Insulin Sensitivity and β-Cell Function in Women With Polycystic Ovary Syndrome

JANA VRBÍKOVÁ, MD
BELA BENDLOVÁ, PHD
MARTIN HILL, PHD
MARKÉTA VANKOVÁ, MS
KAREL VONDRA, MD
LUBOSLAV STÁRKA, MD, DSC

OBJECTIVE — To evaluate insulin sensitivity (IS) and β-cell function (βF) in lean and obese women with polycystic ovary syndrome (PCOS), either separately or by using a disposition index (DI).

RESEARCH DESIGN AND METHODS — A total of 64 women with PCOS and 20 healthy women were examined by anthropometry, oral glucose tolerance tests (OGTTs), and insulin tolerance tests. Statistical analysis used one-way ANOVA, Kruskal-Wallis, and Mann-Whitney *U* tests, as appropriate.

RESULTS — A significantly higher waist-to-hip ratio ($P < 0.0001$) was found in both lean and obese women with PCOS. Higher basal blood glucose ($P < 0.004$) and blood glucose values at 3 h of OGTT ($P < 0.008$) were found in lean and obese PCOS subjects in comparison with control subjects. Insulin resistance by homeostasis model assessment ($P < 0.007$) was significantly higher in obese PCOS than in control or lean PCOS subjects. Early-phase insulin secretion (insulinogenic index [$\Delta I/\Delta G_{30-0}$, where I is insulin and G is glucose]; $P < 0.0007$) was significantly higher in both lean and obese PCOS subjects than in healthy women. All tested combinations of parameters of IS and βF (DIs) followed a physiological hyperbolic relationship. Significantly lower values of the fasting state–derived DIs were found (all $P < 0.05$) in obese PCOS subjects. Significantly higher values of all of these indexes derived from nonfasting values were found in lean PCOS as compared with control and obese PCOS subjects (all $P < 10^{-3}$).

CONCLUSIONS — Increased βF was found even in lean individuals with PCOS. Insulin hypersecretion is thus probably connected to the pathogenesis of PCOS.

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Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women of childbearing age. Endocrine disturbances typical of this syndrome are often also connected to insulin resistance (IR) and its consequences, impaired glucose tolerance (IGT) or type 2 diabetes (1,2).

According to the majority of studies, IR (or its reciprocal value insulin sensitivity [IS]) could be an intrinsic defect in PCOS. Obese women with PCOS are invariably insulin resistant to a greater degree than BMI itself could induce (3–5). Data regarding lean PCOS individuals are ambiguous, either finding IR (6) or not (5–7). It is likely that body fat distribution also plays an important role in PCOS women, and that their IR is connected very tightly with upper-body fat (8). Data concerning insulin secretion in PCOS are sparse and discrepant. Some authors have found defective insulin secretion (9–11), whereas others have described an increase of insulin secretion (12,13).

In the present study, IS and β-cell function (βF) in lean (BMI <27 kg/m^2) and obese (BMI ≥ 27 kg/m^2) women with PCOS were studied using oral glucose tolerance tests (OGTTs) and insulin tolerance tests (ITTs) as methods available in daily practice. The authors have tried to evaluate PCOS women in terms of IS and/or βF either separately or by the tool of disposition index (DI), which could be more informative than isolated evaluations of IS and βF.

RESEARCH DESIGN AND METHODS

— In all, 64 women with PCOS matching National Institutes of Health criteria were examined (2), of whom 37 were lean and 27 were obese. IGT was diagnosed in four patients according to World Health Organization criteria. None of the patients had taken oral contraceptives during the preceding 3 months. The control group consisted of 20 healthy women without a family history of PCOS and type 2 diabetes, of whom 10 were using hormonal contraception at the time of the examination. The women using the contraception pill were slightly older than the nonusers (31.2 ± 8.3 vs. 25.3 ± 3.6 years; $P < 0.07$). There were no differences between them in anthropometric parameters, smoking habits, residential area, education, job or physical activity, or in the parameters of IR and βF (Student's *t* test), and so we analyzed the control group as a whole. After signing a written informed consent approved by the local ethics committee of the Institute of Endocrinology, all women underwent an OGTT with 75 g of glucose. After overnight fasting, blood samples were drawn for the determination of glucose, insulin, and C-peptide before the glucose load, and they were then drawn again at 30, 60, 120, and 180 min (marked as G_x, I_x, and Cp_x, where G is glucose, I is insulin, and Cp is C-peptide).

A subgroup of the study subjects (all of the control subjects and 13 of the PCOS subjects, of whom 8 were obese and 5 were lean; age 20.7 ± 4.3 years) also un-

From the Institute of Endocrinology, Prague, Czech Republic.
Address correspondence and reprint requests to Jana Vrbíková, MD, Institute of Endocrinology, Národní 8, 116 94 Prague 1, Czech Republic. E-mail: jvrbikova@endo.cz.
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Abbreviations: AUC, area under the curve; βF, β-cell function; Cp, C-peptide; DHEA, dehydroepiandrosterone; DHEAS, DHEA sulfate; DI, disposition index; FGIR, fasting glucose-to-insulin ratio; HOMA, homeostasis model assessment; IGT, impaired glucose tolerance; IR, insulin resistance; IS, insulin sensitivity; ITT, insulin tolerance test; K_{ITT}, rate of glucose disappearance; OGTT, oral glucose tolerance test; PCOS, polycystic ovary syndrome; SHBG, sex hormone–binding hormone; WHR, waist-to-hip ratio.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*The indexes used for the evaluation of IR and βF derived from fasting, OGTT, and ITT measurements*

Index	Formula	Reference
βF		
HOMA-F (mIU/mmol)	$20 \times I_0/(G_0 - 3.5)$	20
Insulinogenic index $\Delta I/\Delta G_{30}$ (mIU/mmol)	$(I_{30} - I_0)/(G_{30} - G_0)$	23
IR		
HOMA-R (mIU · mmol · 1^{-2})	$I_0 \times G_0/22.5$	20
FIRI (mIU · mmol · 1^{-2})	$I_0 \times G_0/25$	18
Suma I (mIU/l)	$I_0 + I_{60} + I_{120}$	22
IS		
FGIR (mg/10^{-4} IU)	G_0/I_0	21
Matsuda index ($mmol^{-1}$ · mIU^{-1} · 1^2)	$10^4/\sqrt{[(\text{mean I} \times \text{mean G}) \times G_0 \times I_0]}$	19
Cederholm index (mg · 1^2 · $mmol^{-1}$ · mIU^{-1} · min^{-1})	$M/(\text{mean G.log mean I}) = [75{,}000/120 \times (G_0 - G_{120}) \times 1.15 \times 180 \times 0.19 \times (m/120)]/[\text{mean G} \times \log \text{mean I}]$	16
AUC-G/AUC-I	AUC-G/AUC-I	17
K_{ITT} (min^{-1})	$0{,}693/t_{1/2}$	14
DI	βF × IS	40

dertook an ITT. PCOS women undertaking ITT were comparable with the rest of the group in terms of androgen levels, and they were selected according to availability because not all PCOS subjects were area residents. ITT was performed as previously described (14). Plasma glucose $t_{1/2}$ was calculated from the slope of the straight-line regression analysis of the plasma glucose concentrations between 4 and 15 min. The slope, minimal glucose level (ITT_{min}), area under the curve for ITT (AUC_{ITT}), and rate for glucose disappearance (K_{ITT}) were evaluated.

Analytical determinations

Glucose was measured using the glucose-oxidase method (glucose analyzer; Beckman, Fullerton, CA). Serum C-peptide and insulin levels were determined by immunoradiometric assays (Immunotech, Marseilles, France). Testosterone, androstenedione, dehydroepiandrosterone (DHEA), DHEA sulfate (DHEAS), and sex hormone–binding hormone (SHBG) were determined as stated previously (15).

Calculations and statistics

To estimate βF and IR (or IS) the authors used various indexes derived either from the fasting values of insulin and glucose or from OGTT or ITT measurements (16–23) (Table 1).

All values are given as the median (upper and lower quartiles). For the evaluation of changes in the time profiles, one-way ANOVA was used with status (control subjects, lean PCOS patients, and obese PCOS patients) as the factor. For the testing hypothesis, it was strictly assumed that the model error is normally and independently distributed, and homoscedasticity or constant variance throughout the level treatments is supposed. Because of the non-Gaussian distribution, the original data were subjected to a power transformation to attain the minimum skewness of the normalized residuals. To avoid the influence of outliers, the normalized residues with absolute values >2 were excluded from the calculations. Individual differences between the stages were evaluated by the use of least significant difference multiple comparisons. For nonhomogeneous data, we used the robust Kruskal-Wallis test followed by Mann-Whitney *U* tests. The differences were considered statistically significant if $P < 0.05$.

In all, 12 combinations of IS and βF pair indexes were tested, the best fit of the model being found to be defined by βF × IS = *K*. Given the skewed data distribution, nonconstant variance, and nonhomogeneity of the data, a median of the products βF and IS was chosen as the best estimate of the parameter *K*. The differences between the mean values of *K* determined for PCOS and control subjects were tested using one-way ANOVA or by the robust Kruskal-Wallis test followed by Mann-Whitney *U* tests for nonhomogeneous data. All computations were performed using Statgraphics Plus version 3.3 (Manugistics, Rockville, MD)

RESULTS

Clinical and hormonal features in PCOS women

In terms of a family history of diabetes, 12 PCOS women had one or more affected first-degree relatives and 17 second-degree relatives (grandparents); no cases of diabetes in the family was found for 24 women. There was no statistically significant difference in diabetes family history between lean and obese PCOS subjects. In 11 women a regular pattern of menses was stated (e.g., 21–35 days), whereas an irregular menstrual cycle or secondary amenorrhea was present in 53 women. Vaginal ultrasonography was performed on 56 patients. Polycystic ovaries were found in 35 PCOS subjects, multifollicular ovaries in 6, and sonographically normal ovaries in 15. The median (upper quartile, lower quartile) levels of the main androgens for lean and obese PCOS subjects, respectively, were: testosterone 2.34 (1.77, 2.88) vs. 2.18 (1.75, 2.89) nmol/l (NS), free testosterone index 6.8 (5, 10) vs. 9.57 (7.2, 13.9) ($P < 0.08$), androstenedione 5.36 (3.8, 7.3) vs. 5.81 (3.8, 7.5) nmol/l (NS), DHEAS 6.9 (5.65, 8.4) vs. 8.2 (7.35, 9.4) μmol/l ($P <$

Table 2—*Comparison of anthropometry, OGTT, and ITT between PCOS and control subjects*

	Control			PCOS (BMI <27)			PCOS (BMI ≥27)			Between-group differences	
	Median	Lower quartile	Upper quartile	Median	Lower quartile	Upper quartile	Median	Lower quartile	Upper quartile	*P*	Significant between-group differences ($P < 0.05$)
Age (years)	26.5	23.0	31.0	23.5	19.0	28.0	26.5	23.0	31.0	0.03	CL
BMI (kg/m^2)	21.4	20.5	23.7	21.8	20.3	24.2	31.0	28.7	33.8	0.0001	CO, LO
WHR	77.79	75.27	83.18	87.00	82.00	93.10	100.00	95.60	103.10	0.0001	CL, CO, LO
G_0 (mmol/l)	4.40	4.30	4.75	4.70	4.60	4.70	4.70	4.70	4.70	0.004	CL, CO
G_{30} (mmol/l)	7.20	6.75	7.75	6.55	5.50	7.40	8.00	6.80	8.90	0.0001	CO, LO
G_{60} (mmol/l)	6.35	5.15	7.35	5.45	4.60	6.90	7.20	6.00	8.60	0.02	LO
G_{120} (mmol/l)	4.85	4.15	5.40	4.80	4.00	5.40	5.05	4.10	5.90	NS	—
G_{180} (mmol/l)	3.65	3.45	4.30	4.10	3.80	4.90	4.10	3.90	4.60	0.01	CL, CO
I_0 (mIU/l)	6.78	5.64	10.50	8.80	5.70	12.50	16.80	6.00	25.70	0.005*	CO, LO
I_{30} (mIU/l)	49.75	32.19	64.86	52.65	35.00	74.50	133.50	57.60	162.10	0.00	CO, LO
I_{60} (mIU/l)	52.65	45.22	79.14	43.65	26.00	94.60	117.50	64.50	192.20	0.0006*	CO, LO
I_{120} (mIU/l)	27.06	16.98	40.75	20.35	11.70	51.80	48.30	30.20	112.20	0.02*	CO, LO
I_{180} (mIU/l)	7.61	3.72	13.08	9.40	2.90	18.30	20.00	5.90	29.20	0.01	CO, LO
Cp_0 (nmol/l)	0.54	0.42	0.72	0.67	0.49	0.88	1.23	0.73	1.51	0.0001	CO, LO
Cp_{30} (nmol/l)	2.45	1.92	2.78	2.69	1.76	3.22	3.53	2.38	4.43	0.0003	CO, LO
Cp_{60} (nmol/l)	2.95	2.50	3.51	2.81	2.26	3.53	4.52	3.17	4.66	0.0001	CO, LO
Cp_{120} (nmol/l)	2.45	2.09	2.62	2.03	1.24	2.76	3.36	2.16	4.04	0.003	CO, LO
Cp_{180} (nmol/l)	0.89	0.75	1.47	1.05	0.66	1.44	1.58	1.17	2.37	0.003	CO, LO
AUC-G	975.8	904.5	1,051.5	919.5	816	1,024	1,056	948	1,176	0.005	CO, LO
AUC-I/1000	6.178	5.126	7.256	5.984	3.660	8.837	11.566	7.685	21.002	0.0007*	CO, LO
AUC_{Cp}	394.4	351.7	436.73	349.1	303	439.8	572.4	452.3	649.8	0.0001*	CO, LO
$\Delta I/\Delta G_{30-0}$	15.41	10.04	18.326	22.99	12.92	44.82	34.807	15.55	56.696	0.0007	CL, CO
HOMA-R	1.371	1.094	2.164	1.95	1.312	2.667	3.4658	1.292	5.7916	0.007	CO, LO
HOMA-F	149.2	115.6	194.67	185	126.7	266.7	202.22	67.71	330.42	NS*	—
Matsuda	125.9	107.5	147.13	106	84	164.6	55.418	32.01	118	0.004	CO, LO
FGIR	11.60	7.66	13.25	9.12	6.25	13.12	5.66	3.47	15.72	NS*	—
FIRI	1.23	0.98	1.95	1.75	1.18	2.40	3.09	1.20	5.14	0.05	CO, LO
AUC-G/AUC-I	0.15	0.14	0.18	0.17	0.12	0.25	0.09	0.05	0.13	0.002*	CO, LO
Cederholm	63.00	54.32	77.37	71.47	55.15	86.52	51.75	40.64	62.76	0.003	CO, LO
Suma I	98.28	73.40	116.30	73.00	50.90	133.5	161.20	121.2	307.90	0.0007*	CO, LO
$K_{ITT} \times 100$	4.81	4.37	5.36	4.93	3.49	4.98	4.53	3.41	5.02	NS	—
ITT_{min}	2.00	1.70	2.40	2.40	2.10	3.80	2.50	2.20	2.80	0.004	CL, CO
AUC_{ITT}	64.18	59.70	72.20	74.13	70.90	86.00	74.19	71.10	75.20	0.003	CL, CO

*Due to nonconstant variance even after transformation to minimum skewness of normalized residues with absolute values <2, Kruskal-Wallis test followed by Mann-Whitney *U* test was used instead of ANOVA. CL, control vs. lean PCOS subjects; CO, control vs. obese PCOS subjects; LO, lean vs. obese PCOS subjects.

0.056), and SHBG 33 (23.4, 43) vs. 22 (17.1, 29) nmol/l ($P < 0.013$).

Comparison of the PCOS patients with control subjects

The anthropometric and biochemical data of the PCOS and control women are given in Table 2. Both lean and obese PCOS subjects had remarkably higher waist-to-hip ratios (WHRs) ($P < 0.0001$) than control subjects. Fasting glucose was higher in both lean and obese PCOS than in control subjects ($P < 0.004$). During the OGTT, glucose values at 180 min (G_{180}; $P < 0.008$) was significantly higher in both lean and obese PCOS than in control subjects. In most of the other parameters measured during OGTT (glucose, insulin, and C-peptide), there were significant differences detected between lean and obese PCOS and between control and obese PCOS subjects, but not between lean PCOS and control subjects.

Regarding the indexes of IR/IS: insulin resistance by homeostasis model assessment (HOMA-R) was higher in obese PCOS than in control and lean PCOS subjects ($P < 0.007$). Control and obese PCOS subjects and lean and obese PCOS subjects differed significantly in all other IR indexes (except fasting glucose-to-insulin ratio [FGIR]. Obese PCOS women were more insulin resistant than the other two groups. Regarding the βF parameters, no differences were found in βF by HOMA (HOMA-F), but a significantly higher insulinogenic index [$\Delta I/\Delta G_{30-0}$] was found in both lean and obese PCOS subjects than in control subjects ($P < 0.0007$).

With respect to ITT-derived parameters, no differences between the PCOS group and the control group were found in K_{ITT}. Nevertheless, both lean and obese PCOS subjects differed from the control

Table 3—*Differences between PCOS and control subjects in DI*

Insulin Secretion	Sensitivity	Control n	Control Median	Control Lower quartile	Control Upper quartile	PCOS (BMI <27) n	PCOS (BMI <27) Median	PCOS (BMI <27) Lower quartile	PCOS (BMI <27) Upper quartile	PCOS (BMI ≥27) n	PCOS (BMI ≥27) Median	PCOS (BMI ≥27) Lower quartile	PCOS (BMI ≥27) Upper quartile	Between-group differences P	Between-group differences Significant between-group differences ($P < 0.05$)
HOMA-F	1/HOMA-R	20	113.6	75.95	130.8	37	100	60	153.1	24	60	50.91	82.59	0.03	CO, LO
HOMA-F	I/I_0	20	22.22	16.03	25	37	20	13.33	28.57	24	13.33	11.76	16.87	0.003	CO, LO
HOMA-F	G_0/I_0	20	97.78	76.09	107.5	37	94	66.67	122.3	24	66.67	57.02	79.3	0.002	CO, LO
HOMA-F	1/FIRI	20	126.3	84.39	145.3	37	111.1	66.67	170.1	24	66.67	56.56	91.77	0.007	CO, LO
$\Delta I/\Delta G_{30-0}$	I/I_{120}	20	0.649	0.357	0.965	36	1.104	0.475	2.555	24	0.679	0.28	1.252	0.007	CL, LO
$\Delta I/\Delta G_{30-0}$	AUC-G/AUC-I	20	0.112	0.045	0.169	35	0.182	0.056	0.558	23	0.066	0.016	0.134	0.0003	CO, LO, (CL)
$\Delta I/\Delta G_{30-0}$	Cederholm	20	906.3	581.8	1295	35	1634	882.4	2937	24	1554	962.8	2569	0.0003	CL, CO
$\Delta I/\Delta G_{30-0}$	Matsuda	20	1844	908.4	2294	36	2942	1398	4832	24	1946	1137	2787	0.05	CL, (LO)
$\Delta I/\Delta G_{30-0}$	1/Suma I	20	0.146	0.097	0.216	36	0.317	0.153	0.501	24	0.144	0.1	0.29	0.002	CL, LO
HOMA-F	K_{ITT}	20	7.276	5.533	10.15	5	11.59	9.582	13.5	8	8.828	2.469	20.85	NS*	—
HOMA-F	$1/AUC_{ITT}$	20	2.276	1.48	3.289	5	3.257	2.952	5.692	8	2.621	0.916	7.249	NS	—
HOMA-F	$1/ITT_{min}$	20	67.58	48.7	121.9	5	110	98.72	128.2	8	85.99	23.63	210.5	NS	—
$\Delta I/\Delta G_{30-0}$	K_{ITT}	20	0.727	0.495	0.944	5	2.263	1.988	3.821	8	1.429	0.721	1.785	0.0001	CO, LO, CL
$\Delta I/\Delta G_{30-0}$	$1/AUC_{ITT}$	20	0.243	0.156	0.3	5	1.025	0.612	1.074	8	0.452	0.21	0.656	0.0008	LO, CL
$\Delta I/\Delta G_{30-0}$	$1/ITT_{min}$	20	6.648	4.564	11.2	5	21.5	20.48	29.72	8	14.57	6.295	16	0.0008	LO, CL

*Due to nonconstant variance even after transformation to minimum skewness of normalized residues with absolute values <2, Kruskall-Wallis test followed by Mann-Whitney *U* test was used instead of ANOVA. CL, control vs. lean PCOS subjects; CO, control vs. obese PCOS subjects; LO, lean vs. obese PCOS subjects.

subjects significantly in terms of ITT_{min} ($P < 0.004$) and AUC_{ITT} ($P < 0.003$).

The relationship of βF and IS—the DI

The relationship between the indexes of βF and IS—the DIs—were calculated. All of the combinations of products βF × IS used followed a hyperbolic relationship. DIs derived from the fasting state parameters of IS (1/HOMA-R, $1/I_0$, and FGIR) and βF (HOMA-F) yielded lower values in obese PCOS than in control and lean PCOS subjects (all $P < 0.05$), with no difference between lean PCOS and control subjects (Table 3).

When combinations of $\Delta I/\Delta G_{30-0}$ and ITT-derived IS parameters were evaluated, significantly higher values of DI were found in lean PCOS than in control and obese PCOS subjects ($P < 0.0008$ and $P < 0.0001$, respectively). Combinations of $\Delta I/\Delta G_{30-0}$- and OGTT-derived IS parameters yielded almost consistently higher DI values in lean PCOS than in control subjects. Analogous DI values in obese PCOS subjects were either significantly higher than ($P < 0.0003$ [16]) or no different than those of control subjects.

CONCLUSIONS — Hyperinsulinemia and IR are often described in women with PCOS (2,24), and the connection between PCOS, IR, insulin secretion, and obesity is still not clearly defined. Although a remarkable proportion of women with PCOS develops IGT (up to 30%) and type 2 diabetes (up to 10%), this is not a universal feature (1,25). In the U.S., it has been extrapolated that PCOS-related IR contributes to 20% of IGT and 40% of type 2 diabetes in women of childbearing age (26). Nevertheless, the early screening of impaired insulin action and secretion in women with PCOS could be very useful in clinical practice because it enables the possible prevention of serious metabolic complications.

The present study considered women with PCOS (divided into lean and obese subjects) using OGTT, ITT, and anthropometry with the aim of evaluating IR and βF in this connection. A feedback loop between IR and secretion exists, and it was therefore hypothesized that subtle changes in either of these two inherently connected variables would be more pronounced and informative when using a DI as their product.

As to anthropometric variables, WHR values in PCOS women were significantly higher, even in the lean group, suggesting preferential abdominal fat localization in these patients. This accords well with the results of other authors (5). It is probably not only the total amount of body fat but also fat tissue distribution that plays an important role in the pathogenesis of IR. A central fat depot could (via increased levels of free fatty acids) modulate the βF (27,28). An increase in free fatty acids has been described as elevating the insulin secretion rate (29). Recently, enhanced visceral lipolysis has been found in women with PCOS (30). Nevertheless, information is scarce regarding body fat composition using reference methods such as nuclear magnetic resonance or computed tomography, as is information regarding lipolysis defects in PCOS to date, and it is presumed that this will require further study.

With respect to parameters derived from OGTTs, there were marked differences detected between lean and obese PCOS subjects and between obese PCOS and control subjects, but not between lean PCOS and control subjects. It was not the aim of this study to distinguish the impact of obesity on insulin secretion and clearance. Because both insulin and C-peptide levels were elevated in obese PCOS subjects, increased insulin secretion could be expected. The impact of hepatic insulin clearance is, on the other hand, difficult to ascertain in vivo without using isotope methods. Thus, divergent results in PCOS have been reported, either finding (5,31,32) or not finding (33) defective insulin clearance.

In recent years, it has been shown useful to examine the feedback loop on IR and βF in unison. Only the mutual relationship of these two inherently connected variables could reflect the (in)adequacy of insulin secretion to compensate for defective insulin action (11,34). The product of IS and βF follows, under physiological conditions, a hyperbolic function. Recently, it was shown that DIs derived from fasting values followed the physiological relationship much better than DIs derived from OGTT values in a group of healthy women (35). Both groups of combinations (i.e., those derived from either fasting or stimulated values) followed the hyperbolic relationship equally well in control healthy subjects and in PCOS women in this study. In the fasting state, all DIs were significantly lower in obese PCOS subjects than in control or lean PCOS subjects. When DIs derived from the stimulated values during the OGTT were used, all were significantly higher in lean PCOS subjects than in the control group or obese PCOS subjects. It is probable that lean PCOS subjects were evaluated in an early stage of the disturbance of the glucose metabolism, when an exaggerated insulin secretion for the degree of IR could be found (36). These results are in accordance with those of Holte et al. (13), who found an increase in the early phase of insulin response to glucose. On the other hand, a reduction in the entrainment of insulin pulses in PCOS with a family history of diabetes was detected by O'Meara et al. (9). The results in that study could have been confounded by BMI heterogeneity (from 21 to 46 kg/m^2 in 24 subjects). Our results in obese PCOS subjects are thus mostly in accordance with a study by Ehrmann et al. (10), where defective stimulated secretion of insulin with higher basal insulinemia was found.

The authors are aware of the limitations of the indexes used in the evaluation of IR (37,38) because only a moderate correlation of these indexes with the gold standard—euglycemic-hyperinsulinemic clamp—was found (37,39). Nevertheless, the results underline the necessity of evaluating both IS and βF together in order to achieve a correct phenotypic characterization of PCOS. It is therefore possible to conclude that a reduction in fasting state–derived DI values (βF × IS) was found in obese PCOS women. On the other hand, an increase in those variables derived from OGTTs was found, especially in lean PCOS subjects. This probably reflects insulin hypersecretion as an important mechanism in the pathogenesis of PCOS. It is necessary to determine the prognostic significance of these findings.

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