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Using Simple Clinical Measures to Predict Insulin Resistance or Hyperglycemia in Girls with Polycystic Ovarian Syndrome

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Abstract

Background: Polycystic ovarian syndrome (PCOS) includes insulin resistance (IR) and impaired glucose tolerance (IGT) in youth, and a greatly elevated risk of type 2 diabetes in adulthood. Identifying IR is challenging and documenting IGT requires an oral glucose tolerance test (OGTT). **Objective:** Identify an easily applied surrogate measures for IR and IGT in girls with PCOS.

Methods: We studied 28 girls with PCOS [BMI percentile 98 (83,99); 15.5 (14.5,16.6) years of age] and 20 with normal menses [BMI percentile (97 (88,99); 15.5 (13.3,16.1) years]. Hyperinsulinemic-euglycemic clamps (insulin dose of 80 μ U/ml/min) to determine glucose infusion rate (GIR) and a 75 gram OGTT were performed. Surrogates for IR including fasting insulin, HOMA-IR, Matsuda index and eIS were compared to IGT status and GIR. Spearman correlations were performed between surrogates and GIR or IGT, and receiver operator curve (ROC) analysis to predict GIR below the median or IGT status.

Results: GIR was lower in PCOS (12.9 ± 4.6 vs. 17.1 ± 5.1 mg/kg fat free mass·min; $p=0.01$). Within PCOS, HOMA-IR ($r=-0.78$, $p<0.0001$), e-IS ($r=0.70$, $p<0.001$), and Matsuda ($r=0.533$, $p<0.001$) correlated with GIR. e-IS provided a good sensitivity (100%) and specificity (71%) to identify IR (e-IS cutoff: <6.3 , ROC-area under curve=0.898). Fasting insulin >22 IU/ml had the best sensitivity (88%), specificity (78%) and ROC (0.760) for IGT status.

Conclusions: Girls with PCOS have significant IR, and IGT is common. Both eIS and fasting insulin are obtainable without an OGTT or clamp and could be used clinically to guide treatment in PCOS.

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Keywords

Polycystic ovarian syndrome; Insulin Resistance; Adolescence; impaired glucose tolerance

Introduction:

Polycystic ovarian syndrome (PCOS) is a common endocrine disorder, affecting around 12% of reproductive-aged women (1, 2). Patients with PCOS can have profound insulin resistance (IR) and have an increased risk of developing metabolic aberrations such as type 2 diabetes (T2D), nonalcoholic fatty liver disease and cardiovascular disease, all of which start in adolescence (1, 3, 4). The joint 2017 Pediatric Endocrine Society and North American Society for Adolescent and Pediatric Gynecology Guidelines for PCOS diagnosis and management in adolescents recommend that the presence of IR prompt further co-morbidity testing and treatment with metformin (5). The 2013 Endocrine Society guidelines suggest the use of metformin as a second-line therapy in PCOS youth with hyperglycemia, defined as impaired glucose tolerance (IGT) or T2D (1). It recommends the use of 2-hour oral glucose tolerance test (OGTT) with a 2-hour glucose measurement to screen for IGT, defined as a blood glucose ≥ 140 mg/dL. Both guidelines were developed out of recognition that PCOS in adolescents may not be the same as in adult women, in part due to more severe IR secondary to pubertal changes (1, 6). Yet, despite recognition of unique metabolism of IR in adolescents and screening recommendations, IR is best measured by a hyperinsulinemic euglycemic clamp and IGT by an OGTT, both of which are burdensome for clinical care. A simple surrogate measure of IR for youth with PCOS is needed.

Many surrogate measures of IR have been developed in non-PCOS populations, validated against the glucose infusion rate (GIR) during a hyperinsulinemic-euglycemic clamp, which is considered the gold standard for measuring insulin sensitivity, but impractical for clinical care (7). HOMA-IR is the most used index and has been shown to be a reliable indicator of IR in large scale studies, given its tight correlation ($r=0.88$) with the clamp (2, 8). Nonetheless, HOMA-IR has a 30% intra-individual variation limiting its use in individuals for clinical care. Other insulin-based surrogates of IR include a fasting insulin, the fasting glucose to insulin ratio (FGIR)(9), the quantitative insulin sensitivity check (QUICKI) (10) and OGTT models such as the Matsuda (11) or Stumvoll (12). However, all of these models include fasting insulin, which can vary from day to day and insulin assays are still largely unstandardized (13, 14). These measures have all been shown to have various degrees of success in predicting IR in adults with PCOS, but have not been studied as predictors of IR in youth with PCOS (15–17). Serum triglycerides (TG) and high-density lipoprotein cholesterol (HDL) are also associated with IR, have less inter-assay and day-to-day variability, and don't add additional cost as they are already recommended for screening of lipid abnormalities in PCOS (18). In a PCOS adult cohort, TG alone was identified as an effective marker in identifying IR, tightly correlating to HOMA-IR(19). Song et al. also suggested TG:HDL to be a strong indicator of IR in young women with PCOS, when compared to OGTT models (20). A TG and glucose index (TyG) also correlated well with GIR, and was found to work well in a pediatric obese population of youth (18, 21). We previously developed and validated a surrogate estimate of insulin sensitivity (e-IS) against

GIR, in adolescents of varied BMI and with and without diabetes (22). The e-IS calculation also uses TG, as well as HbA_{1c} and waist circumference and does not use insulin (22). Thus, there are numerous surrogate markers of IR which have been used in obese youth, however, the one most applicable for adolescents with PCOS is not clear.

Many surrogate measures for IGT have also been tested, in an effort to avoid performing an OGTT. The most commonly identified markers are HOMA-IR and fasting insulin, although multiple other markers including HbA_{1c} and adiponectin have been proposed (23–26). However, many studies failed to find strong predictors for IGT in either PCOS or non-PCOS populations (27–29). IGT is likely more related to pancreatic β -cell failure as opposed to IR, and this can be harder to assess in the fasting state (30, 31). Again, studies in youth with PCOS are limited.

In order to identify the most predictive, clinically useful surrogate index of IR and IGT in PCOS youth, we compared multiple surrogate indices of IR to clamp-measured GIR and fasting measures to IGT status in a cohort of adolescents with and without PCOS of varied BMI.

Methods:

Participants

48 participants were enrolled (28 PCOS and 20 control) from the RESistance to InSulin in Type 1 ANd Type 2 diabetes (RESISTANT) study and Androgens and Insulin Resistance Study (AIRS) cohorts with all studies performed between 2006–2014. (3, 21, 32). Inclusion criteria included: female sex, age 11–19 years, and sedentary status (<3 hours of activity per week; validated with both a 3-day activity recall and 7-day accelerometer use). Exclusion criteria were diabetes, alanine transferase (ALT) >80 IU/mL, blood pressure (BP) >140/90 mmHg, hemoglobin <9mg/dl, serum creatinine >1.5 mg/dl, smoking, medications affecting insulin sensitivity (oral steroids, metformin, atypical antipsychotics, hormonal contraceptives), antihypertensive medications, statins, pregnancy, and breastfeeding. PCOS was diagnosed per NIH criteria with adolescent adaptation: oligomenorrhea (<8 menses a year), clinical or biochemical signs of hyperandrogenism, no other cause of oligomenorrhea or hyperandrogenism and at least 1.5 years post-menarche (1, 6). Participants were selected for this analysis from the parent cohorts if they had complete OGTT and clamp data. The study was approved by the University of Colorado Anschutz Medical Campus Institutional Review Board. Informed consent was obtained from all participants 18–19 years old, and parental consent and participant assent from all participants <18 years old.

Insulin Sensitivity and Glucose Testing

Before the clamp visit, participants underwent 3 days of restricted physical activity and a fixed-macronutrient, weight-maintenance diet (55% carbohydrates, 30% fat, 15% protein). On the evening of the visit, participants were admitted to the Colorado Clinical Translational Research Center for an isocaloric meal, followed by a 12-hour overnight monitored fast. An 80 mU/m²/min hyper-insulinemic euglycemic clamp was performed the following morning as previously described, based on the higher insulin requirements in pubertal youth (21, 33,

34). 20% dextrose was infused to maintain blood glucose at 95 mg/dl. Samples were drawn every 5 minutes and analyzed with a bedside Yellow Springs Instrument glucose analyzer (Yellow Springs, OH) (7). GIR expressed as mg/kg of fat free mass [FFM]•min was measured based on steady-state measurements from the final 30 min of the clamp. FFM was determined from DXA. On a separate morning, the participants also underwent a fasting 2-hour OGTT using a dose of 1.75 mg/kg up to a maximum of 75 mg. All OGTT's started prior to 10 AM. Blood was sampled for glucose and insulin at baseline, 30 minutes and 120 minutes.

Sample analysis

Serum insulin and adiponectin were analyzed with radioimmunoassay (Millipore, Billerica, MA); HDL and TG assays were performed enzymatically (Hitachi 917 autoanalyzer; Boehringer Mannheim Diagnostics, Indianapolis, IN). HbA_{1c} was measured by DCCT-calibrated ion-exchange high-performance liquid chromatography (Bio-Rad Laboratories, Hercules, Calif) and C-peptide via chemiluminescent immunoassay (DiaSorin, Stillwater, MN). Testosterone was measured via LC/MS/MS and sex hormone binding globulin (SHBG) and anti-mullerian hormone by electrochemiluminescence immunoassay, all by Esoterix (Calbassas Hills, CA). Free androgen index (FAI) was calculated from total testosterone and SHBG.

Surrogate insulin resistance measures:

A total of 12 surrogate IR measures [fasting HOMA-IR (31), Matsuda index (11), Stumvoll index (12), QUICKI (10), TG:glucose index (TyG) (35), TG:HDL ratio (36), e-IS (22), FGIR (16), TG, insulin, adiponectin, and HDL, as well as 2-hour insulin, 2-hour glucose and waist circumference] were calculated or obtained from fasting samples prior to the clamp and/or OGTT or samples from the 2-hour OGTT. HOMA-IR was calculated as [fasting glucose (mg/dL) × fasting insulin (mU/L)/405]; Matsuda index as $[1000 / \{ \text{fasting glucose (mg/dL)} \times \text{fasting insulin (mU/L)} \times \text{mean glucose} \times \text{mean insulin} \}]$; Stumvoll index as $[0.156 - 0.0000459 \times I_{120} \text{ (pmol/l)} - 0.000321 \times I_0 \text{ (pmol/l)} - 0.00541 \times G_{120} \text{ (mmol/l)}]$; QUICKI as $[1 / \{ \log \text{fasting insulin (mU/L)} + \log \text{fasting glucose (mg/dL)} \}]$; e-IS as $e^{[4.64725 - 0.02032 \text{ (waist, cm)} - 0.09779 \text{ (HbA}_{1c}, \%) - 0.00235 \text{ (TG, mg/dl)}]}$; FGIR as $\text{fasting glucose (mg/dL)} / \text{fasting insulin (mU/L)}$; TyG as $\log[\text{fasting triglycerides (mg/dL)} \times \text{fasting glucose (mg/dl)} / 2]$.

For comparison with IGT, in addition to the above measures, we also included HbA_{1c} and HOMA-β, which is meant to represent pancreatic β-cell function $(360 \times I_0 \text{ (mU/L)} / \text{fasting glucose (mg/dL)}) - 36$ (12, 31).

Statistics:

The distributions of all variables were examined and results presented as mean ± standard deviation (SD), median (25th percentile, 75th percentile), or proportions as appropriate. The associations between fasting HOMA-IR, Matsuda index, Stumvoll index, QUICKI, TyG, TG:HDL ratio, e-IS, FGIR, TG, insulin, adiponectin, HDL, 2-hour insulin, 2-hour glucose and waist circumference and the primary outcome, GIR, were examined using the Pearson's

correlation coefficients for both the PCOS and control groups, combined and separately. Multiple linear regression models were then utilized to examine the relationships between GIR and the surrogate indices while adjusting for potential confounders including BMI Z-score, PCOS status in the combined data set, and family history of T2D. P-values < 0.05 were considered significant. The three surrogate indices best correlated with GIR (HOMA-IR, e-IS and Matsuda Score) were then examined with ROC analysis, with an outcome of GIR above or below the median value, within the entire cohort, as well as in PCOS only and in controls only. For IGT, correlations and ROC curves with HOMA-IR, HOMA- β , FGIR, QUICKI and fasting insulin were performed. Statistics were performed with SAS Software, Version 9.4 (Cary, NC) and Sigmaplot Software (Systat Software, Inc, San Jose, CA).

Results:

48 female adolescents were enrolled, 28 with PCOS and 20 controls. Descriptive statistics of these two groups are shown in Table 1. There was no significant difference in age ($p=0.34$), BMI-percentile ($P=0.497$) or Z-score ($p=0.291$) for sex and age or waist circumference ($p=0.16$) between groups. The majority of the cohort was overweight or obese. As expected per study design, the PCOS group had higher FAI ($p=0.003$), total testosterone concentration ($p=0.016$) and AMH ($p=0.005$). Girls in the PCOS group had fewer menses per year ($p<0.001$).

Table 2 shows raw data and surrogate IR measures stratified by group. Fasting measures were within normal ranges and similar between groups including: HbA1c, adiponectin, fasting glucose from the clamp and OGTT days, and fasting insulin from the clamp and OGTT days. The mean 2-hour OGTT glucose was higher in PCOS, but within “normal” glucose tolerance ($p=0.005$). Additionally, 2-hour OGTT insulin was significantly higher in PCOS ($p=0.025$). The GIR in mg/kgFFM/min was significantly lower in PCOS ($p=0.01$), indicating decreased insulin sensitivity.

Twelve IR surrogate indices were calculated for both groups and compared with GIR (data not shown). *Within the PCOS group*, HOMA-IR ($r=-0.78$, $p<0.001$), e-IS ($r=0.69$, $p<0.001$), and waist circumference ($r=-0.71$, $p<0.001$) tightly correlated with GIR and Matsuda did so as well, although less strongly ($r=0.55$, $P=0.003$) (Figure 1). *Within the entire cohort* HOMA-IR ($r=-0.70$, $p<0.001$) and e-IS ($r=0.53$, $p<0.001$) correlated significantly with GIR.

Associations between GIR and the 3 most related calculated surrogate measures (HOMA-IR, Matsuda Index, and e-IS) were examined after adjustment for potential confounders in the PCOS group. *Within the PCOS group*, HOMA-IR showed a non-significant association with GIR ($\beta=-0.823$, $p=0.081$) after adjusting for potential confounders including SHBG, FAI, family history of PCOS, and BMI-Z. The association between e-IS and GIR also did not reach statistical significance ($\beta=0.873$, $p=0.128$) nor did Matsuda index ($\beta=0.127$, $p=0.578$) after adjustment, indicating that none of the measures were independently associated with GIR. *For the entire cohort*, after adjustment, HOMA-IR ($\beta=-1.00$, $p=0.018$) and e-IS ($\beta=1.229$, $p=0.022$) were still significantly associated with GIR.

The ROC curve analyses showed that e-IS was the best predictor for IR in both groups, with IR defined as GIR below the median for group (13.5 mg/kgFFM/min in the PCOS cohort). For the HOMA-IR, the area under the ROC curve in the PCOS and control group was 0.88 and 0.76, respectively. e-IS had the largest area under the ROC curve of 0.90 and 0.77 respectively for the PCOS and control group (PCOS shown in figure 2A). For Matsuda index, the area under the ROC curve was 0.74 and 0.73, respectively. The PCOS cohort only ROC curves in Figure 2A were used to identify optimal cut-off points of e-IS index for prediction of GIR above or below the median. In the PCOS group, a cutoff of less than 6.3 provided the best sensitivity (100%) and specificity (74%) for prediction of GIR below the median.

Table 3 shows a sub-analysis of the PCOS group, divided by IGT status. Nine of the girls with PCOS (7 obese, 2 normal BMI percentile) had IGT with a 2-hour blood glucose >140 mg/dL. The only measures that were different in girls with IGT compared to normal glucose tolerance (NGT) were fasting ($p=0.030$) and 2-hour OGTT insulin concentrations on the day of the OGTT ($p<0.001$). Thus, OGTT-day measurements that utilize fasting insulin including HOMA-IR, FGIR, QUICKI and Matsuda were also significantly different between the groups. However, there was no differences between groups in insulin values the day of the clamp. No surrogates of IR were different between the groups, including GIR. No surrogate measure of IR correlated with 2-hour glucose concentration by Spearman's analysis (data not shown). ROC analysis for fasting insulin, HOMA-IR, and QUICKI were all similar, with AUC for all between 0.760, $P=0.03$. For fasting insulin, a cut-off of 22 IU/mL had a sensitivity of 84% and a specificity of 78% for predicting IGT at 2 hours. HOMA- β was also a strong predictor of IGT status (AUC 0.737, $p=0.046$).

Discussion:

We identified the strongest of the available surrogate measures of peripheral IR and IGT in adolescents with PCOS. We found that an e-IS score of less than 6.3, an index derived from waist circumference, fasting TG concentrations and HbA_{1c} , was the best predictor for detecting severe IR in PCOS girls with ROC analysis. The fasting insulin was related to 2 hour glucose concentrations, and had the best sensitivity and specificity to predict IGT status, however, the translatability of our absolute cutoff value to other sites is challenging, due to non-standardization of the insulin assay. Thus, whereas we identified a good, simple to use surrogate measure to identify IR in adolescents with PCOS, the measure for IGT in these girls has some caveats precluding its universal use.

It is not surprising that the e-IS gave the best prediction for low GIR in our patient cohort. e-IS is a formula that was designed specifically for estimating insulin sensitivity in adolescents with and without diabetes across the entire glycemic spectrum (22). The other measures were developed in adults, who do not have the confounding effects of puberty-induced IR in addition to obesity, PCOS and/or diabetes. Our results are the first application of this formula and showed that this formula is applicable as well in non-diabetic but IR cohorts (PCOS and obese adolescents). Although e-IS had the same sensitivity and specificity for estimating IR in the PCOS group as HOMA-IR, this formula with its easy-to-obtain parameters has an advantage over HOMA-IR in terms of cost and adaptability in routine

clinical measures (HbA_{1c} and TG are already recommended in this patient population and waist circumference adds no additional cost). Further, each component of e-IS relates to IR or glycemia in PCOS. Park et al. found that fasting TG highly correlated with HOMA-IR and was a good indicator of IR in their study of 458 PCOS Korean women (19). Waist circumference has been shown in previous studies to be correlated in IR in non-diabetic women (37). The third parameter, HbA_{1c}, can reflect early changes in glycemia, due to a combination of IR and β -cell insulin secretion (38). Finally, as seen in Table 3, measures of glucose and insulin can change acutely with changes in diet and thus HOMA score can vary from day to day, whereas measures of TG and HbA_{1c} are more stable. However, e-IS did not distinguish IR differences between PCOS and non-PCOS groups which may be due to the referral bias of the obese girls in the control group, several of who were referred for evaluation of hypertriglyceridemia (30%) and thus have a higher TG than typically seen. In a research setting where diet, activity and insulin assays are controlled, HOMA-IR may provide better discriminatory power. e-IS raises the new possibility of detecting severe IR in PCOS adolescents in a cost-efficient, accurate, and clinically feasible setting from just a fasted blood sample.

Triglyceride-based models of IR have a benefit of less assay variability, and have been utilized in multiple populations. The TG:HDL correlated with Matsuda calculated IR from an OGTT in adults with PCOS (6). In adolescents, Mohd Nor et al. found that the TyG index as a surrogate measure of IR significantly associated with clamp measurements of IR in 225 obese children, although the correlation coefficient with clamp GIR was lower at $r = -0.419$ (35). We did not find that the TG:HDL ratio or TyG were as useful in youth with PCOS, perhaps due to the fact that HDL is nearly universally low in sedentary obese youth with PCOS, and fasting glucose concentrations also were in the normal range with little variability in our cohort. This measure may have greater variability in a cohort with more range in physical activity and thus HDL.

Insulin-based models have been shown in multiple populations to predict GIR. HOMA-IR is the most widely used and generally accepted way of estimating IR in all types of patient populations (15, 31). Nonetheless, this index has a large CV, and is not ideally suited for individual clinical care calculations (31). We did find that HOMA-IR did have a stronger simple correlation with GIR and had a significant difference between groups, yet the ROC analysis for predicting disease was not as strong. As an alternative, the fasting glucose to insulin ratio has been proposed to be a simple and useful surrogate measure for IR in populations of prepubertal children and adult PCOS patients. Silfen et al studied 25 prepubertal girls with premature adrenarche (PA) and found that FGIR highly correlated with OGTT measures of IR (39). In a similar study FGIR was shown to be closely correlated to the frequently sampled intravenous glucose tolerance test (FSIVGTT) in 33 prepubertal girls with PA(40). Legro et al. also validated the use of FGIR in measuring IR of adult PCOS patients in their study of 40 PCOS non-Hispanic white women (16). Our results show that FGIR did correlate with GIR in the PCOS group (data not shown, $r=0.49$, $p=0.008$) and in the entire cohort (data not shown, $r=0.37$, $p=0.010$). However, GIR did not correlate as strongly as some of our other measures and the use of FGIR requires insulin assay with the limitations discussed above.

It has been more challenging to find good surrogate markers for predicting those with IGT on an OGTT, regardless of PCOS status (27–29). Part of the challenge likely relates to the poor reproducibility of an OGTT in any one individual, especially in youth, as well as daily variability in fasting insulin (41, 42). This was again demonstrated in our data set, with variability in glucose and insulin measurements from clamp and OGTT days, likely secondary to difference in preparation for study days. The OGTT was done “free living” whereas the clamp was preceded by 72 hours of no activity and a controlled diet. Unfortunately, the only markers that were related to IGT were the fasting insulin from the OGTT days and 2 hour insulin concentrations, as well as surrogate markers that include fasting insulin in their calculations. These associations have been reported in adult women with PCOS, so this finding is consistent across the age span, and not unique to adolescents (23–26). IGT reflects the ultimate combination of both IR, but more importantly, relative pancreatic β -cell insufficiency (41, 42). Similar to results found in adults with pre-diabetes, and in youth with a spectrum of glycemia, we also found that HOMA- β predicted IGT. Notably, there was no relationship with HbA_{1c} and IGT status in our patients, likely due to the fact that HbA_{1c} relates more to overall average glucose, rather than a response to 75 grams of glucose (43). Thus, similar to adults with and without PCOS, fasting insulin is a moderately accurate marker for IGT status.

Our study has several strengths and weaknesses. As opposed to nearly all studies conducted in youth with PCOS to-date, we compared surrogate indices with peripheral IR as measured by GIR from the gold-standard clamp rather than another 2 hour OGTT derived index. This allowed better evaluation of the accuracy of these indices. We also have a cohort of participants from a diverse background with various ethnicities and varying family history of PCOS. Moreover, our PCOS and control groups were well-matched and studied in a well-controlled setting. However, it is important to note that the sample size is relatively small, which poses challenges as multiple linear regression tests to examine the correlation and ROC between surrogate indices may have been underpowered. We also did not collect data on acanthosis nigricans, another clinical marker of IR. Further, the generalizability of the findings are limited by the sedentary nature of the participants, 80% of the girls were overweight or obese, and as discussed, the obese girls in the “control” group likely have more features of the metabolic syndrome than are typical for the general obese population in the United States.

In conclusion, we found that the e-IS formula, utilizing standardized measurements, is the best predictor of severe IR in PCOS adolescents. The cutoff value of the e-IS formula for predicting GIR above vs. below the median value was 6.3 for adolescents with PCOS. Waist circumference, TG, and HbA_{1c} are parameters that can be easily obtained in clinic. Furthermore, e-IS is capable of being adapted into routine clinical use and large epidemiology studies. In terms of IGT, fasting insulin was the best predictor, although our cut-off of 22 IU/ml is specific to our assay. These markers may be useful tools for early detection of IR and IGT in PCOS adolescents and may allow for more effective prevention of diabetes and CVD in this population.

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Abbreviations:

IR	Insulin Resistance
PCOS	Polycystic Ovarian Syndrome
OGTT	Oral glucose tolerance test
GIR	Glucose Infusion Rate
BMI	Body Mass Index
TG	Triglyceride
HDL-C	High Density Lipoprotein Cholesterol
ROC	Receiver Operating Characteristic
T2DM	Type 2 Diabetes Mellitus
IGT	Impaired Glucose Tolerance
FGIR	Fasting Glucose to Insulin Ratio
TyG	Triglyceride Glucose Index
PA	Premature Adrenarche
FSIVGTT	Frequently Sampled IV Glucose Tolerance Test
eIS	Estimate of Insulin Sensitivity
FAI	Free Androgen Index

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Figure 1: GIR related to surrogate measures of IR

The relationships between measures of GIR from a clamp, and surrogate measures of insulin sensitivity including A) HOMA B) Search-IR and C) Matsuda score are shown in the PCOS cohort.

A: IR surrogates as predictors of low GIR **B: Fasting surrogates for IGT status**

Figure 2:
ROC to detect IR and IGT

Table 1.

Descriptive Statistics of Study Participants Stratified by Group

Characteristics	PCOS (n = 28)	Control (n = 20)	P values
Age (years)	15.5 (14.5, 16.6)	15.5 (13.3, 16.1)	0.340
BMI percentile	98 (83, 99)	97 (88, 99)	0.497
BMI Z-score	1.9 (1.0, 2.3)	1.8 (1.1, 2.1)	0.291
Non-overweight/obese BMI n (%)	6 (21)	3 (15)	0.588
Ethnicity			
Caucasian n (%)	11 (39)	9 (45)	
Hispanic n (%)	14 (50)	6 (30)	
Black n (%)	3 (11)	5 (25)	
Menarche Age (years)	12 (11, 12)	11 (10, 12)	
Menses per year	4 (2,6)	12 (11,13)	<0.001
Hirsutism (Ferriman-Gallwey Score)	5 (3, 8)	2 (1, 3)	0.019
Total Testosterone (ng/dl)	44.0 (33.0, 58.5)	27.7 (23.3, 45.5)	0.016
Sex hormone binding globulin (nmol/L)	22.1 (14.2, 30.5)	31.1 (14.9, 38.4)	0.291
Free Androgen Index	6.76 (3.93, 9.96)	3.65 (3.14, 4.01)	0.003
Anti-mullerian hormone (ng/mL)	7.5 (4.6, 10.3)	2.9 (2, 4.9)	0.005

Table 2.**Measurements and Surrogate Indices Stratified by Group**

Characteristics	PCOS (n = 28)	Control (n = 20)	P values
<i>Measurements</i>			
Waist circumference (cm)	96 (84, 106)	88 (82, 98)	0.164
HbA _{1C} (%)	5.3 ± 0.3	5.2 ± 0.2	0.275
Fasting glucose OGTT (mg/dL)	85 ± 8	84 ± 8	0.615
Fasting glucose Clamp (mg/dL)	86 ± 4	86 ± 5	0.929
Fasting insulin OGTT (IU/mL)	17 (13, 30)	15 (10, 24)	0.420
Fasting insulin Clamp (IU/mL)	20 (12, 26)	16 (9, 21)	0.098
2hr insulin (OGTT) (IU/mL)	152 (95, 351)	101 (48, 159)	0.025
2hr glucose (OGTT) (mg/dL)	128 ± 23	107.90 ± 26	0.005
C-peptide (ng/mL)	2.6 (1.8, 3.3)	2.3 (1.8, 3.3)	0.605
TG (mg/dL)	118 (72, 143)	98 (81, 174)	0.693
HDL (mg/dL)	37 (33, 44)	40 (35, 46)	0.486
Adiponectin (ng/mL)	6.4 ± 2.6	8.6 ± 2.9	0.026
GIR (mg/kgFFM/min)	12.9 ± 4.6	17.1 ± 5.1	0.005
<i>Calculations</i>			
HOMA-IR (clamp)	4.14 (2.77, 5.50)	3.17 (1.93, 4.30)	0.103
HOMA-IR (OGTT)	3.65 (2.75, 6.12)	3.28 (2.10, 5.28)	0.419
QUICKI (clamp)	0.31 (0.30, 0.33)	0.32 (0.31, 0.35)	0.103
QUICKI (OGTT)	0.32 (0.30, 0.33)	0.32 (0.30, 0.34)	0.419
FGIR (clamp)	4.26 (3.42, 6.67)	5.60 (4.26, 8.78)	0.093
FGIR (OGTT)	4.65 (2.82, 6.96)	5.07 (3.78, 7.98)	0.396
TyG index (clamp)	3.69 (3.50, 3.78)	3.62 (3.54, 3.87)	0.655
TyG index (OGTT)	3.66 (3.50, 3.78)	3.60 (3.50, 3.87)	0.860
Matsuda Index	5.43 (3.06, 7.50)	7.34 (5.11, 15.81)	0.027
Stumvoll Index	0.03 (-0.04, 0.06)	0.04 (0.01, 0.09)	0.058
TG:HDL	2.87 (1.52, 4.27)	2.42 (1.83, 6.23)	0.763
e-IS	7.03 (5.04, 8.81)	7.65 (5.15, 9.91)	0.655

Table 3.

Biomarkers and Fasting Surrogate Indices in PCOS Cohort Stratified by IGT Status

Characteristics	PCOS NGT (n = 19)	PCOS IGT (n = 9)	P values
<i>Measurements</i>			
2hr glucose (OGTT) (mg/dL)	117 ± 17	151 ± 15	<0.001
BMI percentile	98 (83, 99)	97 (73, 99)	0.902
Waist circumference (cm)	93 ± 15	96 ± 15	0.605
FAI	6.6 (3.7, 9)	8.7 (2.9, 18.6)	0.386
HbA _{1C} (%)	5.2 ± 0.5	5.2 ± 0.5	0.636
Fasting glucose OGTT (mg/dL)	83 (79, 90)	86 (81, 88)	0.786
Fasting glucose Clamp (mg/dL)	86 ± 4	85 ± 4	0.597
Fasting insulin OGTT (IU/mL)	15 (13, 21)	31 (16, 47)	0.030
Fasting insulin Clamp (IU/mL)	19 (11, 24)	24 (13, 27)	0.431
2hr insulin (OGTT) (IU/mL)	125 (91, 272)	427 (131, 518)	<0.001
C-peptide (ng/mL)	2.6 ± 0.9	2.6 ± 1.3	0.974
GIR (mg/kgFFM/min)	12.8 ± 4.3	13.0 ± 5.4	0.942
TG (mg/dL)	109 ± 42	111 ± 56	0.919
HDL (mg/dL)	37 (31, 44)	35 (34, 47)	0.863
Adiponectin (ng/mL)	6.9 ± 2.5	5.3 ± 2.7	0.129
<i>Calculations</i>			
HOMA-IR (clamp)	3.9 (2.4, 5.5)	5.0 (2.6, 5.6)	0.555
HOMA-IR (OGTT)	3.1 (2.7, 4.2)	6.6 (3.2, 10.9)	0.030
QUICKI (clamp)	0.32 ± 0.03	0.32 ± 0.03	0.845
QUICKI (OGTT)	0.32 (0.31, 0.33)	0.29 (0.26, 0.33)	0.030
FGIR (clamp)	4.4 (3.6, 7.5)	3.5 (3.0, 7.5)	0.431
FGIR (OGTT)	5.5 (4.4, 7.5)	2.7 (2.0, 6.3)	0.044
TyG index (clamp)	3.6 ± 0.2	3.6 ± 0.2	0.898
TyG index (OGTT)	3.6 ± 0.2	3.6 ± 0.2	0.989
HOMA-β (clamp)	125 (94, 178)	164 (105, 227)	0.461
HOMA-β (OGTT)	117 (81, 152)	223 (131, 294)	0.047
TG:HDL	3.1 ± 1.6	3.0 ± 1.8	0.926
Matsuda	5.9 (4.7, 7.6)	2.6 (2.1, 7.3)	0.024
e-IS	7.0 (4.6, 9.2)	7.1 (5.6, 10.0)	0.731