OBJECTIVE — To determine insulin resistance and response in patients with polycystic ovary syndrome (PCOS) and normal glucose tolerance (NGT), impaired fasting glucose (IFG), impaired glucose tolerance, and combined glucose intolerance (CGI).

RESEARCH DESIGN AND METHODS — In this cross-sectional study, 143 patients with PCOS (diagnosed on the basis of National Institutes of Health criteria) underwent oral glucose tolerance testing (OGTT), and 68 patients also had frequently sampled intravenous glucose tolerance tests. Changes in plasma glucose, insulin, cardiovascular risk factors, and androgens were measured.

RESULTS — Compared with patients with NGT, those with both IFG and CGI were significantly insulin resistant (homeostasis model assessment 3.3 ± 0.2 vs. 6.1 ± 0.9 and 6.4 ± 0.5, \( P < 0.0001 \)) and hyperinsulinemic (insulin area under the curve for 120 min 973 ± 40 vs. 1,470 ± 197 and 1,461 ± 172 pmol/L, \( P < 0.0001 \)). Insulin response was delayed in patients with CGI but not in those with IFG (2-h OGTT, insulin 1,001 ± 40 vs. 583 ± 45 pmol/L, \( P < 0.0001 \)). Compared with the NGT group, the CGI group had a lower disposition index (1,615 ± 236 vs. 987 ± 296, \( P < 0.0234 \)) and adiponectin level (11.1 ± 1.1 vs. 6.2 ± 0.8 ng/mL, \( P < 0.0096 \)). Compared with the insulin-resistant tertile of the NGT group, those with IFG had a reduced insulinogenic index (421 ± 130 vs. 268 ± 68, \( P < 0.05 \)). Compared with the insulin-sensitive tertile of the NGT group, the resistant tertile had higher triglyceride and high-sensitivity C-reactive protein (hs-CRP) and lower HDL cholesterol and sex hormone–binding globulin (SHBG). In the entire population, insulin resistance correlated directly with triglyceride, hs-CRP, and the free androgen index and inversely with SHBG.

CONCLUSIONS — Patients with PCOS develop IFG and CGI despite having significant hyperinsulinemia. Patients with IFG and CGI exhibit similar insulin resistance, but very different insulin response patterns. Increases in cardiac risk factors and free androgen level precede overt glucose intolerance.

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Glucose intolerance in PCOS

all were examined by either S.E.K. or A.J.D. Patients using insulin sensitizers or medicines affecting lipids, weight, or insulin sensitivity within 2 months; having diabetes, untreated hypothroidism, or systemic illnesses (i.e., renal, hepatic, and gastrointestinal); smoking; and drinking >2 servings of alcohol per week were excluded. Pregnant, postpartum, or lactating women were excluded. The studies were carried out at the Clinical and Translational Science Center at UC Davis and at Yale University School of Medicine Reproductive Endocrinology and Fertility Center. The subjects consumed their habitual diets and were weight-stable.

Fasting blood tests and OGTT were done in all subjects. Subjects recruited at UC Davis also underwent a frequently sampled intravenous glucose tolerance test (FSIVGTT).

Anthropometric measurements

Weight was measured using a Tanita BWB800-P digital medical scale, and height was measured using an Ayrton model S100 stadiometer.

OGTT

A standard OGTT was performed using 75 g of glucose (Glucola). Blood samples were obtained every 30 min. The subjects remained supine in bed. Samples were collected in tubes containing sodium fluoride, EDTA, or heparin.

FSIVGTT

An intravenous catheter was placed in each forearm. The catheters were kept open with normal saline. Heating pads were used to maximize the blood flow. After blood samples were obtained at −20, −10, and 0 min, glucose (0.3 units/kg as 25% dextrose) was injected intravenously at time 0. Intravenous insulin (0.03 units/kg) (Humulin regular; Eli Lilly) was administered at time 20 min. Additional samples were obtained at 0, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 23, 24, 25, 27, 30, 35, 40, 50, 60, 70, 80, 90, 100, 120, 140, 160, and 180 min. The samples were analyzed for glucose and insulin. Acute insulin response (AIRg), β-cell function, insulin sensitivity index (S), and disposition index were calculated using the MINMOD Millennium software (13).

Statistical analysis

Statistical analyses were performed using SAS statistical software (version 9.1; SAS Institute, Cary, NC). Data were first examined to identify any significant variations between the populations from two sites, UC Davis versus Yale School of Medicine. The age distribution of the subjects from Yale was shifted to younger ages. In addition, age appeared to be confounded with BMI. Therefore, the pooled data were analyzed by including age and BMI as covariates in all of the subsequent statistical analyses. After correction for age and BMI, the association between study site and any outcome was attenuated toward the null. Descriptive statistics were calculated. A Spearman correlation coefficient and its P value for significance of correlation were calculated to assess the magnitude and direction of an association between two given outcomes based on their ordered ranks. The data were log-transformed to improve the normality of residuals and homoscedasticity of errors where appropriate before statistical analysis. Group comparisons for mean in the cross-sectional outcome were performed by ANCOVA, adjusted for the baseline values and covariates (age and BMI). When the overall difference among the group means was significant in ANCOVA, post hoc pairwise group comparisons were conducted using Bonferroni multiple comparisons to identify the groups with different means. The longitudinal trajectories of 120-min changes in glucose and insulin level were estimated by a repeated-measures ANOVA. Individual trajectories of change in glucose and insulin level over five time points, observed every 30 min over 2 h, were estimated from linear random-effects models. Each observed level was entered as the dependent variable. Group (i.e., type of glucose intolerance), time (in 30 min), and a group × time interaction term were entered as independent variables. The coefficients for the interaction term were used to estimate the additional changes in glucose and insulin level over time associated with type of glucose intolerance. To account for between-subject heterogeneity in the change of glucose or insulin level, intercept and time were modeled as random effects. Multiple comparisons were controlled by the Bonferroni method where appropriate. Two-sided P < 0.05 was considered significant.

RESULTS — Forty-six of 143 women with PCOS (32%) had glucose tolerance abnormalities. Sixteen (11%) had IFG, 10 (7%) had IGT, and 20 (14%) had CGI. The remaining 97 women (68%) had normal glucose tolerance (NGT). Different ethnic groups were similarly distributed among NGT, IFG, IGT, and CGI. None of the minorities were overrepresented in any of the groups.
Both IFG and CGI groups had lower insulin resistance compared with the IFG group. CVD, cardiovascular disease; DHEAS, dehydroepiandrosterone sulfate; FAI, free androgen index.

Baseline differences among NGT, IFG, IGT, and CGI groups
The IGT group was older and the IFG group was more obese than the NGT group (Table 1). By definition, the IFG, IGT, and CGI groups had higher glucose levels than the NGT group. All glucose-intolerant groups had higher fasting insulin than the NGT group (IFG 131 ± 16 pmol/l, IGT 112 ± 22 pmol/l, and CGI 145 ± 12 pmol/l vs. NGT 88 ± 5 pmol/l, P = 0.0002). The difference between the fasting insulin values of the CGI and IGT groups was also significant (P = 0.0047).

Insulin resistance
Both IFG and CGI groups had lower ISI_{Matsuda} values than the NGT groups (2.12 ± 0.29 and 1.90 ± 0.28 vs. 4.61 ± 0.34, P = 0.0004 and P < 0.001, respectively) (Table 1, Fig. 2). In 68 women who underwent FSIVGTT, differences in S_{i} did not reach significance (NGT 3.47 ± 0.60, IFG 1.58 ± 0.34, IGT 2.46 ± 0.29, and CGI 2.27 ± 0.44, P = 0.1468). On the other hand, the disposition index was significantly reduced in the CGI group compared with the NGT group (987 ± 296 vs. 1,615 ± 236, P = 0.0234). The CGI group also had lower serum adiponectin than the NGT group (8.64 ± 0.8 vs. 11.1 ± 1.1 ng/ml, P = 0.0096). Compared with the NGT group, both IFG and CGI groups had higher HOMA (6.1 ± 0.9 and 6.4 ± 0.5 vs. 3.3 ± 0.2, P = 0.0006 and P < 0.0001) and lower QUICKI (0.30 ± 0.06 and 0.30 ± 0.04 vs. 0.33 ± 0.03, P = 0.0009 and P < 0.0001).

Insulin response
Compared with the NGT group, the IFG group had an overall increase in insulin response during an OGTT, and the differences were significant at every time point (Table 1, Fig. 1), whereas the IGT and CGI groups exhibited a delayed response. During the first half of the OGTT, the IFG group had higher insulin levels than the CGI group (30 min 820 ± 45 versus 598 ± 45 pmol/l, P = 0.001). In 68 women, the insulin response pattern changed; at 120 min the CGI group had higher insulin than the IFG group (996 ± 34 versus 583 ± 45 pmol/l, P < 0.001). In 68
individuals who underwent FSIVGTTs, there were no significant differences in AIRg (P = 0.4842) or β-cell function (P = 0.0901).

**Insulin response in NGT tertiles, divided based on insulin resistance**
The IFG and CGI groups had similar insulin resistance based on HOMA (6.1 ± 0.9 vs. 6.4 ± 0.5), QUICKI (0.30 ± 0.006 vs. 0.30 ± 0.004), and ISI_Matsuda (2.12 ± 0.29 vs. 1.90 ± 0.28) but different insulin response patterns (Table 2) (Fig. 1). Insulin response in insulin-resistant subjects with NGT was also investigated. When divided into tertiles based on ISI_Matsuda, the insulin-resistant (NGT-IR) tertile was similar to subjects with IFG and CGI, based on their HOMA (5.6 ± 0.3), QUICKI (0.30 ± 0.002), and ISI_Matsuda (1.90 ± 0.09). Their BMI (39.9 ± 1.2 kg/m²) was similar to those of the subjects with IFG (38.7 ± 1.5 kg/m²) and CGI (38.1 ± 1.8 kg/m²). The NGT-IR group had higher a insulinogenic index than the IFG group (421 ± 130 vs. 268 ± 68, P < 0.05).

**Differences among the NGT tertiles**
The tertiles were referred to as insulin-sensitive (NGT-IS), intermediate (NGT-IN), and NGT-IR (Table 2) (Fig. 2). In these tertiles, fasting glucose and insulin increased stepwise (from 4.8 ± 0.02 to 5.0 ± 0.02 and to 5.1 ± 0.02 mmol/l, P < 0.0001 and from 41 ± 2 to 79 ± 2 and to 146 ± 2 pmol/l, respectively, P < 0.0001). The NGT-IN and NGT-IR tertiles had higher BMI, fasting glucose, HOMA, AUCGlucose_0–120, AUCInsulin_0–120, and triglyceride and lower QUICKI and HDL cholesterol than the NGT-IS tertile. In addition, the NGT-IR tertile had higher insulinogenic index, AUCGlucose_0–120, AUCInsulin_0–120, and triglyceride and lower sex hormone-binding globulin than the NGT-IS tertile. Even after correction for BMI, differences in fasting glucose, fasting insulin, AUCInsulin_0–30, AUCGlucose_0–120, AUCInsulin_0–120, and HDL cholesterol remained significant.

Next, partial correlations among insulin resistance parameters, cardiovascular risk factors, and androgens were calculated after adjustment for the differences in BMI. Plasma triglyceride and hs-CRP correlated directly with HOMA (\(r = 0.316\) and 0.253, P = 0.009 and P = 0.037, respectively) and inversely with ISI_Matsuda (\(r = -0.282\) and -0.306, P = 0.020 and 0.011, respectively).

![Figure 1—Changes in glucose and insulin during OGTTs. A and B: o, NGT, n = 97; ▲ with broken line, IFG, n = 16; ●, IGT, n = 10; ■, CGI, n = 20. C: X, NGT-IS, n = 33; ■, NGT-IN, n = 32; ▼, NGT-IR, n = 32; ▲ with broken line, IFG, n = 16. \*P < 0.05 compared with IFG. Data are means ± SEM. a, P < 0.05 compared with NGT; b, P < 0.05 compared with IFG; c, P < 0.05 compared with IGT.](image-url)
CONCLUSIONS — This study demonstrated that, first, patients with PCOS with IFG exhibited severe peripheral insulin resistance and developed IFG despite having an increased early insulin response. Second, having normal glucose levels during an OGTT did not indicate normal insulin sensitivity or a low risk for cardiovascular disease. Third, in the NGT group, the BMI, sex hormone–binding globulin, HDL cholesterol, and hs-CRP levels appeared to have value in assessing insulin resistance. Because we did not have a control group of age- and weight-matched women with normal reproductive function, we cannot conclusively state that these findings are specific to patients with PCOS. However, our observations differ significantly from those obtained from middle-aged men and women (14).

Diabetes risk increases with increasing age and obesity (15). We found age and weight to be important in development of glucose intolerance and insulin resistance, respectively (Tables 1 and 2). Per definition, glucose levels were higher in patients with IFG, IGT, and CGI compared with patients with NGT. Insulin responses of patients with IFG, IGT, or CGI were not decreased. In fact, AUC_{Insulin-120} was higher in both patients with IFG and CGI, indicating that patients with PCOS can develop IFG and CGI in the presence of hyperinsulinemia. This was consistent with the findings of Kulshreshtha et al. (12), who reported increased insulin responses in patients with PCOS with IGT/CGI or type 2 diabetes. The time course of the insulin response was the most significant difference between patients with IFG versus those with IGT and CGI. Patients with IFG had a brisk early insulin response that declined during the second half of OGTT. In contrast, patients with CGI and IGT exhibited a decreased early insulin response followed by delayed hyperinsulinemia. Previous reports showed similar response patterns in those with IFG versus those with IGT and CGI among subjects without PCOS (12,14,16,17).

The brisk, early insulin response of patients with IFG appeared to be specific to PCOS because several studies in different populations, ethnic groups, sex, and age distributions have reported decreased cumulative and early insulin response in patients with IFG (14,17–20), although a recent report in healthy nondiabetic men and women showed an increased insulin response (16). The only available study in PCOS demonstrated an increased insulin response similar to ours (12).

In patients with PCOS who have IGT, the early and cumulative insulin responses (AUC_{Insulin-30} and AUC_{Insulin-120}) did not differ significantly from the responses of those with NGT, whereas Kulshreshtha et al. (12) reported increased insulin response in glucose-intolerant patients with PCOS. However, their study did not distinguish between IGT and CGI, and the subjects were less obese and of different ethnicities.

Studies using intravenous glucose tolerance tests in subjects without PCOS reported that AIR_k was decreased by ~30%
in those with IFG and by 8–18% in those with IGT (20–22). As seen in Table 1, AIRg did not decrease in our patients with PCOS with IFG. Taken altogether, these findings indicate that patients with PCOS can develop fasting hyperglycemia and glucose intolerance even with increased early and cumulative insulin responses.

The literature indicates that primary sites of insulin resistance differ in IFG, IGT, and CGI (9,10,14): hepatic in IFG; peripheral in IGT; and both hepatic and peripheral in CGI. These distinctions cannot be made without using a hyperinsulinemic clamp. The surrogate measures of hepatic insulin resistance include HOMA and QUICKI. Consistent with the literature, we found increased HOMA and decreased QUICKI only when fasting glucose was impaired (IFG/CGI) but not in IGT (Table 1). In contrast with the literature, the surrogates for peripheral insulin resistance, ISIMatsuda and $S_i$, of our IFG group were similar to those of the IGT and CGI groups, indicating that patients with PCOS with isolated IFG also have peripheral insulin resistance.

The cause of IFG was an enigma because this group had significant early and late hyperinsulinemia. Thus, we compared the IFG group to subjects with equal insulin resistance with NTG (NGT-IR). Although the NGT-IR group and those with IFG had similar HOMA, QUICKI, and ISIMatsuda values, the NGT-IR group had a higher insulinogenic index. As shown in Fig. 1, patients with IFG also had decreased overall insulin secretion relative to the degree of insulin resistance.

The studies of tertiles demonstrated that patients with PCOS who have NTG can still be severely insulin-resistant. In addition, cardiovascular risk factors and hyperandrogenemia worsen before overt hyperglycemia. Consistent with these findings, a recent report indicated that low HDL cholesterol levels correlate with hyperinsulinemia in PCOS (23). Previous studies had found increased cardiovascular risk factors only in subjects with IGT and CGI without PCOS (11,21).

We propose the natural course of glucose intolerance in PCOS as follows. Insulin resistance increases with weight gain, as suggested by the stepwise increase in BMI in the NGT tertiles (Fig. 2). As long as insulin response can compensate, plasma glucose remains within the “normal” range. A relatively small decrease in overall insulin response results in isolated IFG. A decrease in the early insulin response results in IGT/CGI, even with late hyperinsulinemia. Factors leading to impairment of the early versus overall response are not known, although genetic factors may be important (4,24).

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