Alterations in Glucose Effectiveness and Insulin Dynamics: Polycystic Ovary Syndrome or Body Mass Index

Patricia Vuguin^a Aviva B. Sopher^a Hailey Roumimper^a Vivian Chin^a
Miriam Silfen^a Donald J. McMahon^b Ilene Fennoy^a Sharon E. Oberfield^a

^aDivision of Pediatric Endocrinology, Children's Hospital of New York-Presbyterian, Columbia University College of Physicians and Surgeons, New York, NY, USA; ^bDivision of Endocrinology, Department of Medicine, Columbia University College of Physicians and Surgeons, New York Presbyterian/Columbia University Medical Center, New York, NY, USA

Keywords

Polycystic ovary syndrome in adolescents ·
Insulin resistance · Metabolic dysregulation ·
Glucose effectiveness · Metabolic syndrome

Abstract

Background/Aims: To delineate the relationship of polycystic ovary syndrome (PCOS), obesity, and hyperandrogenism (HA) with glucose and insulin dynamics in adolescents across a broad body mass index (BMI). **Methods:** Seventy-four PCOS subjects (aged 16 years) and 82 controls (aged 16 years) were evaluated by an oral glucose tolerance test. Subjects were categorized by BMI: normal weight (21 ± 0.4), overweight/obesity (OO; 33 ± 1.0), and severe obesity (SO; 48 ± 1.4). Indices of glucose and insulin dynamics were determined. Multiple linear regression analysis was used to evaluate the contribution of PCOS, HA, and BMI to these indices. **Results:** BMI was significantly associated with systolic and diastolic blood pressure and insulin resistance. A significant interaction between BMI and PCOS and indices of post-glucose load was observed. The mean difference in peak glucose, early glucose response, area under the curve for glucose, and glucose effectiveness (S_{gl}) between PCOS and control subjects was significantly different between OO and SO. In PCOS subjects,

testosterone was positively associated with BMI, fasting insulin, early insulin response, and diastolic blood pressure, and negatively associated with S_{gl} . **Conclusions:** Abnormal glucose dynamics in adolescents with PCOS is mainly due to SO. The combination of PCOS and SO has a synergistic effect on glucose dynamics when compared to all other groups.

© 2017 S. Karger AG, Basel

Introduction

Polycystic ovary syndrome (PCOS) affects 6–15% of reproductive-age women [1] and accounts for 72–84% of hyperandrogenism (HA) in women [2, 3]. In adolescents, PCOS is associated with a 50% reduction in insulin sensitivity (IS) [4, 5] and a higher rate of the metabolic syndrome (10%) than in controls (1.7%) [6]. Similarly, insulin resistance (IR) and a greater glucose area under the curve (G_{AUC}) are seen in obese adolescents with PCOS when compared to their lean counterparts [7, 8].

The origin of metabolic dysfunction in PCOS subjects is still being delineated. HA, obesity, and IR have all been

P. Vuguin and A.B. Sopher contributed equally to this paper.

implicated in this role. HA may confer IR and metabolic inflammation [9, 10], and the odds of having metabolic syndrome are almost 4 times greater for every quartile increase in testosterone adjusting for BMI and IR [11]. Even lean PCOS subjects are at an elevated risk of metabolic disease compared with lean controls [9, 12]. This relationship becomes more complicated in obese PCOS subjects as obesity seems to be the major factor that leads to the development of the metabolic syndrome in obese PCOS subjects rather than HA subjects [13]. In fact, obesity is strongly associated with the metabolic syndrome in adolescents independent of their PCOS diagnosis [14]. A recent study further demonstrated that the risk of type 2 diabetes mellitus (T2DM) in women with PCOS is mainly attributable to their overweight/obesity status and that weight gain during early adulthood significantly increased the risk of developing abnormal glucose metabolism [15].

The aim of this study was to examine adolescents and young women with PCOS over a wide range of body mass indices (BMI) in order to refine our understanding of the relationship of PCOS and BMI with glucose and insulin dynamics assessed by an oral glucose tolerance test (OGTT) using validated indices of glucose and insulin action. The overall goal is to explore these relationships as well as to evaluate the presence of an independent contribution of PCOS status or BMI toward the development of metabolic disease.

Materials and Methods

Subjects

We studied an ethnically diverse group of 156 adolescents and young women with and without PCOS who were recruited between January 2004 and May 2014. PCOS and control subjects were recruited from pediatric endocrinology, bariatric, and adolescent clinics and practices at Columbia University Medical Center (CUMC) as well as by posted flyers, social media, and Listserv postings. PCOS subjects and controls (13–22 years old) were at least 2 years after menarche. PCOS was diagnosed using the NIH criteria [16] in subjects who were biochemically euthyroid and without biochemical evidence of congenital adrenal hyperplasia [17]. Exclusion criteria included the use of medications known to affect hormone, lipid, or insulin levels at the time of enrollment. Controls had regular menses and absence of clinical (hirsutism) or biochemical HA (normal testosterone levels). Seventy-four subjects with PCOS aged 16 ± 0.2 years (BMI 17–64) and 82 controls aged 16 ± 0.1 years (BMI 18–56) were divided into 6 groups based on their BMI, because data have shown that the more severe forms of obesity are associated with greater risks for complications: (1) normal-weight PCOS subjects (NW-PCOS) and controls (NW-C); BMI <25; (2) overweight/obese PCOS subjects (OO-PCOS) and controls (OO-C); BMI 25 to <40; (3) severely obese PCOS subjects (SO-PCOS) and controls (SO-C); BMI ≥ 40 [18].

Informed consent was obtained from a legal guardian of each subject aged <18 years and from subjects ≥ 18 years. The protocols were approved by the Institutional Review Board of CUMC.

Biochemical Analysis

Basal levels of glucose (G_0), insulin (I_0), testosterone, and HbA_{1c} were measured after an overnight fast. Glucose was assayed by the glucose hexokinase method. Insulin was measured via chemiluminescence, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were assessed by electrochemiluminescent assay and testosterone by high-performance liquid chromatography with tandem mass spectrometry (Esoterix, Inc., Calabasas Hills, CA, USA). Glucose and HbA_{1c} analyses were performed at the laboratory of New York Presbyterian Hospital.

Assessment of IS, Insulin Secretion, β -Cell Function, and Glucose Effectiveness

A 75-g 2-h OGTT was performed after an 8-h overnight fast [8]. Sixty-seven controls (11 NW-C, 17 OO-C, and 39 SO-C) and 56 PCOS subjects (19 NW-PCOS, 16 OO-PCOS, and 21 SO-PCOS) completed the OGTT.

IR/IS were estimated by (1) the homeostasis model (HOMA-IR) and (2) the Matsuda index/whole-body IS index (ISI) [8].

Fasting and post-glucose load were estimated by (1) G_0 and I_0 ; (2) early incremental glucose response (change in glucose levels from 0 to 30 min, ΔG); and (3) total G_{AUC} integrated glucose response to an oral glucose load during 120 min by the trapezoidal method [19]; (4) time to peak for glucose (min) was defined as the time between the start of the OGTT to the highest glucose levels recorded ($Time_G$); and (5) peak glucose levels (mg/dL) were defined as the highest glucose levels during the OGTT ($Peak_G$).

Insulin secretion was estimated by (1) early incremental insulin response (change in insulin levels from 0 to 30 min, ΔI); (2) I_{AUC} integrated insulin response to an oral glucose load during 120 min using the trapezoidal method; (3) time to peak for insulin was defined as the time from the start of the OGTT to the highest insulin levels recorded ($Time_I$); and (4) peak insulin levels ($\mu UI/mL$) were defined as the highest insulin levels during the OGTT ($Peak_I$).

β -cell function was estimated by (1) the disposition index (DI_0) relationship between IS and first-phase insulin secretion; and (2) the Insulin Secretion Sensitivity Index-2 (ISSI-2), the relationship between whole-body IS and I_{AUC} and G_{AUC} [20].

Glucose effectiveness (SgI_0) determines the capacity of glucose to enhance its own cellular uptake and to suppress endogenous glucose production, as formulated by Nagasaka et al. [21]:

$$\frac{[PPG - \text{without insulin and } Sg] - [PPG - \text{without insulin and with } Sg] \times \left[\frac{2hPG}{2hPG_E} \right]}{120},$$

where PPG = post-loading plasma glucose, Sg = glucose effectiveness, 2hPG = 2-h post-glucose PG, and 2hPG_E = expected 2hPG. “PPG-without insulin and Sg” was calculated using:

$$\text{fasting plasma glucose} \left(FPG, \frac{mg}{dL} \right) + \frac{[0.75 \times 75,000]}{[0.19 \times \text{body weight (kg)} \times 10]}.$$

Table 1. Clinical characteristics of PCOS subjects and controls

	Controls (<i>n</i> = 82)	PCOS subjects (<i>n</i> = 74)
Age, years	16.2±0.24	16.2±0.5
BMI	37.3±1.0	34.5±1.0
Age at menarche, years	11.8±0.3	11.6±0.2
Years after menarche	4.2±0.2	4.6±0.2
Ethnicity, <i>n</i>		
Caucasian	30	26
Hispanic	30	32
African American	8	3
Asian American	11	10
Other	3	3
Diastolic blood pressure, mm Hg	71±1	70±1
Systolic blood pressure, mm Hg	115±1	112±1
Fasting glycemia (<i>G</i> ₀), mg/dL	86±0.9	86±1.9
Fasting insulin levels (<i>I</i> ₀), µUI/mL	15.9±1.7	18.1±1.7
HbA _{1c} , %	5.3±0.1	5.3±0.1
FSH levels, µUI/mL	5.3±0.3	5.4±0.2
LH levels, µUI/mL	8.5±1.4	10.1±0.7
Testosterone, ng/dL	29.7±2.5 ^b	52.4±2.4 ^a

All data are presented as mean ± SE, unless otherwise indicated. Data points which are significantly different from PCOS and controls are denoted by different letters (a, b) ($p < 0.001$). PCOS, polycystic ovary syndrome; BMI, body mass index; *G*₀, basal level of glucose; *I*₀, basal level of insulin; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

Data Analysis

Continuous data were presented as means ± SD. Student *t* tests were used to compare the means of the continuous variables between the PCOS and control groups. Of note, subjects diagnosed with diabetes were excluded from the analysis ($n = 1$ PCOS subject). In PCOS subjects, relationships between testosterone levels and indices of glucose and insulin dynamics were evaluated by bivariate analysis. For continuous outcomes, multiple linear regression models were fitted to compare the PCOS and control groups adjusting for BMI as categorical variable (NW, OO, and SO). We first tested the interaction between PCOS status and BMI, then removed the interaction when the interaction was found to be not significant. Parameter estimates from the multiple regression model were reported as well as SE, *p* value, and 95% confidence intervals. With a sample size of 74 PCOS subjects and 82 controls, the study had 80% power and 5% two-tailed α level to detect a 0.45 standardized difference between the groups. Statistical analyses were performed using JMP IN version 7.0.2 software and SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Clinical Characteristics

The clinical and metabolic characteristics of PCOS subjects and healthy controls are presented in Table 1. PCOS and control subjects did not differ significantly in age,

BMI, age of menarche, and years after menarche. Of the PCOS subjects, 35% were Caucasian, 43% Hispanic, 13% Asian American, 4% African American, and 4% were multiracial or other. Of the controls, 37% were Caucasian, 35% Hispanic, 10% African American, 13% Asian American, and 4% other. Ethnicity did not impact age of menarche ($p > 0.1$), BMI ($p > 0.7$), PCOS status ($p > 0.6$), testosterone levels ($p > 0.4$), or any of the glucose or insulin indices described below ($p > 0.5$). Similarly, no differences were seen in blood pressure, *G*₀, *I*₀, HbA_{1c}, LH, and FSH levels between PCOS and control subjects. As expected, all PCOS subjects as a group exhibited higher serum testosterone when compared to all controls as a group ($p < 0.001$).

Of the PCOS subjects, 4% (3 of 74) had glucose dysfunction including impaired fasting glucose (IFG) (2.7%) and diabetes (1.3%). Similar to PCOS subjects, 3% of the controls had IFG (3 of 82) but none had diabetes. Impaired glucose tolerance (IGT) occurred in 15% of PCOS subjects and 1.4% of controls ($p < 0.003$). Time_I occurred, on average, 12 min later in SO-PCOS subjects when compared to NW-PCOS subjects and 13 min later than in SO-C. Time_G occurred, on average, 5 min later in SO-PCOS subjects when compared to NW-PCOS subjects and 7 min later than in SO-C ($p = \text{ns}$) (Fig. 1).

Fig. 1. Glucose (**a**) and insulin (**b**) response during oral glucose tolerance test in polycystic ovary syndrome (PCOS) and control subjects divided into 6 groups based on their body mass index (BMI): normal-weight PCOS subjects (NW-PCOS) and controls (NW-C): BMI <25; overweight/obese PCOS subjects (OO-PCOS) and controls (OO-C): BMI 25 to <40; severely obese PCOS subjects (SO-PCOS) and controls (SO-C): BMI ≥40.

In all PCOS subjects, higher testosterone levels were associated with higher BMI ($p = 0.0141$), I_0 ($p = 0.018$), ΔI ($p = 0.0083$), HOMA-IR ($p = 0.036$), and diastolic blood pressure (DBP) ($p = 0.015$), and with lower SgI_0 ($p = 0.048$). Based on multiple linear regression analyses, ΔI ($p = 0.005$) and DBP ($p = 0.004$) were significantly related to testosterone levels independent of BMI.

BMI Had a Significant Impact on Blood Pressure

Table 2 shows the results from multivariable general linear models. Severe obesity was associated with higher

systolic blood pressure (difference in means, 11.73 ± 2.54 mm Hg, $p < 0.001$, and 6.29 ± 2.87 mm Hg, $p = 0.031$) and DBP (difference in means, 10.47 ± 2.09 mm Hg, $p < 0.0001$, and 5.55 ± 2.39 mm Hg, $p < 0.022$) when compared to NW-PCOS and NW-C and OO-PCOS and OO-C subjects, respectively. PCOS status did not affect blood pressure.

BMI Had a Significant Impact on Indices of IS/IR

Table 2 shows the results from multivariable general linear models. As expected, SO status was associated with higher HOMA-IR (difference in means, 2.27 ± 0.67 , $p = 0.001$) when compared to NW-PCOS and NW-C subjects and lower ISI (difference in means, 6.63 ± 2.22 , $p = 0.003$) when compared to NW-PCOS subjects and NW-C. PCOS status did not affect indices of IS/IR.

BMI and PCOS Status Had a Significant Impact on Indices of Post-Glucose Load

Table 3 shows the results from multivariable general linear models. As expected, NW-PCOS and OO-PCOS subjects had a lower risk of having abnormal post-glucose load indices determined by an OGTT than SO-PCOS subjects. Whereas PCOS status was found to be a significant predictor of $Peak_G$, ΔG , and G_{AUC} , the interaction between the presence of PCOS and BMI was statistically significant. Thus, the mean difference in $Peak_G$, ΔG , and G_{AUC} between PCOS and controls was significantly different between OO and SO subjects.

NW subjects had lower I_{AUC} when compared to SO subjects independent of their PCOS status (difference in means, 122.54 ± 61.34 , $p = 0.048$). Similarly, PCOS status was associated with higher I_{AUC} (difference in means, 103.94 ± 51.50 , $p = 0.046$) independently of BMI status. On average, neither PCOS nor BMI independently or together significantly impacted ΔI , DI , and $ISSI-2$ indices (data not shown).

Figure 2 shows the average and SE differences across all BMI categories in both PCOS and control subjects for the indices of $Peak_G$, ΔG , G_{AUC} , and I_{AUC} , although the multivariable analyses described in Table 3 represent the statistical differences between individual categories.

BMI and PCOS Status Had a Significant Impact on Glucose Effectiveness

Figure 3 shows the results from multivariable general linear models. For each unit increase in BMI, SgI_0 decreased on average by 0.09 for both the PCOS and control group ($p < 0.0001$). That relationship is exacerbated in the SO-PCOS and SO-C groups in which SgI_0 decreased on

Table 2. Multiple regression model showing the effect of BMI on fasting and post-OGTT indices of carbohydrate metabolism and blood pressure in PCOS subjects and controls divided into 6 groups based on their BMI

Outcome	Parameter	Estimate	SE	<i>t</i> value	Pr > <i>t</i>	95% CI
HOMA-IR	Intercept	3.61	0.45	8.00	<0.0001	2.71 to 4.50
	PCOS+	0.85	0.54	1.58	0.117	−0.21 to 1.91
	BMI NW vs. SO	−2.27	0.67	−3.39	0.001	−3.59 to −0.95
	BMI OO vs. SO	0.96	0.62	1.56	0.120	−0.25 to 2.18
DI (1/[mmol/L] ² × [pmol/L] ² × [μUI/mL])	Intercept	12.58	3.40	3.70	0.000	5.84 to 19.32
	PCOS+	−8.03	4.35	−1.85	0.067	−16.64 to 0.58
	BMI NW vs. SO	7.61	5.21	1.46	0.147	−2.72 to 17.94
	BMI OO vs. SO	−2.99	5.14	−0.58	0.563	−13.18 to 7.21
ISI (1/[mmol/L] ² × [pmol/L] ²)	Intercept	6.71	1.41	4.75	<0.0001	3.91 to 9.50
	PCOS+	−2.52	1.81	−1.39	0.168	−6.11 to 1.08
	BMI NW vs. SO	6.63	2.22	2.99	0.003	2.23 to 11.03
	BMI OO vs. SO	−0.08	2.15	−0.04	0.970	−4.34 to 4.18
Systolic blood pressure	Intercept	118.90	1.56	76.20	<0.0001	115.80 to 122.00
	PCOS+	−1.55	2.15	−0.72	0.474	−5.82 to −2.73
	BMI NW vs. SO	−11.73	2.51	−4.68	<0.0001	−16.71 to −6.75
	BMI OO vs. SO	−6.29	2.87	−2.19	0.031	−11.99 to −0.58
Diastolic blood pressure	Intercept	74.24	1.30	57.15	<0.0001	71.66 to 76.82
	PCOS+	0.58	1.79	0.32	0.749	−2.98 to 4.13
	BMI NW vs. SO	−10.47	2.09	−5.01	<0.0001	−14.61 to −6.32
	BMI OO vs. SO	−5.55	2.39	−2.32	0.022	−10.30 to −0.80

Normal weight (NW), BMI <25; overweight/obese (OO), BMI 25 to <40; severely obese (SO), BMI ≥40. Parameter estimates from the multiple regression model are reported as SE, *p* values, and 95% confidence intervals (CI). BMI, body mass index; OGTT, oral glucose tolerance test; PCOS, polycystic ovary syndrome; DI, disposition index; ISI, Matsuda index.

average by 2.27 when compared to NW-PCOS subjects and NW-C (*p* = 0.001).

Interestingly, PCOS status had a significant relationship with SgI₀ when the BMI was >36.76. The combination of PCOS and a BMI >36.76 explained 88% of the variance in SgI₀ (*r*² = 0.88; *p* < 0.0001). This hyperbolic relationship demonstrated that SgI₀ was significantly lower in PCOS subjects as compared to controls when the BMI was >36.76 consistent with the premise of declining SgI₀ in SO-PCOS subjects.

Discussion

In this relatively large, ethnically diverse group of adolescents and young adults with and without PCOS who span a wide range of BMIs, the interaction between SO and PCOS together is associated with impaired glucose dynamics, specifically higher post-load glucose levels

(Peak_G, ΔG, and G_{AUC}) and decreased SgI₀. This study suggests that SO-PCOS subjects are metabolically different than OO-PCOS subjects when compared to OO-C and SO-C and proposes that SO-PCOS adolescents and young adults are in a unique risk group for the development of abnormalities in glucose and insulin dynamics.

Several studies have tried to address whether PCOS or HA are independent risks factor for developing metabolic disease [10, 11, 22], or whether this is simply a synergistic effect between PCOS-HA and BMI [23, 24], or even if the risk is only related to obesity.

In our study, the presence of PCOS was associated with higher I_{AUC}, an index of IR and insulin response to a glucose load. This increase in insulin concentrations after glucose load seen in PCOS subjects may be due to an increase of insulin secretion by the pancreas or a delay in insulin degradation. Similar findings have been seen in nonobese subjects with PCOS, again suggesting that PCOS is an independent risk factor for the development

Table 3. Multiple regression model showing the effect of BMI and PCOS on post-OGTT indices of carbohydrate metabolism in PCOS subjects and controls divided into 6 groups based on their BMI

Outcome	Parameter	Estimate	SE	<i>t</i> value	Pr > <i>t</i>	95% CI
Peak _G (mg/dL)	Intercept	131.08	4.29	30.54	<0.0001	122.58 to 139.58
	PCOS+	28.83	7.26	3.97	0.0001	14.46 to 43.20
	BMI NW vs. SO	-0.26	9.15	-0.03	0.978	-18.38 to 17.86
	BMI OO vs. SO	3.51	7.79	0.45	0.653	-11.92 to 18.94
	PCOS+ × BMI NW vs. SO	-18.54	12.48	-1.49	0.140	-43.26 to 6.18
	PCOS+ × BMI OO vs. SO	-26.36	11.71	-2.25	0.026	-49.55 to -3.16
ΔG (0–30 min)	Intercept	39.45	3.74	10.56	<0.0001	32.05 to 46.84
	PCOS+	25.50	6.36	4.01	0.0001	12.90 to 38.10
	BMI NW vs. SO	2.22	7.02	0.32	0.753	-11.69 to 16.12
	BMI OO vs. SO	-0.98	6.72	-0.15	0.885	-14.28 to 12.33
	PCOS+ × BMI NW vs. SO	-24.82	10.12	-2.45	0.016	-44.85 to -4.79
	PCOS+ × BMI OO vs. SO	-23.33	10.14	-2.30	0.023	-43.41 to -3.24
G _{AUC} (mg × h/dL)	Intercept	439.10	15.13	29.02	<0.0001	409.13 to 469.07
	PCOS+	92.01	25.51	3.61	0.001	41.49 to 142.52
	BMI NW vs. SO	-74.90	27.62	-2.71	0.008	-129.61 to -20.19
	BMI OO vs. SO	16.43	26.46	0.62	0.536	-35.98 to 68.84
	PCOS+ × BMI NW vs. SO	-16.28	39.82	-0.41	0.683	-95.14 to 62.58
	PCOS+ × BMI OO vs. SO	-95.69	40.28	-2.38	0.019	-175.47 to -15.91
I _{AUC} (μUI × h/mL)	Intercept	237.86	41.56	5.72	<0.0001	155.57 to 320.14
	PCOS+	103.94	51.50	2.02	0.046	1.97 to 205.92
	BMI NW vs. SO	-122.54	61.34	-2.00	0.048	-243.99 to -1.08
	BMI OO vs. SO	67.61	61.75	1.09	0.276	-54.66 to 189.88

Normal weight (NW), BMI <25; overweight/obese (OO), BMI 25 to <40; severely obese (SO), BMI ≥40. Parameter estimates from the multiple regression model are reported as SE, *p* value, and 95% confidence intervals (CI). BMI, body mass index; OGTT, oral glucose tolerance test; PCOS, polycystic ovary syndrome; Peak_G, peak glucose levels; ΔG, early incremental glucose response; G_{AUC}, total area under the curve for glucose; I_{AUC}, total area under the curve for insulin.

of metabolic disease [25]. To further support this hypothesis, when PCOS subjects were analyzed separately, higher testosterone levels were associated with an increased insulin release during the first 30 min of an OGTT (ΔI) independently of their BMI, suggesting that HA can be associated with IR.

Higher testosterone levels in PCOS subjects were also associated with elevated DBP. The effects of androgen level on blood pressure have been controversial [26], but a recent study has also suggested that elevated testosterone levels in a group of young women with PCOS is correlated with DBP independent of age, IR, obesity, and dyslipidemia [27].

In our study, BMI had a significant association with indices of insulin action, specifically HOMA-IR and ISI, in addition to an effect on blood pressure. This finding supports the notion that BMI status likely plays a major role in risk for metabolic disease in PCOS. Similar findings have been supported by other studies in which only

obese women with PCOS are at increased risk of T2DM [23, 28, 29].

Abnormal glucose metabolism in this relatively large ethnically diverse group of adolescents and young adults is mainly associated with SO and PCOS status. Thus, the significant interaction between the presence of PCOS and BMI is consistent with the notion that the risk of T2DM in PCOS is mainly attributable to being SO and NW-PCOS subjects are not at increased risk. Our findings do confirm that whereas PCOS is generally associated with an increased risk of T2DM development, the excess risk is largely confined to SO women [23].

The interaction of SO and PCOS leads to an increase in post-load glucose levels, specifically Peak_G, ΔG, and G_{AUC}. In addition, SO was associated with a later insulin peak in response to an OGTT when compared to other PCOS groups. SO-PCOS subjects also have a decreased capacity for glucose to enhance its own cellular uptake and to suppress endogenous glucose production, as determined by

Fig. 2. Post-meal indices of carbohydrate metabolism in polycystic ovary syndrome (PCOS) and control subjects divided into 6 groups based on their body mass index (BMI): normal-weight PCOS subjects (NW-PCOS) and controls (NW-C): BMI <25; overweight/obese PCOS subjects (OO-PCOS) and controls (OO-C): BMI 25 to <40; severely obese PCOS subjects (SO-PCOS) and controls (SO-C): BMI ≥40. All data are presented as mean ± SE for indices of peak glucose levels (Peak_G) (**a**), delta change in glucose levels (ΔG) (**b**), area under the curve for glucose (G_{AUC}) (**c**), and area under the curve for insulin (I_{AUC}) (**d**). Multivariable analyses described in Table 3 represent the statistical differences between individual categories.

Fig. 3. a Hyperbolic relationship between SgI₀ and body mass index (BMI) in adolescent subjects with polycystic ovary syndrome (PCOS) and controls. PCOS subjects have lower SgI₀ when the BMI is >36.76 (arrow) when compared to control subjects ($p = 0.01$). **b** The table represents the results of a multivariate linear regression analysis. All variables entered into the model included those with a $p < 0.15$ in univariate analysis: BMI and the diagnosis of PCOS.

Term	Estimate	SE	<i>t</i> ratio	Prob > <i>t</i>
Intercept	4.402	0.20	21.33	<0.001
BMI	-0.085	0.005	-16.65	<0.001
(BMI > 36.76) × (BMI > 36.76)	0.0027	0.0002	9.25	<0.001
(BMI > 36.76) × PCOS (yes = 1, no = 0) [1-0]	-0.018	0.0071	-2.54	0.001

b

SgI₀. The hyperbolic relationship between BMI and SgI₀ exists in both control and PCOS subjects; however, despite this similarity, PCOS subjects have lower SgI₀ when their BMI is >36 compared to their respective controls (Fig. 3). This observation suggests that the combination of SO and PCOS, both independently and in combination, increases the risk for disturbances in glucose metabolism. This is extremely important because decreased glucose effectiveness similarly to a delayed insulin release has been associated with the development of IGT or T2DM in various populations [30, 31]. Thus, the degree of obesity, altered SgI₀, and delayed insulin peak in response to a glucose load may be in part responsible for the increase in Peak_G, ΔG, and G_{AUC} seen in SO-PCOS subjects.

Our study has several strengths. This is the largest cohort of adolescents and young adults with PCOS and controls over a wide BMI range that has been assessed for abnormalities in glucose metabolism using an OGTT. Although our program represents a single center, our population is ethnically diverse and demonstrated that ethnicity did not impact the indices of glucose and insulin dynamics.

Limitations of our study include the use of OGTT-derived indices as a surrogate method of determining glucose and insulin dynamics rather than an intravenous glucose tolerance test. Although these indices have been validated against complex tests by cross-sectional analysis [32], there is concern that they may perform relatively poorly in determining subtle changes in insulin sensitivity and/or secretion.

Other studies have suggested that abnormal oral glucose tolerance and/or diabetes is present in 30–40% of PCOS women and adolescents as well [11, 22, 33–36]. In our study, only 1 subject was found to have diabetes, 3% of PCOS had IFG, and 15% had IGT. The lower rate of these disorders in our population may be related to heterogeneity of populations, age, and the PCOS diagnostic criteria used, or cohort size. Thus, if the differences between the prevalence of IGT and/or diabetes between PCOS subjects and controls are mainly dependent on the degree of obesity, our cohort is the first to demonstrate

the usefulness of determining the prevalence of IFG, abnormal OGTT, and diabetes compared to age-comparable controls. The choice of utilizing an OGTT to evaluate glucose and insulin dynamics in this cohort has given us the unique opportunity to gather clinically important information and a better understanding about the underlying physiology beyond the fasting state.

Conclusions

This study sought to delineate the intricate relationship between obesity and PCOS adolescents across a wide BMI spectrum. Whereas abnormal IS and insulin secretion were not identified in NW-PCOS subjects; alterations in glucose response to an OGTT decreased glucose effectiveness and delayed insulin secretion was observed in SO-PCOS subjects. This observation underscores the complex effects of BMI and PCOS on metabolic abnormalities. Thus, in a large cohort of ethnically diverse adolescents and young adults with PCOS who span a wide range of BMIs, we have identified that those with PCOS and who are SO are a unique group with increased risk of developing abnormalities in glucose metabolism. Future longitudinal studies are needed to better elucidate the long-term implications and potential preventive measures that may be implemented in this high-risk group.

Acknowledgments

This publication was supported by the National Center for Advancing Translational Sciences, National Institutes of Health (KL2 TR000081, A.B.S.), The Driscoll Children's Fund Award (Columbia University Medical Center, A.B.S.), a CTO/CTSA Pilot Grant (UL1RR024156, A.B.S.), and a Pediatric Endocrine Fellowship Training Grant (NIH NIDDK-T32DK065522) (PI S.E.O.).

Disclosure Statement

The authors have nothing to disclose.

References

- 1 Fauser BC, Tarlatzis BC, Rebar RW, Legro RS, Balen AH, Lobo R, Carmina E, Chang J, Yildiz BO, Laven JS, Boivin J, Petraglia F, Wijeyeratne CN, Norman RJ, Dunaif A, Franks S, Wild RA, Dumesic D, Barnhart K: Consensus on women's health aspects of polycystic ovary syndrome (PCOS): the Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group. *Fertil Steril* 2012;97:28–38.e25.
- 2 Azziz R: PCOS: a diagnostic challenge. *Reprod Biomed Online* 2004;8:644–648.
- 3 Carmina E, Azziz R: Diagnosis, phenotype, and prevalence of polycystic ovary syndrome. *Fertil Steril* 2006;86(suppl 1):S7–S8.
- 4 Alemzadeh R, Kichler J, Calhoun M: Spectrum of metabolic dysfunction in relationship with hyperandrogenemia in obese adolescent girls with polycystic ovary syndrome. *Eur J Endocrinol* 2010;162:1093–1099.

- 5 Hart R, Doherty DA, Mori T, Huang RC, Norman RJ, Franks S, Sloboda D, Beilin L, Hickey M: Extent of metabolic risk in adolescent girls with features of polycystic ovary syndrome. *Fertil Steril* 2011;95:2347–2353.e2341.
- 6 Roe AH, Prochaska E, Smith M, Sammel M, Dokras A: Using the androgen excess-PCOS society criteria to diagnose polycystic ovary syndrome and the risk of metabolic syndrome in adolescents. *J Pediatr* 2013;162:937–941.
- 7 Chin V, Censani M, Lerner S, Conroy R, Oberfield S, McMahon D, Zitsman J, Fennoy I: Gonadal dysfunction in morbidly obese adolescent girls. *Fertil Steril* 2014;101:1142–1148.
- 8 Silfen ME, Denburg MR, Manibo AM, Lobo RA, Jaffe R, Ferin M, Levine LS, Oberfield SE: Early endocrine, metabolic, and sonographic characteristics of polycystic ovary syndrome (PCOS): comparison between nonobese and obese adolescents. *J Clin Endocrinol Metab* 2003;88:4682–4688.
- 9 Fruzzetti F, Perini D, Lazzarini V, Parrini D, Genazzani AR: Hyperandrogenemia influences the prevalence of the metabolic syndrome abnormalities in adolescents with the polycystic ovary syndrome. *Gynecol Endocrinol* 2009;25:335–343.
- 10 Munzker J, Hofer D, Trummer C, Ulbing M, Harger A, Pieber T, Owen L, Keevil B, Brabant G, Lerchbaum E, Obermayer-Pietsch B: Testosterone to dihydrotestosterone ratio as a new biomarker for an adverse metabolic phenotype in the polycystic ovary syndrome. *J Clin Endocrinol Metab* 2015;100:653–660.
- 11 Coviello AD, Legro RS, Dunaif A: Adolescent girls with polycystic ovary syndrome have an increased risk of the metabolic syndrome associated with increasing androgen levels independent of obesity and insulin resistance. *J Clin Endocrinol Metab* 2006;91:492–497.
- 12 Flannery CA, Rackow B, Cong X, Duran E, Selen DJ, Burgert TS: Polycystic ovary syndrome in adolescence: impaired glucose tolerance occurs across the spectrum of BMI. *Pediatr Diabetes* 2013;14:42–49.
- 13 Forrester-Dumont K, Galescu O, Kolesnikov A, Raissouni N, Bhangoo A, Ten S, Suss A: Hyperandrogenism does not influence metabolic parameters in adolescent girls with PCOS. *Int J Endocrinol* 2012;2012:434830.
- 14 Rossi B, Suklich S, Droz J, Griffin A, Cook S, Blumkin A, Guzik DS, Hoeger KM: Prevalence of metabolic syndrome and related characteristics in obese adolescents with and without polycystic ovary syndrome. *J Clin Endocrinol Metab* 2008;93:4780–4786.
- 15 Ollila ME, West S, Keinänen-Kiukaanniemi S, Jokelainen J, Auvinen J, Puukka K, Ruokonen A, Jarvelin MR, Tapanainen JS, Franks S, Piltonen TT, Morin-Papunen LC: Overweight and obese but not normal weight women with PCOS are at increased risk of Type 2 diabetes mellitus—a prospective, population-based cohort study. *Hum Reprod* 2017;32:423–431.
- 16 Zawadzki JK, Dunaif A: Diagnostic Criteria for Polycystic Ovary Syndrome: Towards a Rational Approach. Boston, Blackwell Scientific Publications, 1992.
- 17 Trapp CM, Oberfield SE: Recommendations for treatment of nonclassic congenital adrenal hyperplasia (NCCAH): an update. *Steroids* 2012;77:342–346.
- 18 Skinner AC, Perrin EM, Moss LA, Skelton JA: Cardiometabolic risks and severity of obesity in children and young adults. *N Engl J Med* 2015;373:1307–1317.
- 19 Yeh KC, Kwan KC: A comparison of numerical integrating algorithms by trapezoidal, Lagrange, and spline approximation. *J Pharmacokinet Biopharm* 1978;6:79–98.
- 20 Manco M, Castagneto-Gissey L, Arrighi E, Carnicelli A, Brufani C, Luciano R, Mingrone G: Insulin dynamics in young women with polycystic ovary syndrome and normal glucose tolerance across categories of body mass index. *PLoS One* 2014;9:e92995.
- 21 Nagasaka S, Kusaka I, Yamashita K, Funase Y, Yamauchi K, Katakura M, Ishibashi S, Aizawa T: Index of glucose effectiveness derived from oral glucose tolerance test. *Acta Diabetol* 2012;49(suppl 1):S195–S204.
- 22 Legro RS, Kunesman AR, Dodson WC, Dunaif A: Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women. *J Clin Endocrinol Metab* 1999;84:165–169.
- 23 Boudreaux MY, Talbott EO, Kip KE, Brooks MM, Witchel SF: Risk of T2DM and impaired fasting glucose among PCOS subjects: results of an 8-year follow-up. *Curr Diab Rep* 2006;6:77–83.
- 24 Joham AE, Ranasinha S, Zoungas S, Moran L, Teede HJ: Gestational diabetes and type 2 diabetes in reproductive-aged women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2014;99:E447–E452.
- 25 Takeuchi T, Tsutsumi O, Taketani Y: Abnormal response of insulin to glucose loading and assessment of insulin resistance in non-obese patients with polycystic ovary syndrome. *Gynecol Endocrinol* 2008;24:385–391.
- 26 Legro RS: Polycystic ovary syndrome and cardiovascular disease: a premature association? *Endocr Rev* 2003;24:302–312.
- 27 Chen MJ, Yang WS, Yang JH, Chen CL, Ho HN, Yang YS: Relationship between androgen levels and blood pressure in young women with polycystic ovary syndrome. *Hypertension* 2007;49:1442–1447.
- 28 Espinos-Gomez JJ, Corcoy R, Calaf J: Prevalence and predictors of abnormal glucose metabolism in Mediterranean women with polycystic ovary syndrome. *Gynecol Endocrinol* 2009;25:199–204.
- 29 Gambineri A, Patton L, Altieri P, Pagotto U, Pizzi C, Manzoli L, Pasquali R: Polycystic ovary syndrome is a risk factor for type 2 diabetes: results from a long-term prospective study. *Diabetes* 2012;61:2369–2374.
- 30 Basu A, Caumo A, Bettini F, Gelisio A, Alzaid A, Cobelli C, Rizza RA: Impaired basal glucose effectiveness in NIDDM: contribution of defects in glucose disappearance and production, measured using an optimized minimal model independent protocol. *Diabetes* 1997;46:421–432.
- 31 Hayashi T, Boyko EJ, Sato KK, McNeely MJ, Leonetti DL, Kahn SE, Fujimoto WY: Patterns of insulin concentration during the OGTT predict the risk of type 2 diabetes in Japanese Americans. *Diabetes Care* 2013;36:1229–1235.
- 32 Ahren B, Pratley RE, Soubt M, Dunning BE, Foley JE: Clinical measures of islet function: usefulness to characterize defects in diabetes. *Curr Diabetes Rev* 2008;4:129–145.
- 33 Coles N, Bremer K, Kives S, Zhao X, Hamilton J: Utility of the oral glucose tolerance test to assess glucose abnormalities in adolescents with polycystic ovary syndrome. *J Pediatr Adolesc Gynecol* 2016;29:48–52.
- 34 Moran LJ, Misso ML, Wild RA, Norman RJ: Impaired glucose tolerance, type 2 diabetes and metabolic syndrome in polycystic ovary syndrome: a systematic review and meta-analysis. *Hum Reprod Update* 2010;16:347–363.
- 35 Arslanian SA, Lewy V, Danadian K, Saad R: Metformin therapy in obese adolescents with polycystic ovary syndrome and impaired glucose tolerance: amelioration of exaggerated adrenal response to adrenocorticotropin with reduction of insulinemia/insulin resistance. *J Clin Endocrinol Metab* 2002;87:1555–1559.
- 36 Palmert MR, Gordon CM, Kartashov AI, Legro RS, Emans SJ, Dunaif A: Screening for abnormal glucose tolerance in adolescents with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2002;87:1017–1023.