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Usefulness of Oral Glucose Insulin Sensitivity Index in Women with Polycystic Ovary Syndrome

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Objectives: Insulin resistance is a major pathophysiology in polycystic ovary syndrome (PCOS), and assessment of insulin sensitivity is important. Various insulin sensitivity indices from fasting state or oral glucose tolerance test (OGTT) have been compared with euglycemic hyperinsulinemic clamp. We aimed to evaluate the usefulness of these indices in young Korean women with PCOS.
Methods: Euglycemic hyperinsulinemic clamp test and 75 g OGTT were performed in 290 women with PCOS. Insulin mediated glucose uptake (IMGU), the insulin sensitivity index from clamp, was compared with various insulin sensitivity indices such as composite insulin sensitivity index (ISI_{comp}), estimated metabolic clearance rate (MCR_{est}) of glucose and estimated insulin sensitivity index (ISI_{est}), area under the curve of glucose and insulin ratio (AUC-GIR), OGTT-derived Belfiore index, and oral glucose insulin sensitivity index (OGSI) by Kazama. Fasting state indices such as glucose insulin ratio (GIR), homeostasis model assessment for insulin resistance (HOMA-IR), fasting Belfiore index, and quantitative insulin sensitivity check index (QUICKI) were also compared with IMGU.
Results: The correlation coefficients of ISI_{comp}, MCR_{est}, ISI_{est}, AUC-GIR, OGTT-Belfiore index, and OGSI with IMGU were all about 0.5 (Ps' < 0.001) in PCOS women as a whole. The MCR_{est} and ISI_{est} were significantly correlated with IMGU in both obese ($r=0.58$ and 0.58, $P < 0.0001$) and non-obese subjects ($r=0.33$ and 0.32, $P < 0.001$). Fasting glucose and insulin-derived indices showed worse correlation with IMGU than OGTT-derived ones.
Conclusion: The MCR_{est} and ISI_{est} from OGTT might be the best replacement for the insulin sensitivity index from hyperinsulinemic euglycemic clamp independent of obesity. **(Ewha Med J 2011;34(2):27-32)**

Key Words: Insulin sensitivity index; Oral glucose tolerance test; Polycystic ovary syndrome

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders of women with reproductive ages, and associated with significant reproductive, endocrine, metabolic and cardiovascular morbidity [1]. Insulin resistance is a major pathophysiology of PCOS and measurement of insulin sensitivity is important [2]. Euglycemic hyperinsulinemic clamp test is a gold standard to assess the insulin sensitivity, but it is labor-intensive and expensive, and not routinely available [3]. To overcome these obstacles, alternative tests have been proposed including frequently sampled intravenous glucose tolerance test (FSIVGTT), insulin tolerance test (ITT), insulin suppression test (IST) and continuous infusion of glucose with model assessment (CIGMA) [4-7]. However, all of these methods require intravenous access and multiple venipunctures, making them relatively impractical for office assessment. Alternative methods applicable to large scale studies

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have been proposed. Calculations of the glucose insulin ratio (GIR), homeostasis model assessment for insulin resistance (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI) are easily applied methods which required only basal glucose and insulin samples, but their accuracies are not fully demonstrated [8-10]. Several formula from OGTT such as composite insulin sensitivity index proposed by Matsuda and estimated metabolic clearance rate by Stumvoll have been examined being comparable with insulin sensitivity index from euglycemic hyperinsulinemic clamp test [11,12]. Recently new computational methods have been developed to provide an accurate and easily accessible tool to assess the insulin sensitivity and insulin secretion from clinically available data. Kazama et al [13] reported that the oral glucose insulin sensitivity index (OGSI) by autoregressive model approach was comparable to insulin sensitivity index from clamp.

The aim of this study is to evaluate the validity of various insulin sensitivity indices comparing to IMGU by euglycemic hyperinsulinemic clamp in women with PCOS.

Methods

Subjects

A total of 290 women with PCOS and twenty eight regular menstrual cycling women as control group were included in the study after informed consent was obtained. The diagnosis of PCOS was based on Rotterdam criteria, that includes 1) presence of chronic ovulatory dysfunction with oligomenorrhea (eight or less cycles per year) or amenorrhea (no cycles in the last 6 months), 2) clinical or biochemical signs of hyperandrogenism, and 3) the presence of polycystic ovaries on ultrasonography, as well as exclusion of other etiologies (congenital adrenal hyperplasia, androgen-secreting tumors, Cushing's syndrome) [14]. According to their BMI, subjects were divided into obese (BMI $\geq$ 23 kg/m^2) or non-obese (BMI $<$ 23 kg/m^2) group.

OGTT-derived insulin sensitivity indices

After an overnight fast (10$\sim$12 hours), the 75 g OGTT was performed and blood samples were taken at 0, 30, 60, 90 and 120 min after the glucose load to measure the plasma glucose and insulin concentrations.

The composite insulin sensitivity (ISI_{comp}) was calculated with the method introduced by Matzuda et al. The estimated metabolic clearance rate (MCR) of glucose and the insulin sensitivity index (ISI) considering BMI were obtained from the calculation equation reported by Stumvoll et al. Area under the curve of glucose and insulin ratio [15], and OGTT-derived Belfiore index were calculated as previously reported methods [16]. The OGSI was calculated on the following Web named GSI calculator: http://www18.ocn.ne.jp/$\sim$ogsi/.

We also calculated the glucose insulin ratio (GIR), homeostasis model assessment for insulin resistance (HOMA-IR), fasting Belfiore index, and quantitative insulin sensitivity check index (QUICKI) from fasting glucose and insulin concentrations [8-10,16].

Euglycemic hyperinsulinemic clamp test

All patients underwent a glucose clamp study, which was carried out as described by DeFronzo et al [17]. After an overnight fast, the subjects were studied while resting in the recumbent position at 9:00 AM after an 8-h overnight fast. A small polyethylene catheter was inserted into an antecubital vein for infusion of 20% dextrose water. Blood glucose was sampled every 5 minutes at $-$20, $-$10, 0, 5 to 120 min. Another small polyethylene catheter was inserted on the opposite arm and insulin was infused at a rate of 2 mU/kg/min in the first 20 min and maintained at 1 mU/kg/min afterwards until 120 min to suppress hepatic glucose production. 20% dextrose solution was infused at 20 ml/hr from $-$20 min to 5 min and the serum glucose concentration was maintained at 90 mg/dl by monitoring the glucose level at 5-min intervals and adjusting the infusion rate of a 20% glucose solution. The glucose infusion rate was calculated every 5 min and was averaged over the last 15 min of the clamp study. Insulin mediated glucose uptake (IMGU) was used for insulin sensitivity index.

Statistical analysis

Data analysis was performed using SAS version 9.1 (SAS institute, Cary NC). All data were expressed as

means±SD. Student's t-test was used to compare differences between various parameters. Pearson's correlation coefficients were calculated to determine the strength of associations. Because plasma insulin, TG, and HDL cholesterol showed slightly skewed distributions, P values were based on logarithmic data, but mean values were presented for untransformed data. All P values were two-tailed, and statistical significance was defined as $P<0.05$.

Table 1. Clinical characteristics in women with PCOS according to obesity

	Obese PCOS (n=85)	Non-obese PCOS (n=131)
Age (yr)	28±6*	25±5
BMI (kg/m^2)	27.6±3.5*	20.2±1.6
Waist (cm)	85.7±10.1*	68.2±4.6
Systolic BP (mmHg)	124±15*	113±13
Diastolic BP (mmHg)	78±9*	72±10
Fasting glucose (mg/dl)	87.4±13.0	85.1±7.4
Postload 2 h glucose (mg/dl)	133.5±31.4*	111.0±20.7
Fasting insulin (pmol/L)	10.1±8.6*	5.3±5.5
Postload 2 h insulin (pmol/L)	75.5±66.8*	34.9±24.8
Total testosterone (nmol/L)	60.9±28.8	57.3±26.8
Free testosterone (pmol/L)	1.1±0.6*	0.8±0.4
SHBG (mmol/L)	33.2±18.0*	58.0±35.8
LH (IU/L)	6.5±3.6†	10.1±7.1
FSH (IU/L)	4.8±1.2‡	5.5±1.6

Data are means±SD. Fasting insulin, postload 2 h insulin were analyzed after log transformation. *P<0.001, †P<0.01, ‡P<0.05 vs. non-obese PCOS.

Statement of Ethics

The institutional review board of Ewha Womans University Mokdong Hospital approved the study. Informed consent was obtained from all participants. We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research.

Results

A total of 216 women with PCOS were enrolled in this study. Among them, 85 (39%) were obese and 131 were non-obese. Table 1 showed the clinical and biochemical characteristics in obese and non-obese subjects. Obese women with PCOS were significantly older than non-obese counterparts (28±6 vs. 25±5 years old, $P<0.001$). Systolic and diastolic blood pressure, postload 2h glucose, fasting and postload 2 h insulin, free testosterone levels were significantly higher and SHBG was significantly lower than those of non-obese subjects. IMGU, the gold standard of insulin sensitivity index, was significantly lower in obese subjects than in non-obese (3.5±1.6 vs. 5.7±1.8 μmol/kg · min, $P<0.001$). OGTT-derived insulin sensitivity indices including MCR_{est}, ISI_{est}, OGTT-Belfiore, ISI_{comp}, AUC-GIR, and OGSI were all significantly lower in obese group than those in non-obese group (Table 2). Fasting glucose and insulin derived insulin resistance indices such as GIR, HOMA-IR, fasting Belfiore, and QUICKI also

Table 2. Fasting-, and OGTT-derived insulin sensitivity indices in women with PCOS according to obesity

	Obese PCOS (n=85)	Non-obese PCOS (n=131)
IMGU (μmol/kg · min)	3.5±1.6*	5.7±1.8
MCR_{est} (mg · kg^{-1} · min^{-1})	6.8±2.9*	10.5±1.0
ISI_{est} (μmol · kg^{-1} · min^{-1} · pmol/L^{-1})	0.08±0.04*	0.12±0.01
OGTT-Belfiore (mg · hr/dl)$^{-1}$ · (μU · hr /ml)$^{-1}$	$1.0\times10^{-4}\pm0.8\times10^{-4}$*	$1.8\times10^{-4}\pm1.4\times10^{-4}$
ISI_{comp} (mg/dl)$^{-1}$ · (μU/ml)$^{-1}$	10.0±19.8*	15.9±16.6
AUC-GIR (mg/dl) · (μU/ml)$^{-1}$	3.3±1.9*	5.0±3.2
OGSI	2.2±5.9*	4.8±11.5
GIR (mg/dl) · (μU/ml)$^{-1}$	40.0±134.9*	72.6±171.2
HOMA-IR (mmol/L) · (μU/ml)	2.3±2.0*	1.1±1.2
Fasting Belfiore (mg/dl) · (μU/ml)$^{-1}$	0.024±0.13*	0.019±0.04
QUICKI (mmol/L)$^{-1}$ · (μU/ml)$^{-1}$	4.2±36.8†	0.4±0.9

Data are means±SD. All parameters were analyzed after log transformation. *P<0.001, †P<0.05 vs. non-obese PCOS.

Table 3. Correlation coefficients of various insulin sensitivity indices with IMGU by euglycemic clamp

	Total (n=216)		Obese PCOS (n=85)		Non-obese PCOS (n=131)	
	r	P	r	P	r	P
Using OGTT-derived glucose and insulin data						
MCR_{est}	0.62	<0.0001	0.58	<0.0001	0.33	0.0001
ISI_{est}	0.62	<0.0001	0.58	<0.0001	0.32	0.0002
OGTT-Belfiore	0.55	<0.0001	0.55	<0.0001	0.31	0.0004
ISI_{comp}	0.44	<0.0001	0.49	<0.0001	0.16	0.061
AUC-GIR	0.44	<0.0001	0.39	0.0002	0.27	0.0019
OGSI	0.41	<0.0001	0.49	<0.0001	0.21	0.017
Using fasting glucose and insulin data						
GIR	0.30	<0.0001	0.49	0.0002	0.07	0.42
HOMA-IR	−0.30	<0.0001	−0.37	0.0004	−0.06	0.45
Fasting Belfiore	0.29	<0.0001	0.37	0.0002	0.07	0.45
QUICKI	0.19	0.0055	0.21	0.06	0.06	0.49

All parameters were analyzed after log transformation.

showed that obese PCOS women were significantly insulin resistant than obese counterparts. Table 3 presented the correlation coefficients for various insulin sensitivity indices with IMGU. In total subjects with PCOS regardless of obesity, these insulin sensitivity indices were all significantly correlated with IMGU. Among them, MCR_{est} and ISI_{est} showed the same and highest coefficients (r=0.62, respectively) and the OGTT-Belfiore was the next (r=0.55). These indices were also significant in both obese and nonobese group although the OGSI showed marginal significance in nonobese group (r=0.21, P=0.061).

Fasting indices such as GIR, HOMA-IR, fasting Belfiore, and QUICKI were significantly correlated with IMGU in total women with PCOS, but the coefficients were lower than OGTT-derived indices (all coefficients were 0.3 or less). When we analyzed in obese and nonobese group separately, however, these fasting indices were significantly correlated only in obese subjects.

Discussion

In this present study, we observed that various insulin sensitivity indices including recently introduced OGSI by Kazama et al. were significantly correlated with IMGU, the insulin sensitivity index from euglycemic hyperinsulinemic clamp, in young Korean women with PCOS. Among these indices, the MCR_{est} and ISI_{est} showed the highest correlation coefficients with IMGU in obese and non-obese subjects as well as in total subjects. And the OGTT-derived Belfiore index was the second.

Although the euglycemic hyperinsulinemic clamp test is considered as gold standard method for quantifying insulin sensitivity, it is expensive, time-consuming, and labor-intensive, therefore, it cannot be easily performed in routine clinical practice or in large-scale epidemiological studies. Through many efforts to seek alternative methods for determining insulin sensitivity, various OGTT-derived indices were introduced to be comparable with euglycemic hyperinsulinemic clamp. Especially, since Matsuda et al [11] and Stumvoll et al [12] proposed the new equations for insulin sensitivity using glucose and insulin data obtained from OGTT, many studies reported satisfactory results that these indices having good correlation with euglycemic hyperinsulinemic clamp. In white postmenopausal women with varying degree of glucose tolerance status, the coefficients of Matsuda index and MCR from Stumvoll were 0.74 and 0.75, respectively [18]. In study with obese Caucasian women with mean age 35, these two indices were also significantly correlated with clamp index (r=0.59 and 0.51, respectively) which were comparable with our results from young obese subjects [19].

Our study did not show the recently introduced OGSI having better correlation with other OGTT-derived

indices. Because entering the 0, 30, 60, 90, and 120 min glucose and insulin data into the Web named GSI calculator provides us the insulin sensitivity index, it is easily obtainable and undemanding. Kazama et al [13] suggested that this method could be considered as being the most adequately representative because it reflected the feedback system regulating glucose and insulin levels. Although we could not explain the mechanism, this new method did not provide the best correlation in our study subjects, and further evaluation subjecting the larger population should be required.

In our study, fasting state indices showed poor correlation than OGTT-derived indices in both obese and non-obese subjects. In obese non-Hispanic white women with PCOS, fasting GIR was suggested as a useful parameter for screening the insulin resistance with 95% sensitivity and 84% specificity. They also obtained quite high correlation coefficient with insulin sensitivity index from FSIVGTT (r=0.73) [8]. Our study showed the consistent result that the coefficient of GIR was the highest (r=0.49) among fasting state indices in our obese subjects. This discrepancy could be explained when considering that the GIR did only significantly correlated in obese subjects in our study, and non-Hispanic white women were more obese than our study subjects (mean BMI 39.0 kg/m^2 vs. 27.6 kg/m^2).

Although the HOMA index has been most frequently used as a reliable parameter in large-scale or epidemiological studies, some studies did not validate the use of a simple HOMA in PCOS or general population [20-22]. We also found the HOMA-IR not the best parameter among fasting state data.

In summary, we observed that the MCR_{est} and ISI_{est} were correlated with insulin sensitivity index from euglycemic hyperinsulinemic clamp, and recently introduced index from autoregressive model analysis by Kazama was not superior to other OGTT-derived indices. We can suggest that MCR_{est} and ISI_{est} could be the best replaceable parameters for insulin sensitivity index in young Korean women with PCOS. We can also suggest that the GIR instead of HOMA-IR could be also useful among fasting state indices. However, further studies for larger or other populations to validate this finding should be performed.

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