Clinical Study

The Usefulness of Homeostatic Measurement Assessment-Insulin Resistance (HOMA-IR) for Detection of Glucose Intolerance in Thai Women of Reproductive Age with Polycystic Ovary Syndrome

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Objectives. To study the cut-off point of Homeostatic Measurement Assessment-Insulin Resistance (HOMA-IR) as a screening test for detection of glucose intolerance in Thai women with polycystic ovary syndrome (PCOS).

Study Design. Cross-sectional study.

Setting. Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital.

Subject. Two hundred and fifty Thai PCOS women who attended the Gynecologic Endocrinology Unit, during May 2007 to January 2009.

Materials and Methods. The patients were interviewed and examined for weight, height, waist circumference, and blood pressure. Venous blood samples were drawn twice, one at 12-hour fasting and the other at 2 hours after glucose loading.

Results. The prevalence of glucose intolerance in Thai PCOS women was 20.0%. The mean of HOMA-IR was 3.53 ± 7.7. Area under an ROC curve for HOMA-IR for detecting glucose intolerance was 0.82. Using the cut-off value of HOMA-IR >2.0, there was sensitivity at 84.0%, specificity at 61.0%, positive predictive value at 35.0%, negative predictive value at 93.8%, and accuracy at 65.6%. Conclusion. HOMA-IR >2.0 was used for screening test for glucose intolerance in Thai PCOS women. If the result was positive, a specific test should be done to prove the diagnosis.

1. Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders, affecting around 4–7% of the population in women of the reproductive age [1]. Diagnostic criteria for PCOS mostly use the revised Rotterdam 2003 criteria [2]. However, the etiology and pathophysiology of PCOS remain unclear, and the multiple risk factors such as genetics, environment, nutrition, lifestyle, and much more are still under investigation. There is heterogeneity of symptoms and in severity of disease but most have central obesity or android fat deposition (fat at abdominal wall and visceras). Android fat deposition is relatively resistant to insulin hormone [3, 4]. According to International Diabetes Federation 2005 criteria for metabolic syndrome (IDF 2005) [5], central obesity is diagnosed when waist circumference is more than 80 centimeters for Asian women. Both of central obesity and hyperandrogenism in PCOS aggravate insulin resistance which promotes incidence of diabetes mellitus. Several studies showed that overall abnormal oral glucose tolerance test (OGTT) in PCOS is 42–45% which impair glucose tolerance test 25–31%, and diabetes mellitus 7.5–10%, and all the abnormalities are associated with age, higher body mass index (BMI), central obesity, and hyperandrogenemia [6–9]. Acanthosis nigricans is a brown to black, poorly defined, velvety hyperpigmentation of the skin, usually present in the posterior and lateral folds of neck, axilla, groin, and other areas. The most common cause would be insulin resistance.
and/or received steroid within 6 months before participation in the study. The study protocol was approved by the Ethics Committee of the Faculty of Medicine Siriraj Hospital, Mahidol University. This study was financially supported by Siriraj Routine to Research (R2R) Management Fund.

All the women with PCOS who participated in this study received a physical examination including measurement of vital signs and skin lesions, and anthropometric measurements, as a prelude to a review of clinical presentations. Age, body weight, height, waist circumference, blood pressure, and skin manifestations were recorded. After overnight fasting for at least 12 hours, venous blood samples were drawn twice, the first one at 8–10 AM and the second one at 2-hour postglucose loading to measure glucose and insulin level at baseline and 2 hours following oral 75 g glucose loading. The first blood sample was also examined for baseline hormonal profiles (prolactin, cortisol, thyroid stimulating hormone (TSH), and androgen hormone) and baseline metabolic profile (glucose, insulin, and lipid). The second blood sample was examined for glucose and insulin postglucose loading.

2. Materials and Methods

This cross-sectional study was conducted. Using data is based on the records of 250 PCOS women who consecutively attended the Gynecologic Endocrinology Unit of the Department of Obstetrics and Gynecology, Siriraj Hospital between May 2007 and January 2009, which were reviewed and analyzed. The diagnosis of PCOS was defined by the Revised Rotterdam Criteria 2003 [2].

Exclusion criteria included the women who had previous surgery of one or both ovaries, used hormonal treatment, and took the medication for dyslipidemia within 3 months and/or received steroid within 6 months before participation in the study. The study protocol was approved by the Ethics Committee of the Faculty of Medicine Siriraj Hospital, Mahidol University. This study was financially supported by Siriraj Routine to Research (R2R) Management Fund.

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2.1. Diagnostic Criteria. PCOS was diagnosed by the Revised Rotterdam Criteria 2003 [2], that is, including a patient who has at least 2 in 3 of the following: (1) oligomenorrhea or amenorrhea, (2) hyperandrogenism and/or hyperandrogenism, (3) polycystic ovaries, and excluding another causes (e.g., hyper/hypothyroidism, hyperprolac tinemia, Cushing’s syndrome, congenital adrenal hyperplasia (CAH), or hormonal secreting tumor).

Glucose tolerance was evaluated using 75 g OGTT according to the American Diabetes Association (ADA) 2007 criteria [15]. Abnormal OGTT is classified as follows: (i) impaired fasting glucose (IFG), that is, fasting glucose (FG) ≥ 100 and <126 mg/dL, (ii) impaired glucose tolerance test (IGT), that is, 2 hr glucose ≥140 and <200 mg/dL, (iii) type 2 Diabetes mellitus (DM), that is, fasting blood glucose ≥126 mg/dL and/or 2 hr glucose ≥200 mg/dL. In our study, glucose intolerance was composed of IFG, IGT, and Type 2 DM.

The HOMA-IR was calculated by multiplying fasting Insulin (U/mL) by fasting glucose (mmol/L) and dividing by 22.5.

Obesity was defined as body mass index (BMI) ≥25 kg/ m² according to the WHO cut-off points for Asian populations [19]. Central obesity was defined as WC ≥80 cm according to the International Diabetes Federation (IDF) 2005 [5].

Hyperandrogenemia was defined as total testosterone >0.8 ng/mL, or free testosterone >0.006 ng/mL, or dehydroepiandrosterone sulphate (DHEAS) >350 microgram/dL [20].

2.2. Laboratory Assays. All laboratory assays were performed at the laboratory unit of Department of Clinical Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University, the central laboratory certified by ISO 15189. All assays were done using an automatic analyzer (Modular P800, Roche; for glucose and Modular E170, Roche; for insulin, TSH,
The mean age, BMI, and waist circumference (WC) were mean using SPSS version 13 (SPSS Inc.). Data were presented in 2.3. Statistical Analysis. Statistical analysis was performed using SPSS version 13 (SPSS Inc.). Data were presented in mean ± SD or number (%) as appropriate. The sensitivity specificity positive predictive value, negative predictive value, and diagnostic accuracy were calculated from 2 × 2 tables for HOMA-IR at each cut-point for detection of abnormal OGTT. Receiver operator curves (ROCs) for HOMA-IR and abnormal OGTT were created by calculating the sensitivity and specificity of fixed cut-off points of the various parameters examined.

3. Results

A total of 250 women with PCOS were studied. The clinical and laboratory characteristics were summarized in Table 1. The mean age, BMI, and waist circumference (WC) were 25.4 ± 5.8 years old, 26.2 ± 7.6 kg/m² and 82.3 ± 16.3 cm, respectively. The diagnostic criteria of PCOS were 98.4% of oligomenorrhea, 49.2% of hyperandrogenism, and 97.2% of polycystic ovaries. In this study 27.2% had acanthosis nigricans. The blood level of carbohydrate metabolic profiles showed the fasting blood glucose was 85.4 ± 22.9 mg/dL, 2 hr blood glucose was 116.4 ± 53.8 mg/dL, fasting insulin was 15.6 ± 34.2 µ/mL, 2 hr insulin was 106.6 ± 89.0 µ/mL, and HOMA-IR was 3.53 ± 7.74.

Table 1: Characteristics of 250 PCOS Thai women.

| Characteristics                        | Mean ± SD or n (%)         |
|----------------------------------------|----------------------------|
| Age (yr)                               | 25.4 ± 5.8                  |
| Body mass index (kg/m²)                | 26.2 ± 7.6                  |
| Waist circumference (cm)               | 82.3 ± 16.3                 |
| Systolic blood pressure (mmHg)         | 112.5 ± 12.5                |
| Diastolic blood pressure (mmHg)        | 70.3 ± 9.1                  |
| Presence of acanthosis nigricans       | 68 (27.2, 21.7–32.7)        |
| Carbohydrate metabolism                |                            |
| Fasting plasma glucose (mg/dL)         | 85.4 ± 22.9                 |
| Fasting plasma insulin (µg/mL)         | 15.6 ± 34.2                 |
| 2 hour plasma glucose (mg/dL)          | 116.4 ± 53.8                |
| 2 hour plasma insulin (µg/mL)          | 106.6 ± 89.0                |
| HOMA-IR                                | 3.53 ± 7.74                 |
| Lipid profiles                          |                            |
| Cholesterol (mg/dL)                    | 189.2 ± 37.6                |
| Triglyceride (mg/dL)                   | 103.2 ± 66.2                |
| High density lipoprotein cholesterol (mg/dL) | 55.4 ± 14.6                |
| Low density lipoprotein cholesterol (mg/dL) | 112.0 ± 32.5                |
| Androgen profiles                      |                            |
| Total testosterone (ng/mL)             | 0.735 ± 0.388               |
| Free testosterone (ng/mL)              | 0.014 ± 0.009               |
| DHEAS (µg/dL)                          | 256.8 ± 107.2               |

HOMA-IR: Homeostatic Measurement Assessment-Insulin Resistance, DHEAS: dehydroepiandrosterone sulphate.

Table 2: Prevalence of glucose intolerance in 250 Thai women with polycystic ovary syndrome.

| Glucose intolerance‡ | Prevalence n (%) | 95% CI |
|----------------------|------------------|-------|
| Overall              | 50               | 20.0 (15.04–24.96) |
| Impaired fasting glucose (IFG)† | 8               | 3.2 (1.02–5.38) |
| Impaired glucose tolerance (IGT) | 34             | 13.6 (9.35–17.85) |
| Diabetes mellitus (DM) | 14             | 5.6 (2.75–8.45) |

†Glucose intolerance: impaired fasting glucose (fasting plasma glucose ≥ 100 and <126 mg/dL), impaired glucose tolerance test (2 hr glucose ≥ 140 and <200 mg/dL) or the presence of diabetes mellitus (fasting plasma glucose ≥ 126 mg/dL and/or 2 hr glucose ≥ 200 mg/dL).
‡4 women had combined IFG and IGT and 2 women had combined IFG and 2 hr glucose ≥ 200 mg/dL.

Table 3: Sensitivity, specificity, positive predictive value, negative predictive value and accuracy of HOMA-IR >2.0 for detection of glucose intolerance in Thai PCOS women.

| Parameter                | Percent (%) | 95% CI |
|--------------------------|-------------|-------|
| Sensitivity              | 84.0        | 79.5–88.5 |
| Specificity              | 61.0        | 55.0–67.1 |
| Positive predictive Value| 35.0        | 29.1–40.9 |
| Negative Predictive Value| 93.8        | 91.1–96.9 |
| Accuracy                 | 65.6        | 60.1–71.9 |

The prevalence of an glucose intolerance is shown in Table 2. An glucose intolerance was found in 20.0%, with 5.6% having type 2 diabetes mellitus, 3.2% having impaired fasting glucose levels, and 13.6% having an impaired glucose tolerance test.

Figure 1 showed ROC curve of HOMA-IR and glucose intolerance. The area under the curve was 0.82.

Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the cut-off HOMA-IR of more than 2.0 for detection of glucose intolerance in PCOS women were 89.74%, 58.82%, 38.46%, 95.24%, and 65.71%, respectively, as in Table 3. Table 4 shows the relation between associating factors of glucose intolerance in PCOS and HOMA-IR >2.0. All had statistical significance with HOMA-IR >2.0. Odds ratio for age ≥ 30 = 2.45, BMI ≥ 25 = 23.37, WC ≥ 80 cm = 24.55, hyperandrogenism = 1.97, and presence of acanthosis nigricans = 50.03.

Using cut-off point HOMA >2.0 and the number of clinical associating factor for insulin resistance, odds ratio in each condition is shown in Table 5. The significant odds ratio included the conditions of HOMA >2.0 combined with 4 clinical associating factors and HOMA >2.0 combined with 5 clinical associating factors; odds ratio (95% CI) were 2.67 (1.31–5.42) and 9.75 (3.16–30.10), respectively.

prolactin, cortisol). All techniques had intra- and interassay coefficients of variation (CV) less than 5%.

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Table 4: Relation of HOMA-IR and associating factors of glucose intolerance.

| Variables                  | HOMA-IR ≤2 n (%) | HOMA-IR >2 n (%) | Odds ratio | 95% CI odds ratio |
|----------------------------|------------------|-----------------|------------|------------------|
| Age (years old)            |                  |                 |            |                  |
| <30                       | 110 (57.0)       | 83 (43.0)       | 2.45       | 1.33–4.53        |
| ≥30                       | 20 (35.1)        | 37 (64.9)       |            |                  |
| BMI (kg/m²)                |                  |                 |            |                  |
| <25                       | 111 (82.2)       | 24 (17.8)       | 23.37      | 12.07–45.26      |
| ≥25                       | 19 (16.5)        | 96 (83.5)       |            |                  |
| Waist circumference (cm)   |                  |                 |            |                  |
| <80                       | 108 (84.4)       | 20 (15.6)       | 24.55      | 12.64–47.67      |
| ≥80                       | 22 (18.0)        | 100 (82.0)      |            |                  |
| Hyperandrogenism           |                  |                 |            |                  |
| No                        | 76 (60.3)        | 50 (39.7)       | 1.97       | 1.19–3.26        |
| Yes                       | 54 (49.3)        | 70 (56.5)       |            |                  |
| Acanthosis nigricans       |                  |                 |            |                  |
| Absent                    | 127 (69.8)       | 55 (30.2)       | 50.03      | 15.07–166.08     |
| Present                   | 3 (4.4)          | 65 (95.6)       |            |                  |

Table 5: Odds ratio in each condition which showed HOMA >2.0 with number of clinical associating factors.

| Condition                                  | n (%) | OR (95% CI) | P value |
|--------------------------------------------|-------|-------------|---------|
| HOMA >2.0 with 1 clinical associating factor | 2 (0.8) | 0.79 (0.74–0.85) | 0.219   |
| HOMA >2.0 with 2 clinical associating factors | 6 (2.4) | 1.10 (0.42–2.89) | 0.805   |
| HOMA >2.0 with 3 clinical associating factors | 11 (4.4) | 1.97 (0.89–4.35) | 0.113   |
| HOMA >2.0 with 4 clinical associating factors | 16 (6.4) | 2.67 (1.31–5.42) | 0.008   |
| HOMA >2.0 with 5 clinical associating factors | 20 (8.0) | 9.75 (3.16–30.10) | <0.001  |

Clinical associating factors are age ≥30 year old, BMI ≥25 kg/m², waist circumference ≥80 centimeters, presence of acanthosis nigricans, and hyperandrogenism.

4. Discussions

Insulin resistance and the consequent development of hyperinsulinemia seem to be an important pathophysiological mechanism that links PCOS to its concurrent metabolic derangements [1]. An insulin resistance is due to alterations in β-cell function, it might have a key role in the impaired glucose tolerance test and the development of frank diabetes in women with PCOS. It is well known that type 2 DM is an important risk factor for coronary heart disease. In previous studies, type 2 DM was found to contribute significantly to the morality of women with PCOS (odds ratio 3.6; 95% confidence interval 1.5–8.4) more than that expected in unaffected women [21]. In this study, our data indicated that the prevalence of abnormal glucose tolerance in our study was lower than that of American women with PCOS but similar to that of Chinese women with PCOS [22]. According to some, differences among these studies in the selection criteria of PCOS cannot be ignored and the factors of ethnic background, dietary composition, and lifestyle might play an important role in the prevalence of abnormal glucose tolerance in women with PCOS.

Therefore, an OGTT is currently the only reliable way to detect impaired glucose metabolism in PCOS. This procedure is relatively time-consuming and inconvenient for the patient, which limits its use as a general screening instrument in daily practice. Therefore, a more convenient screening test that minimizes the need for an OGTT is desirable. In this study, HOMA-IR had the close relation for detection of abnormal OGTT in Thai PCOS women. If using the cut-off level of HOMA-IR >2.0 for detecting the glucose intolerance, it can give more sensitivity, but specificity was less than the higher cut-off level. It may be suitable for use as a screening test for detecting of glucose intolerance or insulin resistance in Thai PCOS women. In the cases which had a false positive test, if they received the treatment to control insulin intolerance, it did not have a serious effect on the treatment. Because the early step of treatment is life style modification, control of body weight, control of diet and exercise, these methods are the better way for controlling other metabolic disorders, too. Insulin sensitizing drug for example, metformin, provides benefit to control insulin resistance in PCOS women. Nevertheless this drug would give minor gastrointestinal side effect and no serious adverse event was reported [23].

Many studies use the HOMA-IR as the diagnostic criteria for insulin resistance [2, 17, 18, 24]. The European Group for the Study of Insulin Resistance (EGRIR) uses the cut-off level of HOMA-IR >2.0 to indicate insulin resistance or glucose intolerance [24]. Some studies used different cut-off levels of
HOMA-IR, because of the differences of each ethnic group, the prevalence of obesity or central obesity or age group. And no consensus on the cut-off level of HOMA-IR exists for Thai PCOS women. A screening strategy that uses BMI and waist circumference, which is a low-cost and rapidly performed approach, could save about 23% of OGTT [25]. However, if PCOS women have the risk factors to develop insulin resistance, the diagnostic procedure should be done.

Many studies showed clinical risk factors of glucose intolerance in PCOS: age, BMI, central obesity, hyperandrogenism, presence of acanthosis nigricans [6–9, 26–28]. Table 4 shows a statistical relation between HOMA-IR >2.0 and these factors. If PCOS women presented clinical risk factor and had abnormal HOMA-IR, especially 4 and 5 clinical risks, these women would have a significant odds ratio to have glucose intolerance (Table 5). On the other hand, we can use the clinical risk to select high risk women for investigation of a specific test for glucose intolerance (75 g OGTT).

Limitations of this study were that it was cross-sectional study and had no control group. The majority of population in this study was younger and was an urban population; this might not be able to fully represent all Thai PCOS women. To overcome these limitations, a prospective, multicenter study is needed.

5. Conclusion

HOMA-IR was an easily obtainable, safe, low cost, and less invasive test than OGTT. HOMA-IR >2.0 was used as a screening test for glucose intolerance in Thai PCOS women. If the result was positive and had many clinical risk factors, a specific test should be done to prove the diagnosis.

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