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Association between the serum estrone-to-estradiol ratio and parameters related to glucose metabolism and insulin resistance in women with polycystic ovary syndrome

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Objective: We aimed to evaluate associations between the ratio of serum estrone (E1) to estradiol (E2) and parameters related to serum glucose metabolism and insulin resistance in women with polycystic ovary syndrome (PCOS).
Methods: In total, 133 women between the ages of 18 and 35 diagnosed with PCOS were enrolled in this study. All participants with PCOS underwent blood tests to determine hormonal and biochemical metabolic parameters and a standard 2-hour 75-g oral glucose tolerance test. They were divided into two groups according to the serum E1-to-E2 ratio: group 1 (E1/E2 ratio <2.0) and group 2 (E1/E2 ratio ≥2.0).
Results: In the comparative analysis, the waist-to-hip ratio (WHR) was the only clinical variable that was significantly different between the two groups. Patients with a higher E1/E2 ratio showed higher fasting insulin levels, homeostasis model for insulin resistance, and postprandial glucose level at 2 hours (PPG2). In a correlation analysis, only PPG2 was significantly related to the serum E1/E2 ratio. However, after controlling for the confounding effects of body mass index (BMI) and WHR, fasting glucose was also significantly correlated with the serum E1/E2 ratio.
Conclusion: Women with PCOS with a higher serum E1/E2 ratio were found to be more likely to show higher fasting insulin and postprandial glucose levels. Significant correlations were found between the serum E1/E2 ratio and both fasting and postprandial serum glucose levels after adjusting for BMI and WHR in women with PCOS.

Keywords: Estradiol; Estrone; Glucose; Insulin resistance; Polycystic ovary syndrome

Introduction

Polycystic ovary syndrome (PCOS) is regarded as the most common endocrine disorder in women of reproductive age [1,2]. The prevalence of PCOS in women of reproductive age is approximately 3%–10%. PCOS is one of the major causes of infertility with anovulation, and it is present in approximately 25%–30% of patients with infertility [1].

The common characteristic clinical features of PCOS are amenorrhea or oligomenorrhea, inappropriate hormonal secretion (including hyperandrogenism), and abnormal metabolic status [1-3]. Hormonal imbalances besides hyperandrogenism in PCOS include increased luteinizing hormone levels, a reversed ratio of luteinizing hormone to follicle-stimulating hormone, increased anti-Müllerian hormone levels, mild prolactin elevation, increased inhibin and estrone (E1) levels, and a reversal of the ratio of E1 to estradiol (E2) (E1/E2 ratio) [1,2]. Common metabolic problems associated with PCOS are glucose intolerance, type 2 diabetes mellitus (T2DM), central obesity, insulin resistance, and hyperinsulinemia [1-6].

Insulin resistance and hyperinsulinemia are the cardinal factors involved in the pathogenesis of PCOS [7,8], and the reported preva-

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lence of insulin resistance in women with PCOS varies depending on race, ethnicity, and nationality [9-14]. Obese women with PCOS are characterized by insulin resistance, which increases the risk of metabolic and cardiovascular diseases [15]. In obese patients with PCOS, insulin resistance is higher than in non-obese patients with PCOS [16], but even in non-obese patients, insulin resistance is higher than that of controls [17,18]. Insulin resistance is defined as a state of subnormal to abnormal glucose utilization and homeostasis under normal concentrations of insulin production, and PCOS with obesity commonly amplifies the degree of these metabolic abnormalities [19,20]. Several assays can be used to evaluate insulin resistance, including the hyperinsulinemic clamp, homeostasis model for insulin resistance (HOMA-IR), fasting glucose-to-insulin ratio (GIR), quantitative insulin sensitivity check index (QUICKI), and the results of oral glucose tolerance testing (OGTT) [2,21,22]. The Endocrine Society Clinical Practice Guidelines [21] recommend the use of OGTT to screen adolescents and adult women with PCOS, who are at high risk for impaired glucose tolerance and T2DM. The OGTT is a standard diagnostic tool for impaired glucose tolerance and T2DM [2,21].

Elevated serum E1 levels and the resulting reversal of the E1/E2 ratio are common abnormal hormonal characteristics in patients with PCOS [1,2,6,23]. In women with PCOS, aromatase and 17-ß hydroxysteroid dehydrogenase activities are increased in cumulated peripheral fat cells along with increased peripheral aromatization and weight gain. E2 levels remain in the follicular phase range without mid-cycle level changes; on the contrary, E1 levels increase because of peripheral aromatization in response to increased androstenedione levels [24-26]. In a chronic hyperestrogenic state with reversal of the E1/E2 ratio, hormonal status and outcomes are unopposed by progesterone [1,23].

Several studies have explored the relationship between hormonal characteristics and insulin resistance-related parameters in women with PCOS [27-30]. A reversed E1/E2 ratio is a distinctive hormonal characteristic of PCOS; however, to our knowledge, no study has been conducted to evaluate the relationships between an increased E1/E2 ratio and parameters related to glucose and insulin metabolism in PCOS. The aim of the present study was to evaluate whether the serum E1/E2 ratio is related to other metabolic parameters associated with insulin resistance in women with PCOS.

Methods

1. Subjects

This study was approved by the Institutional Review Board of Inje University Haeundae Paik Hospital (IRB No. 129792-2014-035), and patient's informed consent in this study was waived by the IRB. All patients were newly diagnosed with PCOS at 18–35 years of age from January 2010 to December 2013 at the above-mentioned university hospital. The patients were diagnosed with PCOS on the basis of the 2003 Rotterdam criteria. All patients who met at least two of the three criteria, including (1) oligo-anovulation, (2) biochemical and/or clinical signs of hyperandrogenism (e.g., hirsutism, acne, androgenic alopecia), and (3) ultrasonographically identified polycystic ovarian morphology (PCOM) of at least 1 ovary, were diagnosed with PCOS after excluding other diseases or etiologies [31]. Using the transvaginal or transrectal ultrasound approach, PCOM was defined as an ovarian volume of over 10 cm^3 and/or the presence of over 12 follicles (2–9 mm in size). Pelvic ultrasonography (through the vagina or rectum) for assessing PCOM was conducted in the early follicular phase using a Voluson LOGIQ S7 (GE Ultrasound Korea, Seongnam, Korea) equipped with a transvaginal probe with a frequency range of 3.6–9 MHz, and all ultrasound examinations were conducted by the same reproductive endocrinologist. Oligo-anovulation was estimated on the basis of menstrual history and the presence of amenorrhea or oligomenorrhea. Amenorrhea was defined as a menstrual cycle interval of over 90 days without menstruation, and oligomenorrhea was defined as an interval of over 35 days. The most common clinical sign of hyperandrogenism is the presence of hirsutism, which was identified using a modified Ferriman-Gallwey score >6, based on a previous study of hirsutism in Korean women [32]. Biochemical hyperandrogenism was confirmed by elevated serum androgen concentration beyond the 95% confidence limits in the control group of a previous study (total testosterone >0.68 ng/mL and/or free testosterone >1.72 pg/mL) [9,32]. Patients with a previous history of diagnosed diabetes, thyroid disease, hyperprolactinemia, or ovarian surgery were excluded. Patients who were taking oral contraceptives with or without prescriptions within the last 6 months and anti-diabetic drugs, including insulin sensitizers, were also excluded. All patients were divided into two groups based on the serum E1/E2 ratio: group 1 (E1/E2 ratio <2.0) and group 2 (E1/E2 ratio ≥ 2.0).

2. Clinical and biochemical measurements

All clinical variables of the study participants were assessed when they first visited the outpatient department. Blood samples for biochemical laboratory analyses were taken from all subjects in the early follicular phase after overnight fasting. Serum E1 was measured using the Dsl-8700 Estrone ELISA kit (Beckman Coulter, Brea, CA, USA) and serum E2 was measured using Elecsys Estradiol II (Roche, Indianapolis, IN, USA) [23]. Serum insulin and glucose levels were analyzed using an Elecsys Insulin assay (Roche) and an L-Type Glul device (Wako, Osaka, Japan), respectively. Cholesterol and triglyceride levels were measured using Pureauto S (Sekisui, Tokyo, Japan), and serum high-density lipoprotein and low-density lipoprotein levels were

measured using Cholestest (Sekisui) [30]. Both intra- and inter-assay coefficients of variation for all assays were below 8%.

3. Assessment of insulin resistance

After overnight fasting, serum glucose and insulin levels were checked. Glucose levels at 60 minutes and 120 minutes after glucose ingestion during a 2-hour 75-g OGTT were measured. The fasting glucose level and postprandial glucose level at 2 hours (PPG2) were analyzed using an L-Type GluI device (Wako, Osaka, Japan). The insulin resistance parameters included HOMA-IR, QUICKI, and GIR. The GIR was calculated by dividing the glucose value (mg/dL) by the insulin value (μU/mL); HOMA-IR was calculated as fasting glucose (mg/dL) × fasting insulin (μU/mL)/405; and QUICKI was calculated as 1/{log[insulin value (μU/mL)]+log[glucose value (mg/dL)]}.

4. Statistical analysis

All values are expressed as mean ± standard deviation. All statistical analyses were performed using SPSS ver. 18.0 (SPSS Inc., Chicago, IL, USA). The paired *t*-test was used to compare clinical and biochemical parameters, including hormonal and glucose and insulin metabolism-related parameters, between the two groups categorized by the E1/E2 ratio. The correlations between the serum E1/E2 ratio and insulin resistance-related parameters were analyzed with Pearson correlation coefficients, and partial correlation coefficients were used after adjusting for body mass index (BMI) and the waist-to-hip ratio (WHR). In all analyses, *p*-values < 0.05 were considered to indicate statistical significance.

Results

The mean E1/E2 ratio in group 1 (n = 74) was 1.31 ± 0.42 and that in group 2 (n = 59) was 3.23 ± 1.40. The comparisons of anthropometric parameters and serum hormonal levels, including E1 and E2, of the two groups are shown in Table 1. Among various clinical parameters, the WHR was the only parameter that was significantly different between the two groups ($p = 0.010$). As shown in Table 2, the

Table 1. Comparison of clinical characteristics between the two groups defined according to the serum E1-to-E2 ratio in women with polycystic ovary syndrome

Variable	Group 1 (n = 74)	Group 2 (n = 59)	*p*-value
Age (yr)	27.35 ± 5.69	26.54 ± 5.29	0.402
Parity	0.23 ± 0.54	0.20 ± 0.61	0.792
Height (cm)	162.35 ± 5.18	160.85 ± 5.36	0.103
Body weight (kg)	55.67 ± 14.10	57.78 ± 12.65	0.371
Body mass index (kg/m^2)	21.10 ± 5.22	22.31 ± 4.60	0.165
Waist-to-hip ratio	0.78 ± 0.06	0.81 ± 0.06	0.010
E1/E2 ratio	1.31 ± 0.42	3.23 ± 1.40	< 0.001

Values are presented as mean±standard deviation. Group 1, E1/E2 <2.0; group 2, E1/E2 ≥2.0. A *p*-value was obtained by paired sample *t*-test.
E1, estrone; E2, estradiol.

Table 2. Comparison of insulin resistance-related parameters between the two groups defined according to the serum E1-to-E2 ratio in women with polycystic ovary syndrome

Variable	Group1 (n = 74)	Group2 (n = 59)	*p*-value
Fasting insulin (μIU/mL)	6.87 ± 5.85	9.60 ± 8.43	0.047
Fasting glucose (mg/dL)	91.48 ± 20.28	94.05 ± 19.36	0.468
PPG2 (mg/dL)	103.97 ± 29.07	120.91 ± 56.09	0.034
HOMA-IR (fasting)	1.57 ± 1.36	2.46 ± 2.93	0.044
GIR (fasting)	18.81 ± 9.98	16.46 ± 11.76	0.243
QUICKI (fasting)	0.37 ± 0.04	0.36 ± 0.05	0.089
Cholesterol (mg/dL)	170.86 ± 28.41	178.22 ± 31.92	0.167
Triglyceride (mg/dL)	89.55 ± 78.11	105.20 ± 97.98	0.313
HDL (mg/dL)	58.46 ± 12.30	58.31 ± 14.75	0.947
LDL (mg/dL)	95.65 ± 25.18	98.19 ± 31.09	0.615

Values are presented as mean±standard deviation. Group 1, E1/E2 <2.0; group 2, E1/E2 ≥2.0. A *p*-value was obtained by paired sample *t*-test.
E1, estrone; E2, estradiol; PPG2, postprandial glucose level at 2 hours; HOMA-IR, homeostasis model assessment of insulin resistance; GIR, glucose-to-insulin ratio; QUICKI, quantitative insulin sensitivity check index; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

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fasting insulin level, HOMA-IR, and PPG2 were significantly higher in group 2 (E1/E2 ratio ≥ 2.0) than in group 1.

In the correlation analysis, only PPG2 was significantly correlated with the serum E1/E2 ratio (Table 3). However, after adjusting for BMI and WHR (as anthropometric parameters known to be closely related to insulin resistance), postprandial and fasting glucose levels were significantly correlated with the serum E1/E2 ratio.

Discussion

A reversed E1/E2 ratio is a distinctive hormonal characteristic of PCOS [1,2]. The authors recently reported that serum E1 levels and the E1/E2 ratio were correlated with blood androgen levels, and in particular, the E1/E2 ratio was significantly correlated with the serum free testosterone level ($r = 0.260$, $p = 0.003$) [23]. Insulin resistance and hyperinsulinemia are the cardinal factors involved in the pathogenesis of PCOS, which is associated with a high risk of glucose intolerance and T2DM [1-6,9,19-21]. However, to our knowledge, studies evaluating the relationship between increased serum E1 levels and parameters related to glucose and insulin metabolism are still lacking. Moreover, no previous study has evaluated the correlation between an increased E1/E2 ratio and the parameters related to insulin resistance in PCOS. This may be due to the high cost of commercial kits for determining E1 and the need for more complex laboratory techniques other than hormonal assays [23]. To the best of our knowledge, this is the first study conducted to evaluate the association between the serum E1/E2 ratio and parameters related to insulin and glucose metabolism in women with PCOS, and the results of our study suggest that the serum E1/E2 ratio is significantly related to both fasting and postprandial serum glucose levels in women with PCOS, after adjusting for confounding anthropometric factors.

Table 3. Correlations of insulin resistance-related parameters with the serum E1-to-E2 ratio in women with polycystic ovary syndrome

Variable	*r*	*p*-value	r^a	*p*-value
Fasting insulin (μIU/mL)	0.154	0.095	0.143	0.162
Fasting glucose (mg/dL)	0.123	0.170	0.270	0.007
PPG2 (mg/dL)	0.251	0.005	0.308	0.002
HOMA-IR (fasting)	0.161	0.081	0.192	0.060
GIR (fasting)	–0.101	0.278	–0.037	0.192
QUICKI (fasting)	–0.156	0.092	–0.119	0.246
Cholesterol (mg/dL)	0.114	0.197	0.146	0.141
Triglyceride (mg/dL)	0.085	0.336	0.065	0.511
HDL (mg/dL)	0.040	0.649	0.085	0.389
LDL (mg/dL)	0.037	0.672	0.095	0.339

r, Pearson correlation coefficient; r^a, partial correlation coefficient adjusted by body mass index and waist-to-hip ratio.
E1, estrone; E2, estradiol; PPG2, postprandial glucose level at 2 hours; HOMA-IR, homeostasis model assessment of insulin resistance; GIR, glucose-to-insulin ratio; QUICKI, quantitative insulin sensitivity check index; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Both fasting and postprandial glucose levels are major factors involved in insulin resistance, but the site of insulin resistance is known to be different between patients with abnormal fasting glucose and those with abnormal postprandial glucose levels according to previous clinical studies [33-37]. Individuals with impaired fasting glucose mainly show hepatic insulin resistance with normal muscle insulin sensitivity; on the contrary, those with impaired glucose tolerance typically show muscle insulin resistance with normal hepatic insulin sensitivity [34]. In the present study, the serum E1/E2 ratio was significantly related to both fasting and postprandial serum glucose levels after adjusting for BMI and WHR, suggesting that the E1/E2 ratio is related to both muscle insulin resistance and hepatic insulin resistance. Increased levels of androgenic precursors in theca cells induce the increased production of androstenedione, which is converted by 17β-hydroxysteroid dehydrogenase to testosterone or E1 by aromatization [6,24,26]. Aromatase and 17β-hydroxysteroid dehydrogenase activities occur in fat cells and ovarian theca cells; thus, weight gain leads to increased peripheral aromatization of androstenedione [6,24]. In PCOS, increased production of androstenedione with increased peripheral aromatization triggers an increase in serum E1 levels, which is frequently accompanied by weight gain and an increase in the WHR. In the present study, the WHR was significantly different between the two groups categorized on the basis of the E1/E2 ratio, which is partially consistent with the previous studies [6,24,26]. However, there was no significant difference in BMI between the two groups, which was contrary to what we had hypothesized.

In the present study, the subjects were divided into two groups based on an E1/E2 ratio of 2.0, which approximately corresponds to the average E1/E2 ratio of the participants in this study (2.16 ± 1.37).

The limitations of our study are its retrospective study design, a relatively small sample size from a single institution, and the inclusion of only a single ethnic group (Korean women) among the study participants. Additionally, the lack of postload insulin data could be a crucial drawback of the present study. Further studies with a much larger sample size and cohorts with various ethnicities and races are needed to clarify these preliminary findings, and comparative studies with healthy controls could confirm these preliminary results.

In conclusion, women with PCOS with higher serum E1/E2 ratios were more likely to show higher fasting insulin and postprandial glucose levels. The serum E1/E2 ratio was significantly related to fasting and postprandial serum glucose levels after adjusting for BMI and WHR in women with PCOS. On the basis of this result, the serum E1/E2 ratio may be a feasible hormonal marker that reflects the status of

insulin and glucose metabolism in women with PCOS; however, additional studies are needed to corroborate our results so that they can be applied clinically.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Author contributions

Conceptualization: all authors. Data curation: all authors. Formal analysis: all authors. Methodology: all authors. Project administration: SC. Visualization: SC. Writing–original draft: all authors. Writing–review & editing: all authors.

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