Adiponectin/(FBG × Flns) as a predictor of insulin sensitivity and metabolic syndrome in patients with polycystic ovary syndrome

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Abstract
The euglycemic–hyperinsulinemic clamp is not available in most clinical settings. An accessible and inexpensive measurement for identifying insulin resistance (IR) is necessary. Our aim is to assess whether the adiponectin (ADI) index (ADI/(FBG × Flns)) is a better surrogate index for the assessment of IR or metabolic syndrome (MetS).

A population-based cross-sectional study was conducted including 100 healthy women and 99 polycystic ovary syndrome patients. The euglycemic–hyperinsulinemic clamp was performed. Circulating ADI levels were determined by ELISA. Polycystic ovary syndrome and polycystic ovary syndrome plus MetS subjects had higher products of fasting triglycerides and glucose (TyG), Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), increased ratios of the area under the curve for insulin/the area under the curve for glucose (AUCi/AUCg), but lower ADI index as compared with healthy subjects. Partial correlation analysis in all populations showed that the M-value was significantly negatively correlated with HOMA-IR, TyG, TG/HDL, and AUCi/AUCg, and correlated positively with the ADI index. The r value of Pearson correlation between the ADI index and M-value was greater than that of the correlation between HOMA-IR, TyG, TG/HDL-C, and AUCi/AUCg. The optimal cut-off value of the ADI index for detection of IR was 0.67, with a sensitivity of 89.4% and a specificity of 88.1%, whereas for detection of MetS, it was 0.32, with a sensitivity of 88.7% and a specificity of 71.0%.

The ADI index may be a surrogate marker in detecting IR and MetS.

Abbreviations: ADI = adiponectin, AUCi/AUCg = the area under the curve for insulin/the area under the curve for glucose, EHC = euglycemic–hyperinsulinemic clamp, FAl = free androgen index, FBG = fasting blood glucose, Flns = fasting insulin, HDL-C = high-density lipoprotein cholesterol, HOMA-IR = Homeostasis Model Assessment of Insulin Resistance, MetS = metabolic syndrome, PCOS = polycystic ovary syndrome, TG = triglyceride, TyG = the product of fasting triglycerides and glucose, ZAG = zinc alpha 2 glycoprotein.

Keywords: ADI index, insulin resistance, metabolic syndrome, polycystic ovary syndrome

1. Introduction
Polycystic ovary syndrome (PCOS) occurs in about 10% of women of reproductive age, thus representing one of the most common endocrine disorders in women. PCOS is characterized by a clustering of hyperandrosgenism, hyperinsulinemia, hypersecretion of luteinizing hormone (LH), menstrual dysfunction, hirsutism, infertility, pregnancy, and neonatal complications.[1] PCOS also contributes to other long-term health risks, metabolic complications, and psychological problems, such as metabolic syndrome (MetS), insulin resistance (IR), type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), venous thromboembolism, poor self-esteem, and anxiety. In PCOS women, IR is highly prevalent, and about 60% of PCOS women suffer from IR,[2,3]
compared with a prevalence of IR in the healthy population of 10%. IR accompanied by compensatory hyperinsulinemia has been known as a key component in the pathogenesis of the PCOS. \( ^{17} \) However, most studies relied on rough surrogate indices of insulin sensitivity, such as glucose/insulin ratio and the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) based on glucose and insulin levels at fasting or after oral glucose tolerance test (OGTT). \( ^{8} \) Although these indices are widely used in epidemiological studies, they correlate poorly with the accurate gold-standard measures of insulin action, the euglycemic–hyperinsulinemic clamp (EHC).

Adiponectin (ADI) is 1 of the adipocytokines secreted from visceral adipose tissue and is only secreted by mature adipocytes. A larger number of studies reported that ADI was correlated with insulin sensitivity, and low levels of ADI were associated with IR and increased risk of T2DM. \( ^{18-22} \) Thus, ADI is known as an insulin-sensitizing agent. Notably, it has been reported that PCOS women with low ADI levels are at higher risk of IR. \( ^{13} \) Therefore, ADI may be a useful mark of IR in PCOS women.

The EHC is considered the “gold-standard” measure of insulin sensitivity, even though it simulates neither the physiological state of continuous changes of glucose, insulin, and hepatic insulin extraction, nor the feedback mechanism between glucose and insulin. The EHC has the fewest drawbacks and most closely approximates the real measure of insulin sensitivity. \( ^{13} \) However, it is not available in a clinical setting and is costly, time-consuming, invasive, and requires trained staff. Therefore, finding a better predictor of insulin sensitivity than the glucose/insulin ratio and HOMA-IR is important. In this study, we assessed the associations between the ADI index (adiponectin/fasting blood glucose [FBG] \( \times \) fasting insulin [FIns]) and insulin sensitivity, compared the ADI index and the HOMA-IR, and the product of fasting triglycerides (TGs) and glucose (TyG), as predictors of insulin sensitivity in healthy and PCOS populations.

2. Materials and methods

2.1. Subjects

In all, 199 Chinese subjects including 100 healthy women, 68 PCOS patients, and 31 PCOS women with MetS were recruited for this study over a 12-month period from the outpatient clinics of the Division of Endocrinology at the Second Affiliated Hospital, the Chongqing Medical University and Chongqing Traditional Medicine Hospital, and various advertising modalities in the greater Chongqing area. PCOS was diagnosed according to the criteria indicated by the Rotterdam European society of human reproduction and embryology/American society for reproductive medicine Workshop, that is, by the presence of at least 2 of the 3 following features: clinical and/or biochemical hyperandrogenism, chronic oligoanovulation, and polycystic ovaries (PCOs), after exclusion of secondary causes. \( ^{13} \) MetS was defined as 3 or more of the following: waist circumference (WC) \( \geq 85 \) cm in women; TGs \( \geq 150 \) mg/dL; high-density lipoprotein cholesterol (HDL-C) \( < 50 \) mg/dL in women; blood pressure \( \geq 130/85 \) mm Hg; and FBG \( \geq 6.1 \) mmol/L. Based on the definitions of MetS above, participants were divided into MetS group and no-MetS group. \( ^{13} \) All control subjects had normal menstrual cycles, and none had clinical and/or biochemical hyperandrogenism. Exclusion criteria for both groups included body mass index (BMI) \( > 35 \) kg/m\(^2\); known CVD, thyroid disease, neoplasms, smoking, diabetes, hypertension, and renal impairment (serum creatinine 120 \( \mu \)mol/L). None of these women was on any hormone medications and medications that would affect insulin sensitivity within the past 6 months. All subjects gave their written informed consent before entering the study, which was conducted in accordance with the Declaration of Helsinki and approved by the Human Research Ethics Committee of Chongqing Medical University (Ethical review of scientific research NO.72, approved December 11, 2014).

2.2. Oral glucose tolerance test

At 8:00 hours on the study days, after an 8 to 10-hour overnight fast, an OGTT was performed on healthy and PCOS women. These subjects ingested 75 g glucose, and venous blood was drawn at 0, 30, 60, and 120 minutes for measurement of glucose and insulin.

2.3. Euglycemic–hyperinsulinemic clamp

The EHC was performed in all subjects as previously described. \( ^{11} \) Briefly, after an overnight fast, an intravenous (IV) 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 hours, and a variable infusion of 20\% glucose was administered to maintain plasma glucose at the fasting level. During the procedure, plasma glucose levels were measured every 10 minutes to guide the glucose infusion. The rate of glucose disposal was defined as the glucose infusion rate (GIR) during the stable period of the clamp, and was related to body weight (M-value).

2.4. Biochemical and hormonal analysis

Plasma glucose and Glycosylated hemoglobin were measured by the glucose oxidase method and anion exchange high-performance liquid chromatography, respectively. Insulin was measured by radioimmunoassay using human insulin as standard (Institute of Atomic Energy, China). Free fatty acid (FFA) was measured with a commercial kit (Randox Laboratories, Antrim, UK). Total cholesterol (TC), HDL-C, low-density lipoprotein cholesterol (LDL-C), and triglyceride (TG) were analyzed enzymatically using an autoanalyzer (Hitachi, Tokyo, Japan). Plasma level of ADI was also measured by ELISA as we previously described. \( ^{12} \) Serum hormonal concentrations including LH, follicle-stimulating hormone (FSH), and testosterone (TST) were measured with well-established electrochemiluminescence immunoassay using COBAS E immunoassay analyzers (Roche Diagnostics GmbH). Total TST levels were measured by coated tube RIA (Diasorin, S.p.A., Sulluggia, Italy). Dehydroepiandrosterone sulfate (DHEA-S) and sex hormone-binding globulin (SHBG) were performed using an automated analyzer (Abbott Architect;Abbott Laboratories, Abbott Park, IL.). Free androgen index (FAI) was calculated as 

\[
FAI = \frac{\text{TEST/SHBG}}{\text{SHBG}} \times 100.
\]

2.5. Anthropometric measurements

Body mass index was calculated as weight divided by height squared. HOMA-IR was calculated using the following equations:

\[
\text{HOMA-IR} = \frac{\text{FIns} \times \text{FBG}}{22.5},
\]

\[
\text{TyG} = \ln (\text{TG} \times \text{FBG})/2.
\]

2.6. Statistical analysis

The data are shown as the mean ± standard deviation (SD). All statistical analyses were performed using SPSS 19.0 software (SPSS Inc., Chicago, IL). A P value of less than 0.05 was considered statistically significant.
data was tested using Kolmogorov–Smirnov test. The variables of non-normal distribution were skewed and transformed by log or square-root to obtain a normal distribution. Comparisons between groups were performed by analysis of variance (ANOVA) test as appropriate. The associations between clinical features and ADI index were assessed using linear regression and correlation analysis. The optimal value of ADI (FBG × FIns) and other indexes for diagnosis of IR were established on a receiver-operating characteristic (ROC) scatter plot. The area under the ROC curve (AUC) as a summary of the overall diagnostic accuracy of the test was evaluated. The best maker has ROC curve that is shifted to the left with AUCs near 1.[18]

3. Results

3.1. Clinical features in different populations

The clinical characteristics of our subjects are shown in Table 1. As expected, the BMI, waist-to-hip ratio (WHR), blood pressure (BP), FBS, 2-hour postglucose load blood glucose, and other indexes for diagnosis of IR were established on a receiver-operating characteristic (ROC) scatter plot. The area under the ROC curve (AUC) as a summary of the overall diagnostic accuracy of the test was evaluated. The best maker has ROC curve that is shifted to the left with AUCs near 1.[18]

3.2. The association of M-value with the ADI index and several surrogate indices of IR in healthy and PCOS women

To evaluate the predictive value of the ADI index for IR, we performed a 2-hour EHC in 100 healthy and 99 PCOS women. As expected, PCOS+MetS and PCOS women had lower M-values than healthy women (4.41 ± 1.65 and 7.12 ± 3.02 vs 10.08 ± 2.60 mg/kg/min; P < 0.01; Fig. 1G). Partial correlation analysis in all study populations showed that the M-value significantly correlated negatively with HOMA-IR (r = −0.517, P < 0.01), TyG (r = −0.451, P < 0.01), TG/HDL (r = −0.338, P < 0.01), AUCi/AUCg (r = −0.351, P < 0.01), and FAI (r = −0.419, P < 0.01), and correlated positively with the ADI index (r = 0.641, P < 0.01). Importantly, the r value of the Pearson correlation between the ADI index and HOMA-IR was greater than that of other surrogate indices in both PCOS and healthy subjects, even after adjusting for age and BMI (Table 2). In addition, the ADI index in PCOS subjects showed a significant linear trend and was independently associated with IR, especially when concen-

### Table 1

Clinical, hormonal, and metabolic features of study population.

|                          | Control (n = 100) | PCOS (n = 68) | PCOS + MetS (n = 31) |
|--------------------------|------------------|--------------|----------------------|
| Age, y                   | 25 (24, 27)      | 26 (23.5, 29.75) | 26 (24, 30)          |
| BMI, kg/m²               | 20.51 ± 2.67**** | 20.45 ± 4.42 **  | 27.20 ± 6.62***      |
| WHR                      | 0.78 (0.75, 0.84)*** | 0.85 (0.80, 0.90)*** | 0.88 (0.82, 0.92)*** |
| SBP, mm Hg               | 109.06 ± 8.01**** | 114.34 ± 10.15**** | 119.84 ± 10.52**** |
| DBP, mm Hg               | 74.78 ± 7.75      | 74.04 ± 5.60      | 80.71 ± 8.35 ***     |
| FBG, mmol/L              | 0.65 ± 0.04       | 0.67 ± 0.04       | 0.73 ± 0.10          |
| 2h-BG, mmol/L            | 5.40 ± 1.12****   | 6.77 ± 1.86       | 9.49 ± 3.73          |
| FIns, μU/mL              | 0.87 ± 0.15       | 1.06 ± 0.27       | 1.32 ± 0.25          |
| 2h-Ins, μU/mL            | 1.52 ± 0.39       | 1.94 ± 0.26       | 2.23 ± 0.28          |
| TC, mmol/L               | 3.85 ± 1.06       | 4.30 ± 1.04       | 4.86 ± 0.69          |
| TG, mmol/L               | 0.80 (0.58, 1.27)**** | 1.08 (0.74, 1.69)**** | 1.97 (1.52, 3.01)**** |
| HDL-C, mmol/L            | 1.16 (0.97, 1.42)  | 1.34 (1.18, 1.54)  | 1.15 (1.03, 1.23)**** |
| LDL-C, mmol/L            | 0.3 ± 0.17****    | 0.13 ± 0.14****   | 0.39 ± 0.17****      |
| FFA, mmol/L              | 0.56 ± 0.27       | 0.57 ± 0.22       | 0.65 ± 0.17          |
| DHEA-S, μg/dL            | 2.26 ± 0.16       | 2.25 ± 0.20       | 2.36 ± 0.17****      |
| UH, μU/L                 | 4.96 ± 2.67****   | 10.25 ± 6.73****  | 9.49 ± 5.80          |
| FSH, IU/L                | 8.06 ± 1.91       | 7.44 ± 2.26       | 7.70 ± 2.24          |
| SHBG, nmol/L             | 60.76 ± 24.80**** | 44.72 ± 26.99**** | 31.90 ± 17.54        |
| TEST, nmol/L             | 1.32 ± 0.26****   | 1.60 ± 0.36****   | 1.73 ± 0.60****      |
| ADI, μU/L                | 46.86 ± 13.97**** | 35.56 ± 16.86**** | 24.23 ± 12.78****    |

Values were given as means ± SD or median (interquartile range).
2h-Ins = 2-hour plasma insulin after glucose overload, 2h-BG = 2-hour postglucose load blood glucose, ADI = adiponectin, BMI = body mass index, DBP = diastolic blood pressure, FBG = fasting blood glucose, FFA = free fatty acid, FIns = fasting plasma insulin, HDL-C = high-density lipoprotein cholesterol, HOMA-IR = Homeostasis Model Assessment of Insulin Resistance, LDL-C = low-density lipoprotein cholesterol, PCOS = polycystic ovary syndrome, SBP = systolic blood pressure, TC = total cholesterol, TG = triglyceride.

* Square root transformation before analysis.
** Log transformation before analysis.
*** P < 0.05.
**** P < 0.01 compared with controls.
adiponectin, AUCglucose, the area under the curve for glucose; FAI, free androgen index; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; TG, triglyceride; TyG, the product of fasting triglycerides and glucose.

### Table 2

|                        | M-value |                          |                          |                          |                          |
|------------------------|---------|---------------------------|---------------------------|---------------------------|---------------------------|
|                        |         | Controls (n = 100)        | PCOS (n = 99)             | Control (n = 100)         | PCOS (n = 99)             |
|                        | Model 1 | Model 2                   | Model 1                   | Model 2                   | Model 2                   |
|                        | r       | P                         | r                         | P                         | r                         | P                         |
| HOMA-IR                | −0.501  | 0.000                     | −0.490                    | 0.000                     | −0.293                    | 0.017                     | −0.290                    | 0.004                     |
| TyG                    | −0.263  | 0.031                     | −0.451                    | 0.000                     | −0.250                    | 0.099                     | −0.357                    | 0.000                     |
| TG/HDL                 | −0.294  | 0.015                     | −0.417                    | 0.000                     | −0.135                    | 0.279                     | −0.319                    | 0.001                     |
| ADI index              | 0.693   | 0.000                     | 0.727                     | 0.000                     | 0.539                     | 0.000                     | 0.603                     | 0.000                     |
| AUC_tissue/AUC_glucose| −0.327  | 0.007                     | −0.319                    | 0.001                     | −0.073                    | 0.559                     | −0.094                    | 0.358                     |
| FAI                    | −0.096  | 0.438                     | −0.231                    | 0.021                     | 0.063                     | 0.616                     | −0.142                    | 0.164                     |

Free androgen index (FAI) = T (nmol/L)/SHBG (nmol/L) × 100. Adiponectin: model 1, unadjusted; model 2, age and BMI-adjusted. ADI = adiponectin, AUC_tissue /AUC_glucose, the area under the curve for glucose; AUC_tissue /AUC_glucose, the area under the curve for insulin, HOMA-IR = Homeostasis Model Assessment of insulin resistance, M = whole body glucose uptake rate.

### Table 3

|                        | All PCOS |                          |                          |                          |                          |                          |
|------------------------|----------|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|
|                        |          |                          |                          |                          |                          |                          |
|                        |          | Row mean scores test     | −3.9483                   | <0.001                    | Row mean scores test     | −3.9483                   | <0.001                    |
|                        |          | Cochran–Armitage trend test | −3.9483                   | <0.001                    | Cochran–Armitage trend test | −3.9483                   | <0.001                    |

All PCOS = polycystic ovary syndrome.

### Figure 1

The surrogates of insulin sensitivity in study population. (A) TyG index; (B) HOMA-IR; (C) FAI; (D) AUC/AUCg; (E) TG/HDL-C; (F) ADI index. Data are means ± SD. *P < 0.01 compared with controls, †P < 0.01 compared with PCOS. ADI index = adiponectin/ (FBG × Fins), AUC/AUCg, the area under the curve for insulin; the area under the curve for glucose; FAI, free androgen index; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; TG, triglyceride; TyG, the product of fasting triglycerides and glucose.

### 3.3. The diagnostic value of different surrogate indices in detecting IR and MetS

All subjects were stratified into tertiles of M-value and ADI indexes. The maximum insulin sensitivity corresponds to tertile I of the ADI index and tertile I of the M-value, and minimum insulin sensitivity to tertile III of the ADI index and tertile III of the M-value. A weighted k coefficient showed a good agreement (0.144; P < 0.01; Table 4).

The optimal value of the ADI index for diagnosis of insulin sensitivity and MetS were established by a ROC scatter plot. The
AUC as a summary of the overall diagnostic accuracy of the test was evaluated. To compare the predictive value of the ADI index for insulin sensitivity (defined as M-value > 6.28), we analyzed the ROC curves of the ADI index in all populations. The ROC curve analyses revealed that the best cut-off value for the ADI index to predict insulin sensitivity was 0.67 (sensitivity 89.4%, specificity 88.1%, positive predictive value 80.8%, negative predictive value 93.7%, and AUC 0.952, 95% CI 0.923–0.980, P < 0.01; Fig. 3A), suggesting that the ADI index is an appropriate surrogate index for identifying insulin sensitivity in the study population. The optimal cut-off value of the ADI index for detection of MetS was 0.32, with a sensitivity of 88.7% and a specificity of 71.0% (positive predictive value 53.7%, negative predictive value 94.3%, and AUC 0.889, 95% CI 0.837–0.942, P < 0.01; Fig. 3B).

4. Discussion

Polycystic ovary syndrome is a common endocrine system disorder that affects metabolism and reproductivity, and is likely multifactorial in origin. IR is important in the pathogenesis of PCOS, but the exact mechanisms of PCOS are unclear. The “central paradox” in PCOS is that the ovary remains sensitive to insulin-induced androgen production, despite a systemic insulin-resistant state.[1] MetS comprises a cluster of metabolic abnormalities associated with IR. With the increase in the
proportion of the population with obesity and a sedentary lifestyle in recent decades, MetS prevalence has been increasing worldwide. MetS is also a well-known risk factor for diabetes and CVD. Although there are a number of methods that can be used to assess insulin sensitivity in these subjects, many, such as EHC, are costly and time-consuming, invasive, require specially trained staff, and cannot be used in the primary care setting. Therefore, it is important to identify a simple and reliable marker for assessing IR and MetS in large-scale studies. So far, there have been numerous ongoing studies focused on finding cost-efficient and effective methods with high sensitivity and specificity for predicting the occurrence of Mets and IR.[19,20]

In this study, we performed a cross-sectional study of the general population including PCOS and MetS subjects to assess the associations among the ADI index, HOMA-IR, TyG, TG/ HDL, AUC/AUCg, and EHC (M-values). We found that PCOS and PCOS+MetS subjects had higher surrogate indices than that of control subjects, except for TG/HDL. PCOS+MetS had higher TG/HDL than the controls, but there was no significant difference between PCOS and controls. The possible reasons for this result could be that the high TG and HDL-C in PCOS women lead to a minor change of TG/HDL-C; and TG/HDL-C could be influenced by some outliers due to the relative small sample size. Therefore, future large-scale studies involving different ethnic groups are needed to address the issue.

Differing with T2DM, women with PCOS are young women with IR, but have no severe disturbance of glucose metabolism. Therefore, PCOS women provide a good model for exploring the association between ADI and IR without hyperglycemia. In the current study, EHCs were performed in healthy and PCOS women with or without MetS. The correlation between several surrogate markers and IR was assessed by M-value from EHCs. The results showed that in the entire study population, the main predictors of insulin sensitivity indicated as M-values were the ADI index, suggesting that it could be a good marker for detecting IR in PCOS, T2DM, and MetS patients. Importantly, the Pearson correlation coefficient between the ADI index and the M-value was the largest among all surrogate markers of IR, indicating that the ADI index is the best marker for assessing IR. Based on these findings, we recommend that if EHC is not available, ADI index should be chosen as a primary surrogate index for estimating insulin sensitivity. Furthermore, unlike OGTT, the ADI index is easy to perform because only fasting blood samples are needed.

In the current study, ROC analysis also showed that when compared with other surrogate indices, the ADI index has the highest sensitivity and specificity for recognizing IR and MetS in the study population. In addition, the optimal cut-off value of the ADI index for identifying MetS was also determined. In general, sensitivity is known as the proportion of subjects correctly identified with a disease, whereas specificity is known as the proportion of correctly identified disease-free subjects. In this regard, the importance of an appropriate diagnostic index for the early finding of the disease is to set up the ability to change lifestyle and/or to give pharmaceutical treatment to prevent the progression of disease. Here, high sensitivity indicates that using ADI index for identifying IR and MetS has fewer false-negative subjects in the clinical setting. The specificity of ADI index is also high, indicating that for screening IR, it is appropriate to identify the proportion of disease-free individuals. Therefore, we recommend using ADI index for identifying IR and MetS in large-scale studies for screening individuals at high risk of developing T2DM. The clinical importance of the ADI index is underlined by its association with IR, an important component of MetS, whereas IR is also known as a crucial causation of coronary heart disease (CHD).[21] Nevertheless, little is known about the impacts of postprandial ADI concentrations on insulin sensitivity.

Limitations of our study also deserve comments. First, this study is limited by its cross-sectional design and provides no temporal interpretation of reported associations. Second, our sample constituted entirely of the Chinese population. Therefore, extrapolation of these results to other ethnic groups should be undertaken with caution. Third, given the cross-sectional nature of our study, we do not ascertain the impact of different ADI indexes and their interaction with MetS components on IR. Nonetheless, the ADI index could be used as a good marker to identify IR in PCOS women.

In summary, our findings suggest that the ADI index is a good marker for identifying IR in PCOS women. The optimal cut-off value of ADI index for prediction of IR was 0.67, and for prediction of MetS was 0.32. Therefore, ADI index could be recommended as surrogate of M-value to identify IR in PCOS women.

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