0001*
LDL (mmol/l)	147.98 ± 23.94	67.65 ± 19.08	0.0001*
Testosterone	0.947 ± 0.153	0.436 ± 0.141	0.0001*
LH/FH Ratio	3.59 ± 0.28	2.25 ± 0.51	0.0001*

BMI = body mass index, HOMA-IR ; Homeostatic Model Assessment for Insulin Resistance, LDL low-density lipoprotein, HDL high-density lipoprotein, MPV—medium platelet volume, RDW red cell distribution width, FSH follicle-stimulating hormone, LH luteinizing hormone

Table 2. The correlation between RDW versus markers for Insulin resistance

Parameter	Coefficient of correlation	P-value
RDW vs BMI	0.90	< 0.004*
RDW vs HOMA-IR	0.98	< 0.001*
RDW vs HDL	-0.92	< 0.005*
RDW vs LDL	0.92	< 0.001*
RDW vs Serum Testosterone	0.93	< 0.001*
RDW vs LH/FSH Ratio	0.95	< 0.001*

*indicate significant P<0.05.
BMI : body mass index, HOMA-IR : Homeostatic Model Assessment for Insulin Resistance, HDL : high-density lipoprotein, LDL : low-density lipoprotein, FSH : follicle-stimulating hormone, LH : luteinizing hormone

RESULTS

This case-control study recruited 128 participants divided into PCOS cases and healthy controls. Regarding the demographic features, neither the age nor abortion number scored statistically significant between PCOS and healthy controls. However, BMI scored meaningful differences in the PCOS groups. The hemogram parameters, hemoglobin, total WBC counts, lymphocytes, and neutrophils counts fail to have statistical significance as P>0.05. As for platelets, counts and RDW were significantly high in cases versus healthy controls as P<0.0004 P<0.0001, respectively.

The metabolic biomarkers HOMA-IR, LDL, Testosterone, and LH/FSH ratio were significantly high in cases compared to controls, while HDL was meaningfully high in the controls, P<0.0001, highlighted in Table 1. Linear regression highlighted a strong positive relationship between RDW vs. BMI, HOMA-IR, Testosterones/LH ratio, and LDL. A strong inverse correlation was described between RDW vs. HDL. All correlations were statistically significant, with P<0.001, described in Table 2. In Table 3., a 2-way analysis of variance (ANOVA) tested the effect of PCOS and BMI as dependent variables against all study parameters ; the result showed insignificant correlations of BMI on (HOMA-IR, LDH, and HDL) and significant correlation with LH/FSH ratio ; conversely, PCOS showed meaningful correlations with all parameters.

Table 3. Mutivariance analysis by two way ANOVA with HOMA_IR, Serum HDL, LDL, Testosterone, and LH/FSH ratios as independent variables against PCOS, BMI, and their interaction as dependant variables

Parameters	BMI > 27	P-value
HOMA-IR	PCOS	< 0.001*
	BMI	0.27
	PCOS×BMI_interaction	< 0.001*
Serum HDL	PCOS	< 0.001*
	BMI	0.97
	PCOS×BMI_interaction	< 0.001*
Serum LDL	PCOS	< 0.001*
	BMI	0.62
	PCOS×BMI_interaction	< 0.001*
Serum Testosterone	PCOS	< 0.001*
	BMI	0.53
	PCOS×BMI_interaction	< 0.001*
Serum LH/FSH ratio	PCOS	< 0.001*
	BMI	0.024*
	PCOSas×BMI_interaction	< 0.001*

The ROC calculated (13.55) as a cut-off value for the RDW correlated with respective 100%, 78.1% sensitivity and specificity with IR markers in PCOS cases, with an AUC of 0.95 and P<0.001, highlighted in Figure 1.

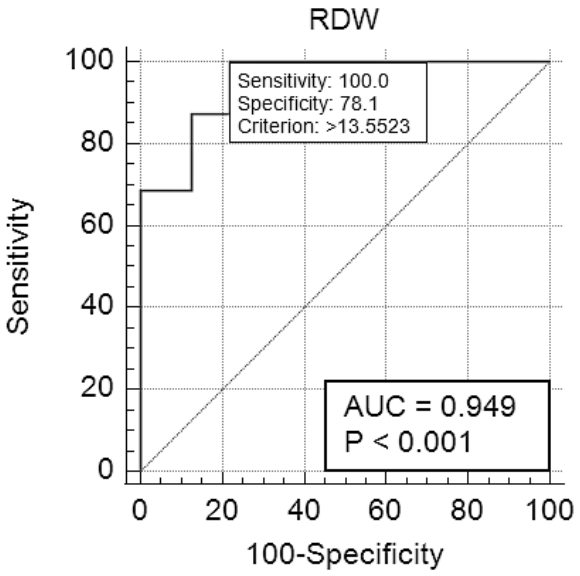

Figure 1. The ROC estimated RDW cut-off value correlated best with IR biomarkers with an area under the curve of 0.95 and P < 0.001.

DISCUSSION

This study highlighted that RDW was significantly higher in PCOS cases. Furthermore, a strong positive relationship was found between RDW vs. BMI, HOMA-IR, LDL, testosterone, and LH/FSH ratio with an inverse relationship with HDL. In line with our results, Yilmaz *et al*. examined RDW value as an inflammatory marker among PCOS cases compared to CRP; they confirmed a significantly higher RDW among PCOS cases, with a positive correlation between RDW vs. HOMA, BMI, and CRP. At a cut-off value of 12.54%, RDW discriminated PCOS cases with high sensitivity and specificity (16).

Rondinelli's study addressed the changes in RDW caused by obesity, using BMI and waist circumference as parameters for overall and central obesity, respectively. Their results showed a negative correlation with BMI and a positive one with waist circumference. Therefore, RDW was suggested to mediate the relationship between waist circumference vs. HOMA-IR, insulin concentration, and HDL in obese women, and for that, RDW was a marker for CVS risk and IR (17). Peker *et al*. study examined the value of RDW in predicting the response to clomiphene citrate treatment in lean women with PCOS ; it was found to be significantly higher among clomiphene citrate resistant patients. Their results showed that RDW at a cut-off value of 12.8 had an odds ratio of 3.1 and a 95% CI (1.25-7.6) to predict clomiphene citrate resistance among lean PCOS patients (18). On the other hand, the Alhabardi study found no significant difference between RDW and other blood indices among the PCOS

and healthy controls they examined ; the author suggested that the small sample size and the presence of complex interaction between PCOS etiological factors were responsible for the shortcoming of their results (19). Our results showed significantly higher serum testosterone in PCOS cases, which was positively correlated to RDW. The pathophysiology of PCOS is intimately connected to hyperandrogenism. Higher quantities of insulin released in response to IR reduce the expression of sex hormone-binding protein, resulting in increased serum androgen. (20). As an inflammatory marker, RDW was tested in the JUPITER trial for its association with other inflammatory markers like CRP and elevated white blood cells. It showed a significant correlation ; it was an independent marker for increased mortality (12). Kucera had used RDW to test the efficiency of atorvastatin drugs to treat patients with dyslipidemia. Although it did not reach the level of statistical significance, a trend of low RDW was seen following treatment (21). In the obstetrics field, RDW was examined to evaluate the severity and predict preeclampsia, a pregnancy-specific syndrome with a high rate of adverse feto-maternal outcomes (22, 23). RDW was significantly higher in pregnant women suffering from severe PE. However, it fails to discriminate those deemed to develop PE as the AUC was 0.37 (24).

PCOS is a common metabolic syndrome where chronic inflammation is attributed to its pathophysiology (25). Many researchers examined higher levels of inflammatory markers, which supported that hypothesis. The correlation between RDW and metabolic syndrome biomarkers ; was accredited to IR. The latter triggers proliferation and differentiation of bone marrow erythropoietic cells via insulin and insulin growth factors I and II (26). Others suggested that iron overload associated with IR impacts insulin-mediated effects; iron overload was strongly associated with obesity and dyslipidemia (27).

Identifying biomarkers that drive the inflammatory process in PCOS may be valuable in managing PCOS and its related comorbidities (22, 23). Moreover, it can offer affected patients the opportunity to adopt a healthy lifestyle, change dietary habits, and increase daily exercise (10, 25). One of the strength points of our study is the exclusion of anemic women, which caused bias in earlier study results since it affected RDW values (28). Another interesting point is that our PCOS cases had higher BMI than controls, in contrast to Yilmaz *et al*.'s study participants (16) ; showing no meaningful differences regarding the adiposity markers (BMI, waist/hip ratio, and body fat percentage). So, RDW is a reliable marker for IR independent of adiposity markers, which were highlighted in the multivariate analysis.

Our results showed that RDW correlated strongly with the clinical, hormonal, and biochemical markers of PCOS independent of BMI. RDW discriminated cases with IR with high sensitivity and specificity (P 0.001), which makes it a reliable surrogate marker for IR. In addition, it is quick, inexpensive, and readily available. Though HOMA-IR is widely implemented for evaluating IR, it still has limitations ; it is coasty, not always accessible, and it has reproducibility issues (29).

Therefore, we recommend serial assessments of RDW with metabolic and hormonal changes during therapy in a cohort study type that will assess RDW's predictive significance during PCOS management.

One limitation is that it is a single-center experience, and another is the small sample size.

CONCLUSIONS

RDW was significantly high in PCOS women and showed a strong correlation to PCOS metabolic abnormalities, particularly IR ; its availability and accessibility make it an appealing option to screen for PCOS-associated insulin resistance and dyslipidemia.

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CONFLICT OF INTEREST

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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