

Metabolic Syndrome and Insulin Resistance in Thai Women with Polycystic Ovary Syndrome

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Objective: To determine the prevalence of metabolic syndrome and insulin resistance in Thai women with polycystic ovary syndrome (PCOS).

Material and Method: Oral glucose tolerance tests were performed in 70 PCOS women. Blood was taken for the measurement of fasting insulin, 2-hr postprandial insulin, lipid profiles, testosterone and sex hormone binding globulin levels.

Results: The prevalence of metabolic syndrome and insulin resistance was 24.3% and 30.7%, respectively. Diabetes mellitus and impaired glucose tolerance was detected in 11.4% and 31.4%, respectively. Homeostatic model assessment (HOMA) was the most sensitive screening test for insulin resistance. PCOS women with metabolic syndrome had significantly higher body mass index, free testosterone index and insulin levels than those without the syndrome.

Conclusion: There was a high prevalence of metabolic syndrome, insulin resistance, diabetes mellitus and impaired glucose tolerance in Thai PCOS women. A combination of fasting glucose, a 2-hr glucose tolerance test and fasting insulin level effectively identified PCOS women who were at high risk of metabolic syndrome.

Keywords: Diabetes mellitus, Impaired glucose tolerance, Insulin resistance, Metabolic syndrome, PCOS

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Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in reproductive women^(1,2). Its prevalence⁽³⁻⁶⁾ and clinical manifestations⁽⁷⁻⁹⁾ can be quite different between ethnic and racial groups. Insulin resistance and metabolic syndrome are reported to be very common in Western women with PCOS⁽¹⁰⁻¹³⁾. There was a relationship between insulin action and hyperandrogenemia, even in lean PCOS women⁽¹¹⁾. PCOS phenotype also correlates with androgen levels, ovarian volumes and insulin levels^(10,11). However, its prevalence among Asian PCOS women is largely unknown.

In the authors' previous study⁽⁶⁾, it was found that Thai women differed from their Western counterparts in certain aspects. For example, hirsutism was uncommon in the presented population and they had lower body weight and BMI than Caucasians. In

addition, their diet and life-style were different. The authors, therefore, expected that Thai PCOS women might have different clinical features with regard to the presence of insulin resistance, glucose intolerance and metabolic syndrome. The present study was, therefore, undertaken to improve the authors' understanding on insulin resistance and metabolic syndrome in this population. The authors also compared 4 common screening tests for insulin resistance, namely fasting insulin level, fasting glucose to insulin ratio, two-hour glucose to insulin ratio and homeostatic model assessment (HOMA), for the ability to identify insulin resistance in the presented Asian population.

Material and Method

The present study was approved by the Ethics Committee of the Faculty of Medicine, Chiang Mai University. Seventy consecutive patients with PCOS, from June 2006 to June 2008, gave their informed consent before enrolling into the present study. A diagnosis of PCOS was based on the presence of 2 or more of the following: 1) chronic

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anovulation; 2) hyperandrogenism; and 3) the presence of polycystic ovaries (the 2003 Rotterdam criteria)⁽¹⁴⁾. Patients with other conditions such as hyperprolactinemia, hypothyroidism and Cushing's syndrome were excluded from the present study by history, physical examination and appropriate laboratory tests. None of those included had a previous history of diabetes mellitus and they were not taking any medication during the 3 months prior to enrollment.

After overnight fasting, blood samples were obtained between 8.00-10.00 am for follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol, prolactin, dehydroepiandrosterone sulfate (DHEAS), androstenedione (ADD), 17-hydroxyprogesterone (17-OHP), testosterone, sex hormone binding globulin (SHBG), insulin, glucose and lipid profiles [total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL) and triglycerides]. The subjects were given 75 g of glucose orally and blood samples were obtained 2 hours later for glucose and insulin levels.

Body weight, height, waist and hip circumferences, hirsutism scores by the Ferriman-Gallway scale and the presence of acanthosis nigricans were determined and recorded. Body mass index (BMI) was calculated by dividing the body weight (in kilograms) by the square of height (in meters). Waist/hip ratio was calculated as waist circumference in centimeters divided by hip circumference in centimeters.

Plasma glucose level was determined by the glucose dehydrogenase method. Impaired fasting glucose level was defined as glucose levels ≥ 110 and < 126 mg/dL; impaired glucose tolerance (IGT) was defined as 2-hour plasma glucose levels ≥ 140 and < 200 mg/dL; type 2 diabetes mellitus (DM) was diagnosed when fasting glucose levels were ≥ 126 mg/dL and/or 2-hour plasma glucose levels ≥ 200 mg/dL⁽¹⁵⁾.

Insulin resistance was diagnosed by the presence of⁽¹⁶⁾:

- Fasting insulin ≥ 20 uU/mL or
- 2-hr glucose/insulin ratio ≤ 1
- Fasting glucose/insulin ratio ≤ 4.5
- A cut-off value of HOMA (homeostatic model assessment) ≥ 3.8 . HOMA was calculated by dividing the product of fasting glucose (Go) and insulin (Io) by 405 (Io x Go/405).

Lipid profiles were measured by photometric determination (MEGA auto-analyzer, Merck, Germany). Triglyceride (TG) was measured by the glycerol-3-phosphate oxidase method (GPO; Ecoline, Germany), cholesterol by the CHODPAP method (Ecoline, Germany), LDL by enzymatic clearance assay (Wako,

Japan) and HDL by the enzymatic selective protection method (Abbot, USA).

Testosterone, FSH, LH, estradiol, insulin, prolactin and SHBG levels were measured by electrochemiluminescence immunoassay (Elecys 2010, Roche, Germany). ADD, DHEAS and 17-OHP were measured by radioimmunoassay. In the present study, the authors used the free testosterone index (FTI; testosterone x SHBG/100) to represent the biologically active fraction of testosterone. FTI has previously been shown to correlate well with free testosterone levels measured by equilibrium dialysis⁽¹⁷⁾.

Metabolic syndrome was diagnosed when subjects fulfilled 3 of the 5 criteria, defined by the International Diabetes Federation (IDF) and the American Heart Association/National Heart, Lung and Blood Institute (AHA/NHLBI) (18), as follows:

- Waist circumference ≥ 80 cm (for Asian women)⁽¹⁸⁾
- Triglycerides level ≥ 150 mg/dL
- HDL ≤ 50 mg/dL
- Blood pressure $\geq 130/85$ mmHg or on anti-hypertensive medication
- Fasting blood sugar ≥ 100 mg/dL or the presence of type 2 DM

Statistical analysis

Data analysis was performed using STATA version 8.2 (College Station, Texas). Unpaired t-tests were used, as appropriate, to compare PCOS women with and without metabolic syndrome and those with and without impaired glucose tolerance. If data were not normally distributed, they were transformed before statistical tests. Mann-Whitney U tests were used when transformation was not possible. A two-tailed p-value < 0.05 was considered as statistically significant for all analyses.

Results

Characteristics and serum hormone profiles of women with PCOS are shown in Table 1. Eight cases (11.4%) had diabetes mellitus (DM), according to the 1999 WHO criteria (three had fasting glucose ≥ 126 mg/dL and five 2-hr glucose ≥ 200 mg/dL). Impaired glucose tolerance test (GTT) was detected in 22 women (Fig. 1), giving a prevalence of 31.4%, (seven cases had fasting glucose ≥ 110 and < 126 mg/dL, eleven cases had 2-hr glucose ≥ 140 and < 200 mg/dL and four abnormality in both the fasting and 2-hr glucose test).

Fasting insulin level, fasting glucose to insulin ratio, 2-hr glucose to insulin ratio and HOMA,

Table 1. Characteristics and hormone profiles of 70 women with PCOS

Variables	Mean \pm SD	Range
Age (yr)	25.6 \pm 5.7	(13-38)
Weight (kg)	61.4 \pm 16.8	(37-105)
BMI (kg/m ²)	24.8 \pm 6.3	(14.5-38.5)
Waist (cm)	78.9 \pm 16.1	(54-121)
Waist/hip ratio	0.8 \pm 0.1	(0.66-0.96)
LH/FSH ratio	2.1 \pm 1.1	(0.17-5.86)
Testosterone (ng/mL)	0.5 \pm 0.3	(0.06-1.36)
Free testosterone index	2.5 \pm 2.5	(0.08-9.94)
SHBG (nmol/L)	43.0 \pm 35.0	(6.38-177.4)
ADD (ng/mL)	2.7 \pm 1.1	(0.89-5.80)

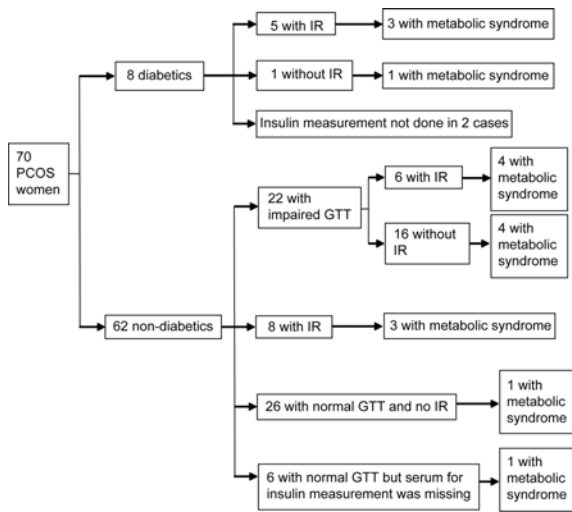


Fig. 1 Flow chart summarizing PCOS women according to their glucose tolerance test (GTT) and insulin resistance (IR) status

either alone or combined, detected insulin resistance (IR) in 19 of the 62 PCOS women (prevalence 30.7%; the sample for insulin measurement was missing in 8 cases). HOMA was the most sensitive of the 4 tests, as it detected 17 of the 19 IR cases (89.5%). The fasting glucose to insulin ratio diagnosed 10 cases of IR, one of whom was missed by HOMA. This particular case, unfortunately, also had metabolic syndrome. The 2-hr glucose to insulin ratio detected only 5 cases of IR, one of whom was not detected by HOMA. Fasting insulin was able to detect 11/19 cases of IR, all of whom were confirmed by HOMA.

Seventeen of the 70 PCOS women (24.3%) fulfilled the IDF and AHA/NHLBI criteria for metabolic

syndrome⁽¹⁸⁾. The prevalence of metabolic syndrome was highest among PCOS women with both insulin resistance and impaired glucose tolerance (4/6; 66.7%), followed by diabetes mellitus (4/8; 50%), insulin resistance (3/8; 37.5%) and impaired glucose tolerance (4/16; 25.0%). In contrast, only 1 metabolic syndrome was present in PCOS women who had normal GTT and no IR (1/26; 3.8%) (Fig. 1).

PCOS women with diabetes and those with IR had significantly higher body weight, BMI, waist circumference, waist-to-hip ratio, free testosterone index and triglyceride level than those without IR (Table 2). Although not statistically different, there was a trend towards an increase in LDL-cholesterol (LDL-C) and a lower HDL-cholesterol (HDL-C) level when subjects were classified by severity, progressing from normal to IR and to frank diabetes.

Factors, which were significantly different between PCOS women with and without metabolic syndromes (Table 3), were the same as those that distinguished women with and without IR (Table 2). In both conditions, serum ADD and testosterone were not significantly different among the affected and non-affected women. However, there was a significant difference in serum free testosterone index between the two groups.

Acanthosis nigricans was present in 11 of 70 women (15.7%). Unfortunately, 1 case with normal serum glucose, did not have an insulin level measured as her serum sample was missing. Insulin resistance was confirmed in the remaining 10 cases. Nine of whom, included the two with DM, were shown to have insulin resistance by HOMA. The fasting glucose to insulin ratio detected insulin resistance in 7 women with acanthosis nigricans, one of whom was missed by HOMA. Fasting blood glucose and 2-hr glucose tests showed that 4 women with acanthosis nigricans and IR also had impaired glucose tolerance. PCOS women with acanthosis nigricans had significantly higher BMI, waist circumference, waist-to-hip ratio, free testosterone index, serum insulin and triglyceride level than those without acanthosis.

Discussion

The prevalence of diabetes mellitus in the present study (11.4%) was comparable to that in the Thai PCOS women (17.7%) reported by Weerakiet et al⁽¹⁹⁾. However, the prevalence of impaired glucose tolerance (31.4%) was higher than that (20.3%) in their study. This prevalence, however, was similar to other studies from Western countries^(12,20). In the Thai

Table 2. Characteristics, hormone and lipid profiles and glucose levels of PCOS women with diabetes, insulin resistance and those without these two conditions

	DM (n = 8)	Insulin resistance (IR) (n = 14)	No IR, non-diabetics (n = 42)	p-value
Age (yr)	29.4 ± 7.8	22.4 ± 5.2	26.1 ± 5.1	0.016 ¹
Weight (kg)	77.5 ± 10.6	76.5 ± 18.0	53.8 ± 11.4	0.000* ^β
BMI (kg/m ²)	29.9 ± 3.2	31.2 ± 5.6	21.8 ± 4.6	0.000* ^β
Waist (cm)	91.9 ± 9.9	96.2 ± 16.1	70.8 ± 10.6	0.000* ^β
Waist/hip ratio	0.86 ± 0.1	0.85 ± 0.1	0.76 ± 0.1	0.000* ^β
Hirsutism scores	10.4 ± 11.7	5.2 ± 3.7	4.2 ± 5.2	0.08
Free testosterone index (testosterone x SHBG/100)	4.6 ± 2.4	5.0 ± 2.6	1.2 ± 1.1	0.000* ^β
SHBG (nmol/L)	18.4 ± 10.8	16.0 ± 5.2	58.0 ± 36.7	0.000* ^β
ADD (ng/mL)	2.6 ± 1.1	2.9 ± 1.2	2.5 ± 1.2	0.559
Fasting glucose (mg/dL)	119.1 ± 22.1	96.3 ± 14.6	97.8 ± 11.4	0.002 ^{β,1}
2 hr-glucose (mg/dL)	205.8 ± 38.2	127.4 ± 23.3	126.1 ± 26.7	0.000 ^{β,1}
Triglyceride (mg/dL)	127.9 ± 50.4	151.6 ± 90.1	82.7 ± 40.4	0.000* ^β
LDL (mg/dL)	156.5 ± 26.7	125.1 ± 32.1	121.2 ± 31.6	0.018 ^β
HDL (mg/dL)	47.0 ± 8.3	45.4 ± 9.4	53.1 ± 11.6	0.043

SHBG = sex hormone binding globulin; ADD = androstenedione; LDL = low-density lipoprotein; HDL = high-density lipoprotein

* Significant difference between non-IR, non-DM and insulin resistance group

^β Significant difference between non-IR, non-DM and DM group

¹ Significant difference between insulin resistance and DM group

Table 3. Characteristics, hormone and lipid profiles and glucose levels of PCOS women, with and without metabolic syndrome (MS)

	MS (n = 17)	Non-MS (n = 53)	p-value
Age (yr)	25.59 ± 5.22	25.64 ± 5.83	0.973
Weight (kg)	73.62 ± 10.13	57.46 ± 16.67	0.000
BMI (kg/m ²)	30.30 ± 3.44	23.05 ± 5.99	0.000
Waist (cm)	92.88 ± 10.56	74.28 ± 14.91	0.000
Waist/hip ratio	0.85 ± 0.06	0.77 ± 0.06	0.000
Hirsutism score	4.94 ± 4.49	5.34 ± 6.40	0.824
Testosterone (ng/mL)	0.58 ± 0.30	0.56 ± 0.31	0.719
Free testosterone index (testosterone x SHBG/100)	0.09 ± 0.06	0.26 ± 0.23	0.001
SHBG (nmol/L)	17.65 ± 7.95	50.99 ± 36.37	0.000
ADD (ng/mL)	2.74 ± 1.15	2.63 ± 1.12	0.693
Fasting glucose (mg/dL)	106.18 ± 14.93	98.02 ± 14.73	0.055
Fasting insulin (uU/mL)	17.09 ± 7.06	9.53 ± 11.74	0.000
Fasting glucose:insulin	7.47 ± 3.77	22.95 ± 22.03	0.001
2-hr glucose (mg/dL)	140.82 ± 48.56	132.13 ± 32.91	0.898
2-hr insulin (uU/mL)	101.20 ± 78.22	59.45 ± 81.56	0.012
2-hr glucose:insulin	2.20 ± 1.28	5.49 ± 6.90	0.009
HOMA (fasting insulin x glucose/405)	4.43 ± 1.90	2.24 ± 2.71	0.000
Triglyceride (mg/dL)	154.12 ± 85.37	87.01 ± 38.22	0.000
LDL (mg/dL)	133.53 ± 28.04	121.19 ± 33.69	0.178
HDL (mg/dL)	42.18 ± 6.29	52.56 ± 11.16	0.000

SHBG = sex hormone binding globulin; ADD = androstenedione; LDL = low-density lipoprotein; HDL = high-density lipoprotein; HOMA = homeostatic model assessment

female population, Aekplakorn W et al⁽²¹⁾ reported the prevalence of DM and impaired glucose tolerance for the 15-34 year old age group to be 1.3-2.4% and 4.0-5.1%, respectively. The present study, therefore, implied that PCOS women were at increased risk of impaired glucose tolerance and diabetes, even when they were young.

Clinical manifestation and metabolic features of PCOS women also relate to androgen levels, ovarian volumes and insulin levels^(10,11). Insulin resistance plays an important role in the pathophysiology of PCOS. Diagnosis and treatment of insulin resistance may, therefore, be clinically relevant in the management of PCOS. Among the four insulin diagnostic tools, HOMA was the most sensitive screening test for insulin resistance, as it detected 89.5% (17/19) of PCOS women with this condition. HOMA alone could identify 11 of the 16 PCOS women with metabolic syndrome. To detect all cases of insulin resistance, a combination of HOMA, fasting glucose to insulin ratio and 2-hr glucose to insulin ratio had to be performed. However, it was more economical to include only fasting glucose to insulin ratio and HOMA, as the two tests together could identify 94.7% of PCOS women with insulin resistance and 80.0% of those with metabolic syndrome. To increase the detection rate of metabolic syndrome to 100%, both fasting glucose and 2-hr glucose tests must be performed in addition to HOMA and fasting glucose to insulin ratio.

The prevalence of metabolic syndrome in the present study (24.3%) represented a 3.5-fold increase over that (7%) observed in Thai females aged 20-39 years⁽²²⁾. Nevertheless, it was still less than that (43-47.3%) among Western PCOS women⁽²³⁻²⁶⁾. This finding might be explained by the fact that Asian women are more slender and they have smaller waist circumference than their Western counterparts. In other words, life-style, diet and genetic factors might play important roles^(18,27).

Although the presented PCOS subjects were young (mean age 25.6 ± 5.7 yr), more than half of them (56.5%) had a low HDL-C level. This was in contrast to a low prevalence of only 10.9% among general Thai females aged 26-40 years⁽²⁸⁾. As the prevalence of low HDL-C levels increase with advancing age⁽²⁸⁾, and low HDL-C levels are one of the diagnostic criteria for metabolic syndrome, concern is raised regarding the presented subjects being at high risk of developing metabolic syndrome when they become older.

The authors did not have an explanation why the prevalence of acanthosis nigricans was lower in

the presented population (15.7%) than those reported in other Asian and Western women (39.7-55.3%)^(7,29,30). Perhaps, it could be the result of an interplay between genetics and the unique Northern Thai life-style.

Prospectively collected data on consecutive cases of PCOS women, using the well-established 2003 Rotterdam criteria, were the strength of the present study. However, it was a hospital- and not community-based study. Women who presented to the authors' tertiary care hospital, might be different from those at large. In addition, normal reference ranges of reproductive hormones and cut-off values to define glucose intolerance and insulin resistance were those used in Caucasians and not derived from normative values in a Thai own population.

Conclusion

There was a high prevalence of metabolic syndrome, insulin resistance, diabetes mellitus and impaired glucose tolerance in Thai PCOS women. A combination of fasting glucose, a 2-hr glucose tolerance test, and fasting insulin level effectively identified PCOS women who were at high risk of metabolic syndrome. Future research should look into the cost-effectiveness of a program that aims at primary prevention and early intervention of metabolic syndrome in the Thai population.

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กลุ่มอาการเมทาบอลิก และภาวะดื้อต่ออินซูลิน ในหญิงไทยที่เป็นกลุ่มอาการ polycystic ovary

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วัตถุประสงค์: เพื่อศึกษาความชุกของกลุ่มอาการเมทาบอลิก และภาวะดื้อต่ออินซูลินในหญิงไทย ที่เป็นกลุ่มอาการ polycystic ovary (PCOS)

วัสดุและวิธีการ: ผู้ป่วยที่เป็นกลุ่มอาการ PCOS จำนวน 70 ราย ได้รับการตรวจ oral glucose tolerance และตรวจระดับอินซูลิน (fasting insulin), ระดับไขมันในเลือด ระดับฮอร์โมน testosterone และ globulin ที่เป็นตัวจับกับฮอร์โมนเพศ (sex hormone binding globulin) รวมทั้งระดับน้ำตาล และอินซูลินหลังรับประทานน้ำตาล 2 ชั่วโมง

ผลการศึกษา: พบความชุกของกลุ่มอาการเมทาบอลิก และภาวะดื้อต่ออินซูลิน 24.3% และ 30.7% ตามลำดับ ภาวะเบาหวาน และภาวะที่ร่างกายควบคุมระดับน้ำตาลได้ไม่ดี (impaired glucose tolerance) 11.4% และ 31.4% ตามลำดับ ทั้งนี้ homeostatic model assessment (HOMA) เป็นวิธีการตรวจคัดกรองภาวะดื้อต่ออินซูลินที่มีความไวที่สุดยังพบว่าสตรีที่เป็นกลุ่มอาการ polycystic ovary และมีกลุ่มอาการเมทาบอลิก มีดัชนีมวลกาย ระดับ testosterone อิสระ และระดับอินซูลินสูงกว่าสตรีดังกล่าวที่ไม่มีกลุ่มอาการเมทาบอลิกอย่างมีนัยสำคัญทางสถิติ

สรุป: พบความชุกของกลุ่มอาการเมทาบอลิกภาวะดื้อต่ออินซูลิน ภาวะเบาหวาน ได้บ่อยในกลุ่มสตรีที่เป็นกลุ่มอาการ PCOS ทั้งนี้การตรวจวัดระดับน้ำตาล และระดับอินซูลินในเลือดหลังอดอาหารร่วมกับการทำ 2-hr glucose tolerance test เป็นวิธีที่มีประสิทธิภาพสูง ในการตรวจหากลุ่มอาการเมทาบอลิกในสตรี ที่เป็นกลุ่มอาการ PCOS
