Endocr (2009) 36:326–332
DOI 10.1007/s12020-009-9226-7

ORIGINAL ARTICLE

The prevalence and risk factors for glucose intolerance in young Korean women with polycystic ovary syndrome

Hyejin Lee · Jee-Young Oh · Yeon-Ah Sung · Hyewon Chung · Wha Young Cho

Received: 27 April 2009 / Accepted: 27 July 2009 / Published online: 14 August 2009

Abstract Insulin resistance and hyperinsulinemia play important roles in the pathogenesis of polycystic ovary syndrome (PCOS). In addition, some women with PCOS have been shown to have insulin secretory defects and can be predicted to be at an increased risk for glucose intolerance. We performed the present study to determine the prevalence and risk factors for glucose intolerance in Korean women with PCOS. We consecutively recruited 194 women with PCOS diagnosed by American Society for Reproductive Medicine/European Society of Human Reproduction and Embryology (ASRM/ESHRE) criteria. Anthropometric measures, 75 g oral glucose tolerance test (OGTT), and measurement of insulin sensitivity (insulin mediated glucose uptake; IMGU) using euglycemic hyperinsulinemic clamp technique were performed. In women with PCOS, the prevalence of impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG) was 17.0% and type 2 diabetes 1.0%, and in lean women with PCOS, the prevalence of IGT and/or IFG was 5.9%. The prevalence of glucose intolerance was 28-fold higher in women with PCOS, and 9.8-fold higher in lean women with PCOS compared to age-matched Korean women. Women with glucose intolerance had higher BMI, waist circumference, free testosterone, fasting insulin, 2-h post-load insulin, total cholesterol, LDL cholesterol, triglyceride and lower sex hormone binding globulin and IMGU than women with normal glucose tolerance (NGT) ($P < 0.05$). IMGU was the most powerful predictor for glucose intolerance after adjustment for age, BMI, waist circumference, and hyperandrogenemia. The 2-h OGTT was the best screening measure for glucose intolerance and diagnosis of diabetes in women with PCOS. Young Korean women with PCOS have high prevalence for glucose intolerance and type 2 diabetes, and insulin resistance is the most important factor associated with glucose intolerance.

Keywords Glucose intolerance · Polycystic ovary syndrome · Prevalence

H. Lee (✉) · J.-Y. Oh · Y.-A. Sung
Department of Internal Medicine, School of Medicine, Mokdong Hospital, Ewha Womans University, Mok 6-dong, Yangcheon-gu, Seoul, Korea
e-mail: hyejinlee@ewha.ac.kr

H. Chung
Department of Obstetrics and Gynecology, School of Medicine, Ewha Womans University, Seoul, Korea

W. Y. Cho
Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders, affecting 5–10% of the population in women of reproductive age [1]. Insulin resistance and hyperinsulinemia were present and pancreatic β-cell dysfunction was also found in PCOS. Insulin resistance and β-cell dysfunction are major pathogenesis for the development of type 2 diabetes, therefore, women with PCOS would have an increased risk for type 2 diabetes [2–4]. It has been reported that impaired glucose tolerance (IGT) is present in 31–35% of women with PCOS, in addition, type 2 diabetes is present in 7.5–10% [3, 5]. The majority of western studies evaluating the prevalence of glucose intolerance in PCOS primarily included obese women, which aggravates their risk for glucose intolerance. But high prevalence of abnormal glucose intolerance also has been documented in Chinese (20.5%) and Thai (20.3%) women with PCOS [6, 7].

Overall, between 50 and 70% of women with PCOS have demonstrable insulin resistance. Several studies using the euglycemic hyperinsulinemic clamp showed that insulin resistance was consistently present in obese PCOS women, however, the results have been conflicting in lean women with PCOS [8–13]. Moreover, the role of insulin resistance as a risk factor for the development of glucose intolerance has still not been clearly defined in women with PCOS.

A few studies have been performed to determine the risk factors for glucose intolerance in women with PCOS [3, 14, 15]. One prospective, controlled study reported that obesity and age were risk factors for glucose intolerance in women with PCOS, however, insulin sensitivity was not included as a variable [3]. Whereas the other study showed that homeostasis model assessment (HOMA), fasting insulin were predictors of abnormal glucose metabolism in women with PCOS [16]. In Chinese women with PCOS, fasting glucose, insulin, 2-h insulin, HOMA-IR, age had a significant impact on 2-h glucose level [17].

Most of the data about the prevalence of glucose intolerance in women with PCOS were available from studies done in the US and European countries. There were a few reports in Asian PCOS women. We performed this large cross-sectional study to determine the prevalence and risk factors of glucose intolerance in Korean women with PCOS. We evaluated the insulin sensitivity using a euglycemic hyperinsulinemic clamp to include insulin sensitivity when analyzing risk factors for glucose intolerance.

Results

Prevalence of glucose intolerance in women with PCOS

Tables 1 and 2 show the clinical, hormonal, and metabolic characteristics. Sixty-one percent of women with PCOS were lean, 10.3% were overweight, and 28.4% were obese. PCOS patients with glucose intolerance had higher body mass index (BMI), waist circumference, fasting plasma glucose (FPG), 2-h post-load plasma glucose (PPG), fasting plasma insulin, total cholesterol (TC), triglyceride (TG), free testosterone, and lower sex hormone binding globulin (SHBG) and insulin mediated glucose uptake (IMGU) than PCOS patients with normal glucose tolerance (NGT).

The occurrence of IGT and/or impaired fasting glucose (IFG) was 17.0% (33 of 194 subjects) and type 2 diabetes was 1.0% (2 of 194) in women with PCOS. The occurrence of glucose intolerance in women with PCOS was nearly 28-fold higher than in age-matched women from an urban Korean population (0.6%, 1 of 162). Thirty-two of 33 subjects with IGT and/or IFG were IGT. Thirty of 32 subjects (94%) with IGT had normal FPG (<110/mg/dl). The FPG values corresponding to the value of 140 mg/dl of

Table 1 Clinical and biochemical characteristics of control and women with polycystic ovary syndrome according to glucose tolerance status

	Control with NGT ($n = 161$)	Control with glucose intolerance ($n = 1$)	PCOS with NGT ($n = 159$)	PCOS with glucose intolerance ($n = 33$)
Individuals with FPG ≥126 and/or 2-h PPG ≥200 mg/dl	0	1	0	2
Age (years)	35 ± 2	33	26 ± 5	29 ± 5
Body mass index (kg/m^2)	22.2 ± 2.7	23.7	22.3 ± 3.8	26.8 ± 4.5[ab]
Waist circumference (cm)[c]	72.4 ± 6.1	89.2	73.0 ± 9.7	83.8 ± 12.6[ab]
Systolic BP (mmHg)	111 ± 10	130	116 ± 13[a]	118 ± 12[a]
Diastolic BP (mmHg)	71 ± 7	80	74 ± 10	76 ± 8[a]
FPG (mg/dl)[c]	84 ± 10	206	86 ± 7	93 ± 10[ab]
2-h PPG (mg/dl)	92 ± 19	344	110 ± 17[a]	159 ± 16[ab]
FPI (μU/ml)	8.2 ± 5.0	17.9	6.3 ± 7.0[a]	11.0 ± 8.7[b]
IMGU (mM/kg·min)			5.1 ± 1.8	3.2 ± 1.7[b]
Total cholesterol (mg/dl)	173 ± 31	271	166 ± 39	197 ± 31[ab]
Triglyceride (mg/dl)[c]	100 ± 74	114	77 ± 65[a]	139 ± 97[b]
HDL-C (mg/dl)	49 ± 11	43	55 ± 15[a]	51 ± 10

Note: Data are *n* (%) or means ± SD

NGT normal glucose tolerance, *BP* blood pressure, *FPG* fasting plasma glucose, *2-h PPG* 2-h post-load plasma glucose, *FPI* fasting plasma insulin, *2-h IMGU* insulin mediated glucose uptake, *HDL-C* HDL cholesterol

[a] $P < 0.05$ vs. control with NGT

[b] $P < 0.05$ vs. PCOS with NGT

[c] Data showed slightly skewed distribution, *P* values are based on logarithmic data, but mean values are presented for untransformed data

Table 2 Reproductive hormone profiles of women with polycystic ovary syndrome according to glucose tolerance status

	PCOS with NGT ($n = 159$)	PCOS with glucose intolerance ($n = 33$)
Free T (ng/dl)[b]	0.9 ± 0.4	1.2 ± 0.6[a]
SHBG (nmol/l)	52.0 ± 32.7	31.2 ± 10.0[a]
LH (IU/l)	9.4 ± 6.3	6.3 ± 4.6
FSH (IU/l)	5.4 ± 1.5	4.7 ± 1.3

Note: Data are n (%) or means ± SD

NGT normal glucose tolerance, *T* testosterone, *SHBG* sex hormone binding globulin, *LH* luteinizing hormone, *FSH* follicle stimulating hormone

[a] $P < 0.05$ vs. PCOS with NGT

[b] Data showed slightly skewed distribution, *P* values are based on logarithmic data, but mean values are presented for untransformed data

PPG was 87.5 mg/dl, and the value of 200 mg/dl was 96.5 mg/dl by receiver operating characteristic (ROC) curve analysis.

The number of individuals that displayed glucose intolerance increased with BMI ($P_{\text{for trend}} < 0.001$) and age ($P_{\text{for trend}} < 0.001$) in women with PCOS (Figs. 1, 2). It is interesting to note that even in lean Korean women with PCOS in the present study displayed an incidence of glucose intolerance that was 9.8 times that observed in our total control population of Korean women without PCOS. Moreover, lean control women showed 0% of occurrence of glucose intolerance. Among 16 subjects with PCOS aged 16–19 years, one had IGT who was lean (BMI 22.9 kg/m^2) and had no family history of diabetes. The occurence of glucose intolerance was 11.2% (14 of 125) in women with PCOS aged 20–29 years, and 34% (18 of 53) in PCOS aged 30–39 years.

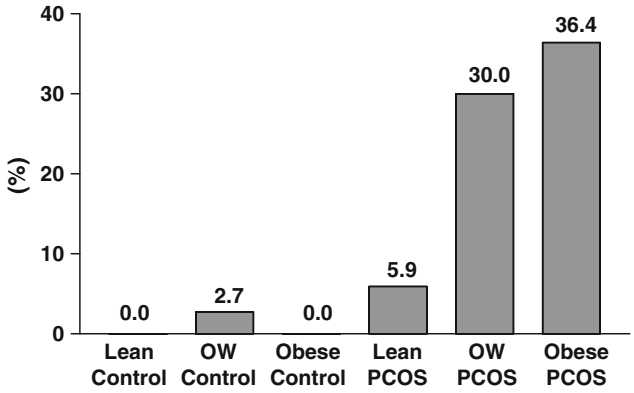

Fig. 1 The BMI-stratified prevalence of glucose intolerance in women with polycystic ovary syndrome and control

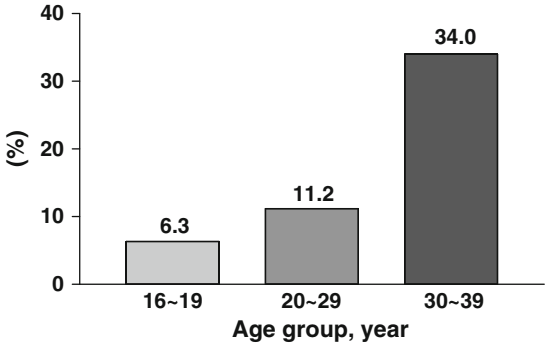

Fig. 2 The age-stratified prevalence of glucose intolerance in women with polycystic ovary syndrome

Factors associated with glucose intolerance in women with PCOS

The statistically significant variables associated with glucose intolerance in women with PCOS were age, BMI, waist circumference, SHBG, free testosterone, and IMGU in the univariate logistic regression analysis. These variables were analyzed via the logistic regression model (Table 3). The variables remaining in the final model were age (OR 1.14, 95% CI 1.03–1.26, $P = 0.013$), IMGU (OR 0.53, 95% CI 0.36–0.78, $P = 0.001$), and free testosterone (OR 3.65, 95% CI 1.23–10.86, $P = 0.02$). The variables such as BMI and waist circumference were not significantly associated with glucose intolerance in multivariate analysis (Table 3).

When adjusted with age, BMI, waist circumference, and free testosterone, IMGU was still significant (OR 0.66, 95% CI 0.45–0.97, $P = 0.033$) (Table 4).

Table 3 Logistic regression analysis of variables associated with glucose intolerance in women with polycystic ovary syndrome

Variable[a]	OR (95% CI)[b]	Adjusted OR (95% CI)[c]	*P* value
Age	1.14 (1.05–1.24)	1.14 (1.03–1.26)	0.013
Body mass index	1.26 (1.15–1.39)	–	–
Waist circumference	1.08 (1.04–1.13)	–	–
IMGU	0.50 (0.37–0.66)	0.53 (0.36–0.78)	0.001
Free T	3.69 (1.78–7.65)	3.65 (1.23–10.86)	0.020
SHBG	0.95 (0.93–0.98)	–	–

IMGU insulin mediated glucose uptake, *SHBG* sex hormone binding globulin

[a] Variables that were significant in univariate analysis

[b] Univariate analysis. Confidence intervals are Wald CIs (All variables, *P* value ≤0.001)

[c] Adjusted for all other predictors in the multivariate model shown in this table. Confidence intervals are Wald CIs

Table 4 Adjusted Odds ratio for glucose intolerance in women with polycystic ovary syndrome

Variables	Age- and BMI-adjusted			Age-, BMI-, and WC-adjusted			Age-, BMI-, WC-, and free T-adjusted		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
IMGU	0.61	0.43–0.87	0.007	0.64	0.44–0.94	0.021	0.66	0.45–0.97	0.033
Free T	2.60	1.12–6.05	0.026	2.33	0.93–5.84	0.072	–	–	–

BMI body mass index, *WC* waist circumference; *T* = testosterone, *IMGU* insulin mediated glucose uptake, *OR* Odds ratio

Discussion

The present study is a large cross-sectional study for prevalence of glucose intolerance and evaluation of predictors for glucose intolerance in Far East Asian women with PCOS. The present analysis of Korean women with PCOS in reproductive age showed that the prevalence of glucose intolerance and diabetes is higher than age-matched control women and insulin resistance is the most important factor associated with glucose intolerance, regardless of obesity, age, and even free testosterone. Most of PCOS women with glucose intolerance have normal FPG and this suggests that 2-h oral glucose tolerance test (OGTT) is the best screening measure for glucose intolerance and diabetes in women with PCOS.

Thus, our data from Korean women with PCOS agree with that of Mediterranean [18] and Chinese women with PCOS [6], which contrast with observations from American women with PCOS [3, 5]. Although some differences may exist in the selection criteria among these various studies [3, 5, 6, 18], our present data provide growing evidence to build a consensus that ethnic difference may play an important role in the occurrence of glucose intolerance in association with PCOS. Our data also tend to agree with and extend the WHO review that suggest that there is a different association between BMI, percentage of body fat, and cardiovascular risk in Asian populations than in European populations [19]; that the proportion of Asian people with a high risk of type 2 diabetes and cardiovascular disease becomes substantial at a lower BMI than that recognized for being "overweight" in European population [19]; and that Asians are more insulin resistant than Caucasians at similar age and BMI [20, 21]. Therefore, it is not surprising that Korean women with PCOS in our study were more insulin resistant even though they display a lower BMI compared to other ethnic groups.

In the present study, PCOS women with glucose intolerance showed features associated with insulin resistance more frequently, such as central obesity, dyslipidemia, and hyperinsulinemia. IMGU using hyperinsulinemic euglycemic clamp, which is the gold standard for measuring insulin sensitivity, was significantly lower in PCOS women with glucose intolerance than NGT. This difference was still significant after adjustment for age, central obesity and free testosterone. The concept that insulin resistance is a more powerful predictor for glucose intolerance than obesity in Korean women with PCOS also is supported by a recent, separate study in which Korean women with PCOS were significantly more insulin resistant than age-and BMI-matched control groups [22].

PCOS women with glucose intolerance had significantly higher levels of free testosterone than women with NGT and it can be interpreted that hyperandrogenemia might play a role in the development of glucose intolerance in PCOS. Insulin resistance and compensatory hyperinsulinemia stimulates ovarian androgen production and inhibits hepatic SHBG synthesis, which in turn, increases free testosterone [1]. Hyperandrogenemia can cause modest insulin resistance and lowering androgen levels results in slight improvement in insulin resistance. Androgen can change body fat distribution in women and result in central obesity; and may also affect insulin sensitivity [2].

The American Diabetes Association has recommended FPG is more efficient as a screening test for pre-diabetes and diabetes than OGTT [23]. However, our data demonstrate that using FPG as a screening test would fail to detect 94% of abnormal glucose tolerance in our subjects with PCOS since only 2 of 32 subjects with IGT displayed elevated FPG. Therefore, our current evidence indicates that the 2-h OGTT is the best screening measure for glucose intolerance and diagnosis of diabetes in at least Korean women with PCOS. Indeed, the measurement of insulin sensitivity by the hyperinsulinemic euglycemic clamp technique made it possible to determine the most significant predictor of glucose intolerance in Korean women with PCOS by excluding potential bias from OGTT-derived insulin sensitivity indices.

The strength of the present study is the measurement of insulin sensitivity by hyperinsulincemic euglycemic clamp technique, the gold standard for the evaluation of insulin resistance. It was possible to determine the most significant predictor of glucose intolerance in women with PCOS by excluding the bias from using OGTT derived insulin sensitivity indices, which may be affected by the status of glucose tolerance. In summary, Korean women with PCOS in reproductive age had significantly increased prevalence

of glucose intolerance than age-matched control women. Although obesity and age substantially increased risk for glucose intolerance, insulin resistance was the most significant independent risk factor in this study group.

Materials and methods

Subjects

Women with PCOS ($n = 194$, 16–41 years) were recruited from the outpatient department of gynecology and endocrinology, Ewha Woman University Mokdong Hospital, studied over time since 2002. The diagnosis of PCOS was made when two or more of the following 3 criteria existed, as proposed at the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) [24]: oligomenorrhea, hyperandrogenemia, and polycystic ovaries. Oligomenorrhea was defined as <8 menstrual cycles per year. Biochemical hyperandrogenemia was defined as elevation of serum testosterone or free testosterone beyond the 90 percentile in 190 ovulatory, non-hirsute controls with regular menstruation cycles (total testosterone level >52.2 ng/dl or free testosterone 0.86 ng/dl). The criteria for polycystic ovaries required visualization of ≥12 follicles, 2–9 mm in diameter per ovary or ovarian volume >10 cm^3 by transvaginal ultrasonography or transabdominal ultrasonography with a distended bladder for virginal women.

The control population was derived from regular cycling women ($n = 162$, age 20–39 years) who participated in our previous study regarding the prevalence of diabetes and metabolic syndrome in the Korean urban community [25]. The study population was selected randomly from 20,222 residents living in Mokdong apartment area, Seoul. Among 1,011 residents selected, 774 (male 269, female 505) subjects participated. Among them, 20–39 years of regular cycling women was included in the present study as control. The Institutional Review Board of Ewha Womans University Mokdong Hospital approved this study. Written informed consent was obtained from each subject.

Anthropometric measurements

Height and weight were measured in all subjects wearing lightweight clothing and without shoes and BMI was calculated as follows; weight (kg)/height (m^2). The degree of obesity was classified as follows, lean, BMI <23 kg/m^2; overweight, BMI 23–25 kg/m^2; obese, BMI ≥25 kg/m^2 according to the Asia-Pacific perspective, 2000 [26].

Waist circumference was also measured on bare skin during mid-respiration at the narrowest indentation between the 10th rib and the iliac crest. Blood pressure was measured twice by sphygmo-manometry and mean value was calculated.

Baseline sampling and OGTT

For control subjects, venous blood was drawn in the early follicular phase to obtain baseline measurements of glucose, lipid, insulin, testosterone, SHBG, LH, and FSH after an overnight fast. In the PCOS group, 3–5 days after a spontaneous menses or independent of cycle phase in the presence of amenorrhea.

Blood samples for OGTT were obtained in 30-min intervals for 2 h to measure glucose and insulin following ingestion of a standard 75 g glucose. Glucose tolerance was evaluated using criteria of the World Health Organization. The diagnosis of glucose intolerance and diabetes was based on 75-g OGTT and World Health Organization 1999 criteria for glucose intolerance [27]. Glucose tolerance in the participants were classified as follows: NGT (FPG <110 mg/dl and 2-h PPG <140 mg/dl); glucose intolerance, including IFG (FPG ≥ 110 mg/dl) and/or IGT (2-h PPG ≥140 mg/dl); and diabetes (FPG ≥126 mg/dl and/or 2-h PPG ≥ 200 mg/dl).

Glucose clamp technique

Insulin sensitivity was assessed using a modified version of the hyperinsulinemic euglycemic clamp described by DeFronzo et al. [28] A quantitative estimate of insulin sensitivity, glucose disposal rate, IMGU, was provided by mean glucose infusion rate (mg/kg min) in the last 15 min of the 2 h of hyperinsulinemic euglycemic clamp.

Assay methods

Plasma glucose was measured by the glucose oxidase method (Beckman Model Glucose Analyzer 2, USA) and plasma insulin was measured by radioimmunoassay using a kit from Diagnostic Products Corporation (Los Angeles, CA, USA).

Total cholesterol, HDL cholesterol (HDL-C), and TG were measured by enzymatic methods using a Hitachi 7150 autoanalyzer (Hitachi, Tokyo, Japan). LDL cholesterol (LDL-C) was calculated as follows: TC (mg/dl) − HDL-C (mg/dl) − TG/5 (mg/dl).

Serum testosterone, SHBG, LH, and FSH were measured with kits from Diagnostic Products Corporations (Los Angeles, CA, USA). Free testosterone was calculated using the formula available on the web site of the International Society for the Study of the Aging Male (ISSAM) (http://www.issam.ch/freetestos.htm) from total testosterone, SHBG, and albumin values in the same sample from

each subject [29]. This method is described in detail by Vermeulen et al. [30].

Statistical analysis

The normality of distributions of the variables was analyzed by the Kolmogorov–Smirnov test. Because waist circumference, VFA, FPG, 2-h post-load plasma insulin (PPI), TG, and free testosterone showed slightly skewed distribution, P values are based on logarithmic data, but mean values are presented for untransformed data.

Differences in family history of diabetes were compared using the Chi-square test and continuous variables were compared between subjects with NGT and glucose intolerance using t-test. Data are expressed as means $\pm$ SD, unless stated otherwise. Statistical significance was set at a value of $P < 0.05$. ROC curves were constructed to examine the FPG corresponding to the 2-h PPG of 140 and 200 mg/dl. The trend of occurrence of glucose intolerance according to BMI or age was analyzed by linear-by linear association.

A univariate logistic regression analysis was performed to determine which variables predicted glucose intolerance and the variables found to be significantly related to glucose intolerance at $P < 0.05$ entered into a multivariate logistic regression model, excepting parameters. The candidate predictive variables were age, BMI, waist circumference, VFA, SHBG, free testosterone, and IMGU.

Data analysis was performed using SPSS version 12.0 (SPSS Inc., Chicago, IL, USA).

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