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ORIGINAL ARTICLE

The association between circulating irisin levels and different phenotypes of polycystic ovary syndrome

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Abstract

Purpose The diagnosis of polycystic ovary syndrome (PCOS) is based on a combination of various clinical phenotypes in each patient. However, insulin resistance (IR) and dysmetabolism are not included in the diagnostic criteria of PCOS. Therefore, the definition of PCOS is controversial. The objective of this study is to investigate whether some PCOS phenotypes can be predicted by a circulating biomarker related to IR and metabolic dysfunction in PCOS women.

Methods One hundred and seventeen women with PCOS and 95 healthy women were recruited for this study. All individuals were assessed by the phenotypic and metabolic characteristics related to PCOS. A euglycemic–hyperinsulinemic clamp was performed to assess insulin sensitivity. Circulating irisin concentrations were determined with ELISA.

Results In our PCOS cohort, 65.8% of individuals were found to have hyperandrogenism. 83.8% had chronic oligoanovulation, and 80.3% of subjects showed polycystic ovaries. According to the diagnostic criteria of PCOS, 30.8% of PCOS subjects were diagnosed with the classic phenotype. In addition, 65.8% of PCOS women had insulin resistance. Serum irisin levels were significantly higher in PCOS women compared with healthy women. However, PCOS women with a normoandrogenic phenotype had similar circulating irisin levels as healthy women. PCOS women with the normoandrogenic phenotype had a low homeostasis model assessment of insulin resistance (HOMA-IR) and higher *M*-values than PCOS women with other phenotypes. Circulating irisin levels were associated with hyperandrogenism, but not with oligoanovulation or PCO morphology.

Conclusions Circulating irisin may allow physicians to establish which women merit screening by a biomarker for PCOS.

Keywords PCOS · Irisin · Euglycemic–hyperinsulinemic clamp · Insulin resistance

Introduction

Polycystic ovary syndrome (PCOS) is an endocrine syndrome, which is found in 10% of reproductive- aged women. Women with PCOS are characterized by ovulatory dysfunction, polycystic ovaries, elevated androgens, and/or clinical (hirsutism and/or acne) hyperandrogenism [1]. In addition, insulin resistance (IR) or hyperinsulinism and obesity are also significant features found in conjunction with PCOS [2]. Many clinical consequences are associated with PCOS, such as infertility, impaired glucose tolerance (IGT), an increased risk of endometrial carcinoma, gestational diabetes, and type 2 diabetes mellitus (T2DM), as well as the possibility of cardiovascular disease later in life [3–5].

Although IR is not considered a disease, it is a common physiological abnormality with multiple metabolic dysfunctions [6]. It is well known that IR plays a crucial role in the onset of PCOS [7]. About 70% of PCOS women are IR [8, 9]. However, the true prevalence of IR in PCOS

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individuals is unclear, due to limitations, such as the assessment methods of IR. Thus, it is important to look for some biomarkers related to IR for predicting different phenotypes of PCOS. Unfortunately, there are no unequivocal criteria for diagnosing PCOS, and its definition remains controversial. According to the Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group for Reproductive Medicine (ESHRE/ASRM) consensus in 2003 [10], PCOS can be diagnosed by the presence of two of three features: hyperandrogenism or clinical manifestations for hyperandrogenism, chronic anovulation, and polycystic ovary (PCO) morphology. However, these features do not include IR, which is known to play an important role in the development of PCOS.

In PCOS women, the secretions of some cytokines related to insulin sensitivity are dysregulated, while altered cytokine levels, including leptin, adiponectin (Adipoq), and retinol-binding protein 4 (RBP-4) have been implicated in aberrations of carbohydrate metabolism and in the pathophysiology of IR [11–13]. However, the association between these cytokines and the different phenotypes of PCOS remains largely unknown. Recently, irisin, a newly identified peptide hormone expressed and secreted mainly by muscle tissues was identified in mice and humans [14].The exogenous treatment of irisin in animal studies led to an increased energy expenditure, improved glucose tolerance, and weight loss [14]. More recently, studies in humans have shown that circulating irisin levels were significantly lower in T2DM patients [15, 16]. Although the previous human and animal studies [14, 17–20] have suggested a correlation between irisin and the metabolic parameters associated with obesity and IR, the results are inconsistent. In particular, the relationship between circulating irisin and different features or phenotypes used for diagnosing PCOS remains unclear. Therefore, in the current study, we investigate whether these features separately or in combinations with PCOS phenotypes may be related to circulating irisin in women with PCOS. To address this question, 212 women with or without PCOS were carefully characterized, using state-of-the-art methods.

Subjects and methods

Study population

117 women with PCOS, aged 20–36 years, were recruited for this study from outpatients attending the Department of Endocrinology from February 2015 to March 2017 due to menstrual irregularities, or anovulation and/or hyperandrogenism. PCOS was diagnosed according to criteria indicated by the 2003 Rotterdam consensus (The Rotterdam ESHRE/ASRM- sponsored PCOS consensus workshop group) [10]. Various combinations of the three diagnostic features in Rotterdam criteria generated distinct PCOS phenotypes: a classic type (characterized by hyperandrogenism and oligoanovulation, with or without PCO morphology), ovulatory (hyperandrogenism and PCO), and normoandrogenic type (oligoanovulation and PCO) [21]. The oligoanovulation is defined by infrequent bleeding at intervals > 35 days [22]. Other known causes for hyperandrogenemia and ovulatory dysfunction including 21-hydroxylase deficiency, congenital adrenal hyperplasia, and Cushing's syndrome were excluded. Inclusion criteria were a confirmed diagnosis of PCOS and age 18–40 years. Patients with T2DM or T1DM were excluded. All PCOS women did not receive oral contraceptives, insulin-sensitizing agents, antiandrogens, or glucocorticoids in the past 3 months. 95 age-matched healthy women with regular periods were recruited as the control group from the community or schools through advertisement, or routine medical check-up. None of healthy women were on any medication within the past 3 months. Written informed consent was signed by all individuals before entering the experiment. This study was conducted in accordance with the Declaration of Helsinki and approved by the ethical committee of the Second Affiliated Hospital of Chongqing Medical University.

Oral glucose tolerance test (OGTT) and hyperinsulinemic–euglycemic clamp (EHC)

At 0730 h on the experiment days, after a 10 h overnight fast, an OGTT was performed in all study individuals. 75 g glucose was given to these subjects and blood samples were drawn at 0, 30, 60, and 120 min after oral glucose for blood glucose and insulin measurements. EHCs were performed on all PCOS and healthy women as previously described [23–25]. Briefly, after a 10–12 h overnight fast, a catheter was placed in the antecubital vein to infuse insulin and glucose. Another catheter was placed retrograde in the dorsal vein of the contralateral hand for blood withdrawal. Regular human insulin (1 mU/kg/min) was infused for 2 h, and a variable infusion of 20% glucose was infused to maintain plasma glucose at the fasting level. During the procedure, plasma glucose levels were measured every 10–15 min to guide the glucose infusion. The rate of glucose disposal (GRd) was defined as the glucose infusion rate (GIR) during the stable period of the clamp and was related to body weight (*M* value). Blood samples for irisin and other measurements were obtained on fasting condition. All blood samples were centrifuged and the separated serum was kept frozen at − 80 °C.

Anthropometric and biochemical measurements

Body mass index (BMI) was calculated as weight divided by height squared. Bioelectrical impedance (BIA-101; RJL

Systems) was used to measure body fat (FAT %). The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as the previous report [26]: HOMA-IR = fasting insulin (FIns, mU/mL) × fasting blood glucose (FBG, mmol/L)/22.5. Blood glucose levels and HbA1c were measured by the glucose–oxidase method and anion-exchange HPLC, respectively. Insulin was measured by an enzyme-linked immunosorbent assay (ELISA). Free fatty acids (FFAs), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein (LDL-C), and TG were measured as previous described [23].

Irisin and hormone measurements

Circulating irisin concentrations were determined with an ELISA kit obtained from CUSABIO Life Science, Inc. following the manufacturer's protocol. The sensitivity of the assay was 0.78 μg/L. The intra-assay and inter-assay variations were 5.5–7.8 and 4.3–8.2%, respectively. Serum hormonal concentrations including luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone were measured with well-established electrochemiluminescence immunoassay using COBASE immunoassay analyzers (Roche Diagnostics GmbH). Total testosterone levels were measured with the coated tube RIA (DiaSorin, S. p. A, Salluggia, Italy). The sex hormone-binding globulin (SHBG) was measured using an automated analyzer (Abbott Architect; Abbott Laboratories). The free androgen index (FAI) was calculated as FAI = (testosterone/SHBG) × 100.

Statistical analysis

Statistical Package (SPSS 22.0, Chicago, IL) was used to analyze all data. The results are expressed as mean ± SD or median (interquartile range). Non-normally distributed data were log-transformed before analysis. Comparisons among groups were done by ANOVA or unpaired *t* test, respectively. Correlations between variables were assessed using partial correlation analyses by controlling for the covariates. The associations of irisin and other anthropometric parameters and hormone were assessed by multiple regression. Logistic regression analyses were performed to assess the associations between the irisin variable as a dependent categorical variable and the PCOS phenotypes as independent variables.

Results

In the 117 PCOS individuals, hyperandrogenism, anovulation, and polycystic ovaries were 65.8, 83.8, and 80.2%, respectively. When all these characteristics were considered, 36 (30.8%) subjects in these PCOS women were classic phenotype and 22 (18.8%) were the no-PCO morphology phenotype, whereas 19 (16.2%) were the ovulatory phenotype and 40 (34.2%) were the normoandrogenic phenotype. Table 1 shows the clinical features of all study individuals. When compared with the healthy women, the classic phenotype subgroup in PCOS was obese (higher BMI, WHR and FAT %) and had higher blood pressure, blood glucose, insulin, HbA1c, TG, TC, LDL-C, and lower LDL-C. In addition, PCOS women with classic phenotype had an increased IR (higher HOMA-IR and lower *M*-values), higher DHEA-S, TEST, LH and FAI, more ovarian follicles, and lower SHBG and FSH compared with the healthy women (Table 1). Importantly, circulating irisin levels in PCOS women with classic phenotype were significantly higher than in the healthy women (Table 1). In addition, when compared with the classic phenotype subgroup, normoandrogenic subgroup had lower BMI, FAT %, insulin, DHEA-S, E2, TEST, FAI and HOMA-IR, and higher SHBG and *M*-values. In the normoandrogenic subgroup, circulating irisin levels were significantly lower than those of classic phenotype subgroup (Table 1). In no-PCO morphology and ovulatory subgroup, adiposity-related parameters (BMI, WHR and FAT %), blood pressure, and glucose-related parameters, including FBG, 2 h-BG, and HbA1c, were significantly higher than the healthy women, but not significantly different with classic PCOS women (Table 1). Serum lipids including TG, TC, and LDL-C in no-PCO morphology and ovulatory subgroup were similar to those of classic PCOS group, whereas no-PCO morphology subgroup had lower HDL-C lower than the classic subjects. Serum FFA levels were no different in all four subgroup.

In the current study, we performed EHCs on all individuals. During the steady state of EHCs, blood glucose concentrations were clamped at 5–6 mmol/L, and insulin concentrations were raised from 45.0 ± 12.4 to 347.4 ± 54.2 pmol/L. In response to hyperinsulinemia, the GIR needed to maintain euglycemia (expressed as *M*-values) rose from 0 to 10.3 ± 2.5 and 5.5 ± 2.4 mg/kg/min in health individuals and classic phenotype of PCOS women, respectively. The highest *M*-value was found in the normoandrogenic phenotype of PCOS women, indicating that this phenotype group had higher insulin sensitivity. In addition, in no-PCO morphology and ovulatory subgroups, IR-related parameters, such as FIns, 2 h plasma insulin after glucose overload (2 h-Ins), *M*-values, and HOMA-IR were similar to the classic subgroup. Their circulating irisin levels were also similar to the classic subgroup. In all three groups, sex hormone levels were similar (Table 1). These results indicate that there was an increased IR in the subjects in no-PCO morphology and ovulatory subgroups.

When the relationship between circulating irisin and the diagnostic phenotype of PCOS was examined (Table 2, model 1), circulating irisin levels were significantly related

Table 1 Main characteristics of the women with PCOS and healthy women

Variable	Healthy women ($n=95$)	Classic ($n=36$)	No-PCO morphology ($n=22$)	Ovulatory ($n=19$)	Normoandrogenic ($n=40$)
Age (year)	25.7 ± 2.3	25.6 ± 4.3	25.9 ± 4.2	25.4 ± 3.9	26.4 ± 4.6
BMI (kg/m^2)	20.4 ± 2.5	26.7 ± 4.3**	26.2 ± 5.5**	25.2 ± 4.7**	22.7 ± 3.9**▲
FAT (%)	26.6 ± 5.5	39.5 ± 8.9**	37.1 ± 10.2**	37.4 ± 9.0**	31.6 ± 8.1**▲
WHR	0.79 ± 0.05	0.87 ± 0.05**	0.88 ± 0.08**	0.86 ± 0.08**	0.85 ± 0.06**
SBP (mmHg)	108.8 ± 8.0	116.3 ± 11.6**	115.4 ± 7.9**	115.9 ± 11.9**	114.9 ± 9.6**
DBP (mmHg)	75.0 ± 7.8	78.2 ± 7.2*	77.7 ± 7.0	75.4 ± 8.7	75.7 ± 6.2
FBG (mmol/L)	4.44 ± 0.46	4.86 ± 0.69**	4.85 ± 0.61***	5.03 ± 0.58**	4.83 ± 0.49**
2 h-BG (mmol/L)	5.29 ± 1.04	7.19 ± 2.23**	7.66 ± 2.54**	7.37 ± 1.88**	6.97 ± 1.96**
FIns (mU/L)	7.0 (6.1–8.6)	16.1 (9.6–24.3)**	19.5 (11.2–32.1)**	17.2 (8.9–20.4)**	10.1 (6.8–19.8)**▲
2 h-Ins (mU/L)	35.6 (22.3–56.9)	58.2 (25.0–95.7)*	50.1 (34.9–182.7)**	48.3 (26.5–58.8)	38.1 (23.0–57.5)
HbA1c	5.30 ± 0.33	5.39 ± 0.29**	5.54 ± 0.41**	5.34 ± 0.35**	5.16 ± 0.25**
M (mg/min/kg)	10.3 ± 2.5	5.7 ± 2.9**	5.3 ± 2.3**	5.5 ± 2.1**	6.6 ± 3.0**
HOMA-IR	0.99 (0.86–1.21)	2.24 (1.36–3.29)**	2.74 (1.62–5.29)**	2.56 (1.30–2.97)**	1.57 (1.02–2.86)**▲
SHBG (nmol/L)	62.6 ± 24.1	26.8 ± 11.9**	25.7 ± 11.3**	34.8 ± 9.9**	57.7 ± 28.1▲
DHEA-S (μg/dL)	179.7 (136.4–213.1)	209.4 (173.9–292.9)**	197.9 (156.2–272.0)*	190.3 (171.1–249.5)	189.9 (150.4–222.4)▲
TEST (nmol/L)	1.75 ± 0.70	3.36 ± 0.77**	3.22 ± 0.99**	3.37 ± 0.77**	2.15 ± 1.13▲
FAI	2.5 (1.8–4.2)	11.8 (9.9–19.7)**	9.9 (8.4–21.7)**	9.2 (8.4–11.2)**	4.3 (2.5–5.8)▲
E2 (pmol/l)	196.4 ± 91.4	228.1 ± 113.7	261.8 ± 127.6*	198.9 ± 93.5	222.4 ± 148.4
LH (IU/L)	4.72 ± 2.30	10.49 ± 6.21**	8.21 ± 4.41**	8.89 ± 4.55**	10.67 ± 6.85**
FSH (IU/L)	8.06 ± 1.94	7.47 ± 1.96	6.84 ± 2.97*	7.75 ± 2.33	7.46 ± 2.12
TG (mmol/L)	0.81 (0.58–1.30)	1.29 (1.01–1.95)**	1.32 (0.74–2.16)**	1.20 (0.68–1.72)	1.39 (0.86–2.21)**
TC (mmol/L)	3.85 ± 1.01	4.54 ± 1.13**	4.18 ± 1.07	4.10 ± 0.0.63	4.72 ± 0.93**
HDL (mmol/L)	1.16 (0.96–1.42)	1.29 (1.08–1.47)*	1.09 (0.98–1.20)▲	1.23 (1.07–1.26)	1.31 (1.19–1.56)**
LDL (mmol/L)	2.18 ± 0.87	2.53 ± 0.84*	2.58 ± 0.78*	2.31 ± 0.56	2.64 ± 0.85**
FFA (μmol/L)	0.56 ± 0.28	0.61 ± 0.22	0.52 ± 0.22	0.55 ± 0.17	0.58 ± 0.21
Ovarian follicles (n)	7 (5–10)	15 (13–17)**	8 (6–10)▲	14 (12–17)**	14 (13–16)**
Irisin (μg/L)	176.9 ± 69.7	259.8 ± 93.6**	245.6 ± 96.7**	236.6 ± 86.1**	181.1 ± 50.9▲
Irisin (μg/L)[a]	191.9 ± 8.2	237.7 ± 13.2**	226.1 ± 16.2**	223.1 ± 16.9**	182.5 ± 11.5▲

Values were given as mean ± SD or median (interquartile range)

PCOS polycystic ovary syndrome, *BMI* body mass index, *FAT (%)* body fat %, *WHR* waist-to-hip ratio, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *FBG* fasting blood glucose, *2 h-PBG* 2 h post-glucose load blood glucose, *FIns* fasting plasma insulin, *2 h-Ins* 2 h plasma insulin after glucose overload, *HbA1c* glycosylated hemoglobin, *M* whole-body glucose uptake rate, *HOMA-IR* HOMA-insulin resistance index, *AUCi* the area under the curve for insulin, *SHBG* sex hormone-binding globulin, *DHEA-S* dehydroepiandrosterone-sulfate, *TEST* testosterone, *FAI* free androgen index, *E2* estradiol, *LH* luteinizing hormone, *FSH* follicular stimulating hormone, *TG* triglyceride, *TC* total cholesterol, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *FFA* free fatty acid

*$P<0.05$, **$P<0.01$ versus healthy women; ▲$P<0.01$ versus Classic group

[a]Data are mean ± SE, Adjustment for BMI

to hyperandrogenism ($P<0.001$), but not related to oligoanovulation or the PCO morphology. However, when *M*-values and HOMA-IR were included (Table 2, model 2), M-value and HOMA-IR were associated with circulating irisin, further suggesting that circulating irisin levels were associated with IR. Notably, despite *M*-values and HOMA-IR were included in the analysis, circulating irisin levels were still related to hyperandrogenism ($P<0.001$, Table 2).

We next further compared individuals with different types of PCOS with the normal controls. Circulating irisin was found to be significantly associated with the Classic, no-PCO morphology, and ovulatory phenotypes, but not the normoandrogenic phenotype (Table 3). When HOMA-IR and M-value were included in this analysis, these associations were not affected. Circulating irisin levels remain a predicting factor for the classic, no-PCO morphology, and ovulatory phenotypes (all $P<0.001$; Table 3, univariable analysis). In multivariable analysis with the inclusions of *M*-values and HOMA-IR, only normoandrogenic phenotype in these PCOS women was independently related to circulating irisin ($P<0.05$, Table 3, multivariable analysis). In addition, 24.8% of all PCOS women were diagnosed as

Table 2 Multiple regression analysis for the association between the different clinical elements used in diagnosis of PCOS and irisin levels

Feature	*b* coefficient	SE	*P*
Model 1			
Hyperandrogenism	83.21	18.63	< 0.001
Oligoanovulation	27.74	22.93	0.229
PCO morphology	25.02	21.60	0.249
Model 2			
Hyperandrogenism	63.68	16.50	< 0.001
Oligoanovulation	25.18	19.96	0.210
PCO morphology	30.97	18.68	0.100
M-value	− 11.66	2.75	< 0.001
HOMA-IR	9.82	4.69	< 0.05

Irisin was considered as a continuous variable. Model 1 includes only PCOS-specific clinical elements. Model 2 includes PCOS-specific clinical elements adjusted by *M*-value and HOMA-IR

MetS by Chinese Diabetes Society [25] (Table 4). Increased BMI (49.6%) is the most common feature in the MetS diagnosis. The MetS frequency was high in PCOS patients with classic and no-PCO morphology subgroups (30.6 and 36.4%, respectively), intermediate in the ovulatory subgroup (21.1%) and less in the normoandrogenic subgroup (15.0%) (Table 4).

Discussion

In the current study, serum irisin concentrations in PCOS patients with different phenotypes were investigated using state-of-the-art methods. PCOS is a syndrome with a variety of clinical manifestations and it is not known how PCOS women are stratified by metabolic influences and pathophysiology [27]. Here, we demonstrated that serum irisin levels were significantly increased in PCOS women compared to healthy individuals. However, the previous studies have produced conflicting results regarding the link between circulating irisin levels, IR, and PCOS. Circulating alarin levels were found to be elevated or decreased or unchanged in PCOS subjects [28, 29]. Therefore, further detailed studies are needed to conclusively address this issue.

In the current study, high circulating irisin levels were found in about 52.1% of subjects with PCOS. In addition, it seems obvious that normoandrogenic women with PCOS had lower irisin level than other PCOS sub-phenotypes, whilst they were leaner and showed better metabolic profiles and were almost comparable to healthy controls, indicating that this protein may possess androgen specific activity and/or regulation. The previous studies have shown that circulating irisin is positively related to IR [30]. Thus, low circulating irisin levels suggest that this phenotype is less IR

Table 3 Regression analysis for the association between the different phenotypes of PCOS and irisin level

PCOS phenotype *vs.* healthy women	Univariable analysis			Multivariable analysis		
	b coefficient	SE	*P*	*b* coefficient	SE	*P*
Classic	2.040	0.441	< 0.001	0.810	0.534	0.129
No-PCO morphology	1.452	0.494	< 0.01	− 0.070	0.628	0.912
Ovulatory	1.403	0.521	< 0.01	0.043	0.624	0.945
Normoandrogenic	0.115	0.426	0.787	− 1.069	0.535	< 0.05
M-value	− 0.289	0.052	< 0.001	− 0.253	0.075	< 0.01
HOMA-IR	0.580	0.131	< 0.001	0.202	0.162	0.213

Irisin was considered as a binary variable

Table 4 Number and percentage of MetS and each clinical component contributing to MetS diagnosis in PCOS women

	All PCOS	PCOS phenotype			
		Classic	No-PCO morphology	Ovulatory	Normoandrogenic
MetS	29 (24.8)	11 (30.6)	8 (36.4)	4 (21.1)	6 (15.0)
BMI ≥ 25	58 (49.6)	25 (69.4)	14 (63.6)	9 (47.4)	10 (25.0)
FBG ≥ 6.1 and/or 2 h-BG ≥ 7.8	41 (35.0)	12 (33.3)	9 (40.9)	8 (42.1)	12 (30.0)
TG ≥ 1.70	41 (35.0)	12 (33.3)	8 (36.4)	5 (26.3)	16 (40.0)
HDL-C < 1.04	24 (20.5)	6 (16.7)	9 (40.9)	3 (15.8)	6 (15.0)
BP ≥ 130/85	24 (20.5)	12 (33.3)	4 (18.2)	3 (15.8)	5 (12.5)

MetS metabolic syndrome, *BMI* body mass index, *FBG* fasting blood glucose, *2 h-PBG* 2 h post-glucose load blood glucose, *TG* triglyceride, *TC* total cholesterol, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *BP* blood pressure

than other phenotypes. Low HOMA-IR and higher *M*-values in this phenotype also further confirmed the above results. Therefore, circulating irisin may be considered as a preliminary indicator of PCOS. Increased levels of circulating irisin in the no-PCO morphology and ovulatory phenotypes may reflect a compensatory up-regulation, as a result of the metabolic stress and hormonal disturbances that counteract IR.

In this study, PCOS women with the normoandrogenic phenotype showed a low HOMA-IR and high M-value, suggesting that this phenotype has low or no IR. Therefore, these results provide evidence that IR is not a main feature of PCOS subjects with normoandrogenism. In addition, this result also suggests that androgen levels are strongly related to IR. Therefore, the focus on treatment for patients with this phenotype is not on improving IR, but on gynecological treatment. This result is important for the determination of clinical treatment strategy.

Based on the ESHRE/ASRM Rotterdam workshop and the AE-PCOS consensus statement, PCOS is considered a syndrome, and there are no well-defined criteria for clinical diagnosis. In the current study, we found that circulating irisin levels is relative to some diagnostic features of PCOS. We thus considered that circulating irisin may be a link between metabolic and reproductive disorders in PCOS women. Our present data may address the following problems: (1) whether circulating irisin levels can contribute to the diagnosis of PCOS; (2) whether circulating irisin may use as a marker for screening PCOS women; (3) whether low irisin levels suggest a better prognosis in patients with PCOS. To clarify these issues, further in-depth research is important.

Since there are no well-defined parameters for the diagnosis of PCOS, it is important to seek new biomarkers. However, if circulating irisin is to be considered a marker for PCOS diagnosis, our results indicate that the normoandrogenic subtype should be classified as a specific condition. As to the second issue, to screen dysmetabolism and IR according to PCOS phenotype, our findings suggest that phenotype distinction in PCOS women may direct doctors in the design of cost-effective strategies. These findings may also direct therapy for preventing complications related to metabolism disorders in PCOS women. Therefore, it would seem reasonable to screen and assess PCOS phenotype related to IR and metabolic abnormalities by circulating irisin concentration.

In the current PCOS cohort, 24.8% of PCOS women met the criteria for MetS according to the 2014 Chinese Diabetes Society Recommendations of MS [31]. Among the components contributing to MetS diagnosis, increased BMI (49.6%), especially in the classic phenotype (69.4%), was the most common alteration. The MetS frequency was the highest in PCOS women with the classic and no-PCO morphology, intermediate in the ovulatory phenotype, and lower in normoandrogenic women with PCOS. The results indicate that PCOS women with normoandrogenemia are less likely to develop MetS, suggesting a link between metabolic disturbances and hyperandrogenism.

The major strengths of this study includes: (1) its population-based sample of young women; (2) the accurate prediction of IR by EHC, a gold standard for IR evaluation; (3) the use of state-of-the-art methods for the characterization of PCOS individuals; (4) sex hormones were measured by routine platform assays. The present study has some limitations. First, the cross-sectional design cannot provide an explanation for the association between serum irisin levels and other parameters. Second, our results could be improperly influenced by some outliers due to the sample size. Finally, the single assay of serum irisin levels may not reflect the changes of serum irisin levels over time. Therefore, serial changes in serum irisin levels should be assessed at each stage of PCOS to investigate its role in each phenotype of PCOS.

In summary, although IR and metabolic dysfunction are not included in any diagnostic feature of PCOS, some biomarkers or cytokines, such as irisin, may guide physicians to conclude which subject should be screened for these biomarkers or cytokines. For PCOS populations with IR and metabolic disorders, irisin can be considered as an indicator for screening and prognosis. However, the normoandrogenic phenotype in PCOS women may behave as a specific cohort in respect to metabolism and IR.

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Compliance with ethical standards

Conflict of interest All authors declare no conflict of interest.

Ethical approval The study was performed in comply with ethical standards which is in accordance with the 1964 Helsinki Declaration and its later amendments.

Informed consent All patients or their guardians of participants gave written informed consent before beginning of the study.

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