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Abnormal glucose tolerance in Chinese women with polycystic ovary syndrome

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BACKGROUND: The aims of this study were to analyse the prevalence of impaired glucose tolerance (IGT) and diabetes mellitus (NIDDM) in Chinese polycystic ovary syndrome (PCOS) patients and to assess the ability of screening tests to predict these abnormalities within this population. METHODS: A total of 102 PCOS patients were evaluated. All patients underwent oral glucose tolerance tests (OGTTs) with blood samples taken at 0, 1 and 2 h. The 2-h plasma glucose level was used to categorize subjects as having IGT or NIDDM. RESULTS: The prevalence of IGT was 20.5% and that of NIDDM was 1.9%. There was no significant relationship between BMI and 2-h plasma glucose levels. The areas under the receiver operating characteristic (ROC) curve for glucose to insulin ratio (G : I), homeostasis model assessment (HOMA) and quantitative insulin sensitivity check index (QUICKI) were 0.702, 0.734 and 0.733 respectively. ROC analysis suggested a threshold value of 10.7 in G : I ratio (73.9% sensitivity and 59.5% specificity), a value of 2.14 in HOMA (73.9% sensitivity and 73.4% specificity) and a value of 0.34 in QUICKI (73.9% sensitivity and 73.4% specificity) for the prediction of abnormal glucose tolerance (IGT and NIDDM). CONCLUSIONS: Chinese women with PCOS are at increased risk of IGT and NIDDM. Even though G : I, HOMA and QUICKI are easier than OGTT, they could not replace the role of 2-h post-challenge plasma glucose level in the screening of IGT and NIDDM in PCOS women.

Key words: diabetes mellitus/impaired glucose tolerance/polycystic ovary syndrome

Introduction

Polycystic ovary syndrome (PCOS) is defined by the presence of hyperandrogenism and chronic anovulation. It is considered to be the most common endocrinopathy among women of reproductive age (4–6%) (Knochenhauer *et al*., 1998; Diamanti-Kandarakis *et al*., 1999). It was first reported in 1980 (Burghen *et al*., 1980) and subsequently confirmed (Pasquali *et al*., 1982; Chang *et al*., 1983; Shoupe *et al*., 1983; Dunaif *et al*., 1985; Flier *et al*., 1985) that insulin resistance is present in PCOS women. Insulin resistance is now recognized as a major risk factor for the development of type 2 (non-insulin-dependent) diabetes mellitus (NIDDM) (Reaven, 1988; Warram *et al*., 1990; Lillioja *et al*., 1993). PCOS women would thus be predicted to be at an increased risk for NIDDM. Impaired glucose tolerance (IGT), a state characterized by mild elevations in blood glucose levels, typically antedates the onset of NIDDM (Polonsky *et al*., 1996). However, IGT is underdiagnosed, even in populations at high risk (Harris *et al*., 1987; King and Rewers, 1993), because it is usually asymptomatic and its detection requires an oral glucose tolerance test (OGTT). With appropriate lifestyle or pharmacological intervention, it may be feasible to delay, or possibly prevent, the deterioration from IGT to NIDDM (Tuomilehto *et al*., 1992; Knowler *et al*., 1995). Thus, great emphasis has been placed recently on earlier detection of IGT (Fujimoto, 1997).

Most of the data about insulin resistance in PCOS women were available from American and European studies. There were fewer reports about the prevalence and features of insulin resistance in Chinese PCOS women. A study about Hong Kong Chinese women with PCOS revealed that about 60% of patients who screened positive for insulin resistance had normal fasting serum glucose levels (Lam *et al*., 2005).

Given the ethnic differences, we intended to explore the prevalence of glucose intolerance in Chinese women. The OGTT has been used for the routine screening of abnormal glucose tolerance in PCOS patients. The fasting plasma glucose (FPG), glucose to insulin ratio (G : I), homeostasis model assessment (HOMA) and quantitative insulin sensitivity check index (QUICKI), also in common use in clinical practice, are much easier than OGTT. We sought to compare the abilities of them to OGTT in screening of abnormal glucose tolerance.

Materials and methods

Subjects

We prospectively studied 102 PCOS women, recruited from the gynaecological outpatient department of The Second Affiliated Hospital of Sun Yat-Sen University. The studies were approved by the institutional review board of the hospital.

The diagnosis of PCOS was based on the revised criteria of the European Society of Human Reproduction and Embryology/American Society for Reproductive Medicine in 2003 (The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004). The diagnosis of PCOS was made by the presence of (i) oligomenorrhoea—and/or anovulation (eight or fewer menstrual cycles in a year or menstrual cycles more than 35 days in length) (Azziz *et al*., 2004); (ii) clinical and/or biochemical signs of hyperandrogenism and (iii) polycystic ovaries (presence of 12 or more follicles in each ovary measuring 2–9 mm in diameter and/or increased ovarian volume>10 ml) and exclusion of other aetiologies (e.g. congenital adrenal hyperplasia, androgen-secreting tumours and Cushing's syndrome). Any medications known to affect sex hormone or carbohydrate metabolism were discontinued for at least a month before the study (expect oral contraceptives, which were stopped 3 months before study entry). All women were in good health and euthyroid.

Protocol

A standardized history form was completed, with emphasis on menstrual dating and regularity, hirsutism (assessed using Ferriman–Gallwey score) and acne, gynaecological history, medications and family history. A fasting blood sample was obtained in the morning for measurement of prolactin, LH, FSH, estradiol, total testosterone, sex hormone-binding globulin (SHBG), non-SHBG-bound testosterone (u-testosterone) and dehydroepiandrosterone sulphate (DHEA-S) were measured by chemiluminescence (ACS180 · SE, Bayer, Germany). Plasma fasting glucose (FPG) was measured by a glucose oxidase assay (Tosoh, Japan). These data allowed us to exclude patients with congenital adrenal hyperplasia, Cushing's syndrome, hyperprolactinaemia depending on clinical and/or biochemical signs of hyperandrogenism. Transvaginal or abdominal ultrasound was performed on all patients.

An OGTT using 75 g of glucose was performed after an overnight fast of at least 10 h, with blood samples taken at baseline and 1 and 2 h after the glucose load for glucose and insulin measurement. Normal glucose tolerance (NGT), IGT and NIDDM were defined using glucose levels during the OGTT, according to the criteria proposed by the World Health Organization (WHO) (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003).

BMI was calculated using the formula [weight (kg)/height^2 (m^2)] (Cooperative Meta-Analysis Group of China Obesity Task Force, 2002). The criteria of the International Life Science Association of China were applied: (i) BMI <24: normal; (ii) 24 ≤ BMI <29: overweight; and (iii) BMI ≥29: obesity.

Data analysis

According to the WHO criteria for IGT and NIDDM, determinations of glucose tolerance were made as follows: normal fasting glucose = FPG <100 mg/dl (5.6 mmol/l), impaired fasting glucose = FPG ≥100 mg/dl (5.6 mmol/l) but ≤125 mg/dl (6.9 mmol/l), provisional diagnosis of diabetes = FPG ≥126 mg/dl (7.0 mmol/l), NGT = 2-h post-oral glucose load (2-h PG) <140 mg/dl (7.8 mmol/l), IGT = 2-h PG ≥140 mg/dl (7.8 mmol/l) but <200 mg/dl (11.1 mmol/l) and provisional diagnosis of diabetes = 2-h PG ≥200 mg/dl (11.1 mmol/l) (World Health Organization, 1999; Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003). Fasting G : I was calculated with glucose expressed as milligrams per decilitre and insulin expressed as microunits per millilitre, as previously described (Legro *et al*., 1998). HOMA was calculated according to the formula [plasma glucose (mmol/l) × insulin (μU/ml)]/22.5 (Matthews *et al*., 1985; Radziuk, 2000). QUICKI was derived by calculating the inverse of the sum of logarithmically expressed values of fasting glucose and insulin: 1/{log[*I*0(μU/ml)]+ log[*G*0(mmol/l)]} (Legro *et al*., 2004).

We divided PCOS women, based on the above criteria, into two groups of NGT and abnormal glucose tolerance (IGT and NIDDM).

Statistical analysis

Continuous data were compared between the two groups using independent sample *t*-test. Partial correlations were used to compare the correlation between 2-h PG and BMI. Fisher's exact test was used to compare the results of FPG levels and G : I with those of the 2-h PG load values. Receiver operating characteristic (ROC) curves were generated, and confidence intervals (CI) for areas under ROC curves, sensitivity, specificity and significance of differences between ROC curves were calculated using the nonparametric method. These statistical analyses were performed using the Statistical Package for Social Sciences 10.0 (SPSS 10.0). Values are reported as mean ± SD; statistical significance was attributed to two-tailed $P < 0.05$.

Results

A total of 102 PCOS women were studied in our research. The clinical and laboratory characteristics are summarized in Table I. The details of the menstrual cycle are shown in Table II. Seventy-two subjects (72/102,70.59%) were oligomenorrhoeic, and thirty subjects were infertile (29.41%). Only four subjects were both infertile and obese (3.92%). Twenty-five percentage (26/102) of PCOS women were overweight (BMI ≥24). The

Table I. Clinical and laboratory characteristics of study population

	All subjects	Normal glucose tolerance	Abnormal glucose tolerance	*P*-value
n (%)	102 (100)	79 (77.5)	23 (22.5)	
Age (years)	24.26 ± 6.00	23.92 ± 5.76	25.43 ± 6.79	Not significant
Menarche (years)	13.28 ± 1.80	13.24 ± 1.84	13.43 ± 1.67	Not significant
BMI (kg/m^2)	21.74 ± 4.33	21.35 ± 4.00	23.07 ± 5.19	Not significant
Total testosterone (nmol/l)	3.13 ± 4.89	3.19 ± 5.38	2.92 ± 2.67	Not significant
u-Testosterone (pg/ml)	8.32 ± 5.61	7.74 ± 5.21	10.30 ± 6.54	Not significant
DHEA-S (ng/ml)	716.64 ± 337.77	708.38 ± 342.82	745.02 ± 325.59	Not significant
SHBG (nmol/l)	71.15 ± 89.78	76.60 ± 102.02	52.50 ± 18.88	Not significant
Fasting insulin (μU/l)	10.05 ± 7.87	8.87 ± 6.86	14.07 ± 9.77	<0.05
1-h insulin (μU/l)	107.28 ± 82.36	94.69 ± 73.89	149.98 ± 96.21	<0.05
2-h insulin (μU/l)	94.90 ± 84.96	75.27 ± 59.47	162.34 ± 120.26	<0.05
Fasting glucose (mmol/l)	4.91 ± 0.53	4.84 ± 0.41	5.17 ± 0.77	Not significant
1-h glucose (mmol/l)	8.19 ± 2.45	7.45 ± 1.87	10.71 ± 2.54	<0.001

DHEA-S, dehydroepiandrosterone sulphate; SHBG, sex hormone-binding globulin. Data are shown as mean ± SD.

Table II. Menstrual cycle of the study population

	All subjects	Normal glucose tolerance	Abnormal glucose tolerance	*P*-value
Regular (%)	7.84	8.86	4.35	Not significant
Oligomenorrhoeic (%)	70.59	72.15	69.57	Not significant
Amenorrhoeic (%)	21.57	19	26.09	Not significant

subjects were from the same ethnic backgrounds, and age ranged from 14 to 41 years. Twenty-one subjects (20.5%) were categorized as having IGT and two (1.9%) as having NIDDM. There were eight cases of abnormal FPG, only five of them were abnormal glucose tolerance with OGTT. This difference was statistically significant ($P = 0.018$, Figure 1). There was no significant relationship between BMI and 2-h post-challenge plasma glucose levels ($r = 0.183$, $P = 0.065$) (Figure 2). The prevalence of IGT in adolescents (≤19 years) was 29.6% (8/27), whereas prevalence of IGT in adults was 20% (15/75). There was no significant difference between them ($P = 0.305$).

In our study, compared to OGTT results, G : I ratio provided 73.9% sensitivity and 59.5% specificity with a threshold value of 10.7 in abnormal glucose tolerance, whereas HOMA, with a threshold value of 2.14, provided 73.9% sensitivity and 73.4% specificity and QUICKI, with a threshold value of 0.34, provided 73.9% sensitivity and 73.4% specificity (Figure 3). The area under the ROC was 0.625 (95% CI = 0.49–0.761) for FPG, 0.702 (95% CI = 0.584–0.820) for G : I ratio, 0.734 (95% CI = 0.619–0.849) for HOMA and 0.733 (95%CI = 0.618–0.848) for QUICKI. But the difference in the ability to assess abnormal glucose tolerance between OGTT and G : I ($P = 0.003$), HOMA ($P = 0.001$) and QUICKI ($P = 0.001$) was statistically significant (Table III).

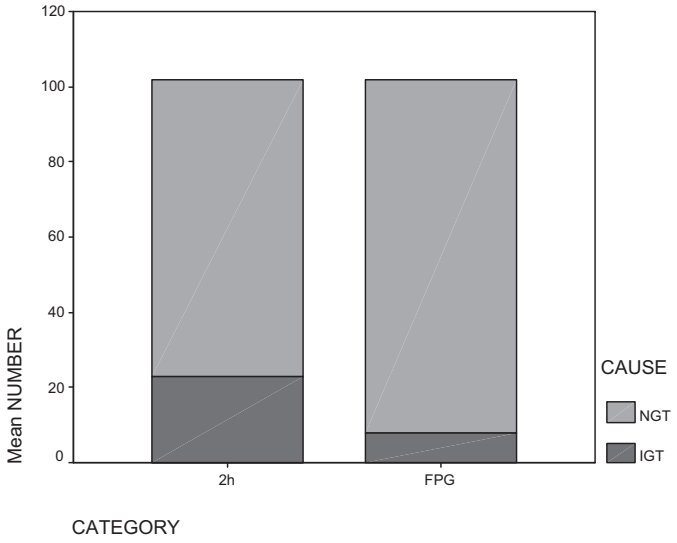


Figure 1. Comparison between 2-h plasma glucose and fasting plasma glucose (FPG) ($P = 0.018$). IGT, impaired glucose tolerance; NGT, normal glucose tolerance.

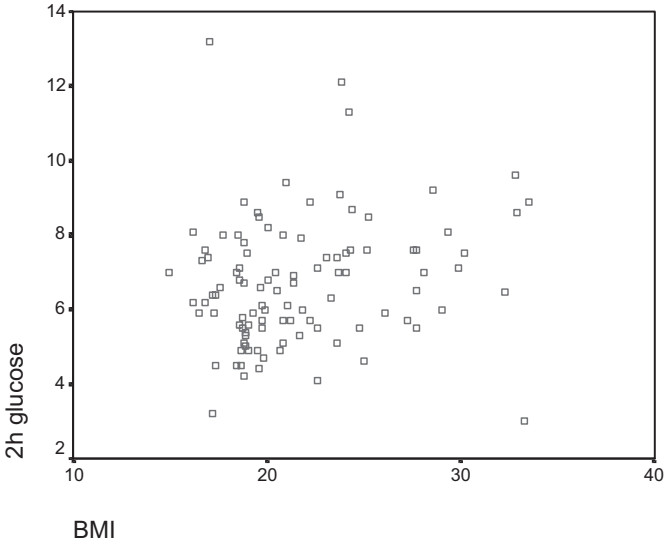
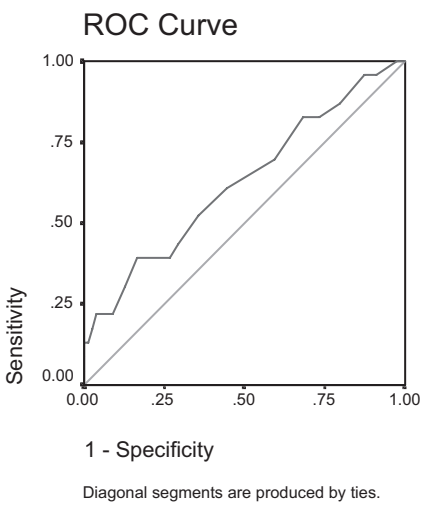


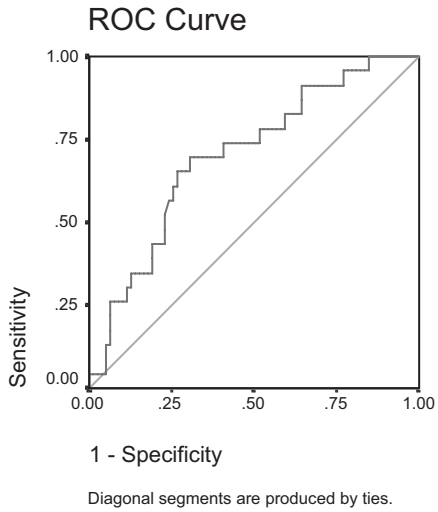
Figure 2. Relationship between 2-h post-challenge plasma glucose levels and BMI (not significant $P = 0.065$).

Discussion

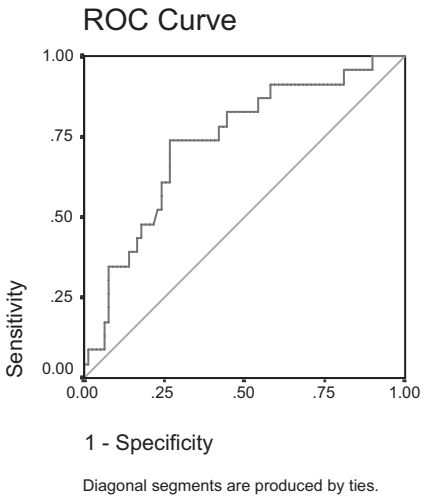
There were fewer reports about glucose intolerance in Chinese PCOS women. In this study, our data indicated that the prevalence rate of glucose tolerance in Chinese PCOS women (IGT 20.5%, NIDDM 1.9%) was lower than that of American PCOS women (IGT 31%, NIDDM 7.5%) (Legro *et al*., 1999) and similar to that of Mediterranean PCOS women (IGT 15.7%, NIDDM 2.5%) (Gambineri *et al*., 2004). Although some differences among these studies in the selection criteria of PCOS cannot be ignored, the factors of ethnic background, dietary composition and lifestyle may play an important role in the prevalence of abnormal glucose tolerance in PCOS. The BMI of our subjects (BMI = 21.35–23.07) was obviously lower than that found in both American (BMI = 29.9–36.9) (Ehrmann *et al*., 1999) and European (BMI = 22.3–34.3) reports (Gambineri *et al*., 2004). From those previous studies, the data indicated that the prevalence of abnormal glucose tolerance significantly increased with BMI and with age. Furthermore, PCOS cohort in our study were younger than those in the previous studies (Ehrmann *et al*., 1999; Legro *et al*., 1999; Weerakiet *et al*., 2001). According to the reports, glucose tolerance tends to worsen with increasing age in PCOS patients (Harris *et al*., 1987). In our study, the prevalence of IGT in adolescents (≤19 years) was 29.6% (8/27), whereas the prevalence of IGT in adults was only 20% (15/75). However, there was no significant difference between them, which indicated that IGT in PCOS women may tend to appear earlier than expected (Ehrmann *et al*., 1999; Legro *et al*., 1999; Weerakiet *et al*., 2001). Although the prevalence of abnormal glucose tolerance in Chinese PCOS women was lower than that of American PCOS women, it was much higher than that of the general population in the same area (IGT 5% and NIDDM 2.9%) (Hua *et al*., 2003), which indicated that Chinese women with PCOS also have an increased risk of IGT and NIDDM. Our data and those of others suggest that screening PCOS patients for IGT and/or NIDDM is indeed warranted.



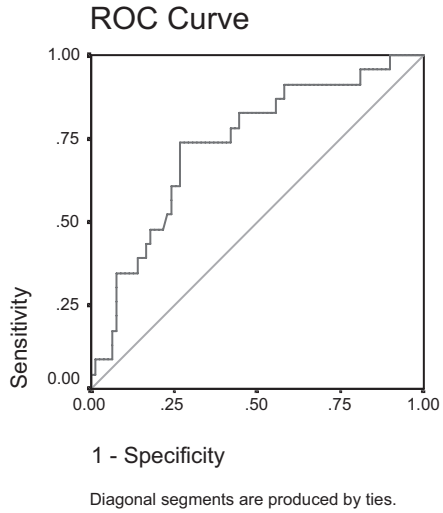
FPG



G:I



HOMA



QUICKI

Figure 3. For each screening test, sensitivity is plotted against 100-specificity. The ideal test would have 100% sensitivity and 100% specificity and reach the upper left corner of the graph; a test with no predictive value would lie along the diagonal between the lower left corner and the upper right corner. These curves facilitate assessment of the sensitivity (Sens) and specificity (Spec) of every value obtained from the screening tests. For each test, examples of data points with associated Sens and Spec are displayed to illustrate the characteristics of the test; these data points are not proposed as thresholds between normal and abnormal results. FPG, fasting plasma glucose (FPG); G : I, glucose to insulin ratio; HOMA, homeostasis model assessment; QUICKI, quantitative insulin sensitivity check index.

Table III. Receiver operating characteristic (ROC) of curves for fasting plasma glucose (FPG), glucose to insulin ratio (G : I), homeostasis model assessment (HOMA) and quantitative insulin sensitivity check index (QUICKI)

	FPG	G : I	HOMA	QUICKI
ROC curve	0.625	0.702	0.734	0.733
CI	0.49–0.761	0.584–0.82	0.619–0.849	0.618–0.848
P-value	0.068	0.003	0.001	0.001

CI, confidence interval; G : I, glucose to insulin ratio.

Our data showed that there was no significant difference of u-testosterone, DHEA-S and SHBG levels between IGT and NGT PCOS groups, which was different from previous studies (Gambineri *et al.*, 2004). But there was also no difference in the BMI between IGT and NGT PCOS groups. As we had discussed above, BMI, which was one of main factors for the difference of u-testosterone, DHEA-S, SHBG levels, of our subjects was lower than that of American and European PCOS patients. Hence, it was understandable that there was no significant relationship between BMI and 2-h post-challenge plasma glucose levels in our study.

Although fasting glucose is an inexpensive assay and does not require mathematical calculations, our study indicated that

FPG did not reliably predict IGT or NIDDM. Applying these criteria to our subjects, we found that 17 subjects with abnormal glucose tolerance and one subject with NIDDM would have escaped detection. The adenosine deaminase threshold values for FPG of 81 mg/dl (4.5 mmol/l) were too insensitive (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003). A lower value of 87 mg/dl (4.85 mmol/l) or more provided only 60.9% sensitivity and 55.7% specificity. This result was similar to other studies, which showed that FPG was a poor predictor of abnormal glucose tolerance in women with PCOS (Ehrmann *et al*., 1999; Legro *et al*., 1999; Arslanian *et al*., 2001).

Then, we also assessed the utilities of G : I ratio, HOMA and QUICKI to evaluate IGT and/or NIDDM in our population. ROC analysis suggested that the highest sensitivity and specificity presented at a G : I ratio value of 10.7 (73.9% sensitivity and 59.5% specificity), 2.14 in HOMA (73.9% sensitivity and 73.4% specificity), 0.34 in QUICKI (73.9% sensitivity and 73.4% specificity) in line with 2-h PG as criteria for IGT. The criterion for insulin resistance from G : I, based on OGTT, in our study was different from that from American PCOS women, which was much lower than ours (G : I ratio ≤7.2 in white women with PCOS, whereas ≤4.0 in Mexican-American women with PCOS) (Kauffman *et al*., 2002). Although G : I ratio, HOMA and QUICKI were all more convenient than OGTT, and may be sufficient as measures of insulin resistance, they may not reliably detect IGT and NIDDM in our PCOS cohort because of their lower sensitivity and specificity.

In summary, Chinese PCOS women have significantly increased prevalence rates of IGT and NIDDM, even in adolescent patients, well above the prevalence of general population in this area. The prevalence rate of IGT and NIDDM in Chinese PCOS women is lower than that of American and European PCOS women. G : I ratio, HOMA and QUICKI may not reliably detect the abnormalities. We, therefore, recommend that all Chinese PCOS women undergo screening for abnormal glucose tolerance using OGTT.

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