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ALTERATIONS IN GLUCOSE EFFECTIVENESS AND INSULIN DYNAMICS: POLYCYSTIC OVARY SYNDROME OR BODY MASS INDEX

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Abstract

Background/Aims—To delineate the relationship of PCOS, obesity, and hyperandrogenemia (HA) with glucose and insulin dynamics in adolescents across a broad body mass index (BMI).

Methods—Seventy-four PCOS (16 yr) and 82 controls (16 yr) were evaluated by an oral glucose tolerance test. Subjects were categorized by BMI: normal weight (NW; 21±0.4 kg/m2), overweight/obese (OO; 33±1.0 kg/m2), and severe obesity (SO; 48±1.4 kg/m2). 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 (SgI_o) between PCOS and C were significantly different between OO and SO. In PCOS, testosterone was positively associated with BMI, fasting insulin, early insulin response, diastolic blood pressure, and negatively associated with Sglo.

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.

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Keywords

PCOS in adolescents; insulin resistance; metabolic dysregulation; glucose effectiveness; metabolic syndrome

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 [4, 5] and a higher rate of the metabolic syndrome (10%) than in controls (1.7%) [6]. Similarly, insulin resistance (IR) and 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 is still being delineated. HA, obesity and IR have all been implicated in this role. HA may confer IR and metabolic inflammation [9, 10] and the odds of having metabolic syndrome are almost four times greater for every quartile increase in testosterone adjusting for BMI and IR [11]. Even lean PCOS are at an elevated risk of metabolic disease compared with lean controls [9, 12]. This relationship becomes more complicated in obese PCOS as obesity seems to be the major factor that leads to development of the metabolic syndrome in obese PCOS rather than HA [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.

Material 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 and controls (13 –22 years old) were at least two years post-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 age 16±0.2 yr (BMI 17–64 kg/m^2) and 82 controls age 16±0.1 yr (BMI 18–56 kg/m^2) were divided into 6 groups based on their BMI because data has shown that the more severe forms of obesity are associated with greater risks for complications: 1) Normal weight (NW) PCOS and control (C): BMI < 25 kg/m^2; B) overweight/obese (OO) PCOS and C: BMI 25 – < 40 kg/m^2; C) severely obese (SO) PCOS and C: BMI ≥ 40 kg/m^2 [18].

Informed consent was obtained from a legal guardian of each subject less than 18 years of age and from subjects 18 years or older. The protocols were approved by the Institutional Review Board of CUMC.

Biochemical analysis

Basal levels of glucose (G_0), insulin (I_0), testosterone, and HgbA1c were measured after an overnight fast. Glucose (G) was assayed by the glucose hexokinase method. Insulin (I) was measured via chemiluminescence, testosterone by high-performance liquid chromatography with tandem mass spectrometry (Esoterix, Inc., Calabasas Hills, Calif., USA). Glucose and HgbA1c were performed at the laboratory of New York Presbyterian Hospital.

Assessment of insulin sensitivity, insulin secretion, β-cell function and glucose effectiveness

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

Insulin resistance (IR)/sensitivity (IS) was estimated by: 1) The homeostasis model (HOMA-IR) and 2) the Matsuda Index/whole-body IS index (ISI) [8]

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

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

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

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

$$\frac{[PPG - without\ insulin\ and\ Sg] - [PPG - without\ insulin\ and\ with\ Sg] \times \left[\frac{2hPH}{2hPGE}\right]}{120}$$

where PPG = post-loading plasma G, Sg = glucose effectiveness, 2hPG = 2-h post-glucose PG, and $2hPH_E$ = expected 2hPG. 'PPG-without I and Sg' was calculated using:

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

Data Analysis

Continuous data were presented as means ± SD. Student's t-tests were used to compare the means of the continuous variables between PCOS and control group. Of note subjects diagnosed with diabetes were excluded from the analysis (n=1 PCOS). 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 PCOS and control group 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 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).

Results

Clinical Characteristics

Clinical and metabolic characteristics of PCOS subjects and healthy controls are presented in Table 1. PCOS and C subjects did not differ significantly in age, BMI, age of menarche, and years post menarche. Thirty-five percent of PCOS were Caucasian, 43% Hispanic, 13% Asian American, 4% African American, and 4% were multiracial or other. Thirty-seven percent of C 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 G or I indices described below ($p>0.5$). Similarly, no differences were seen in blood pressure, G_0, I_0, HbA1c, LH and FSH level between PCOS and C subjects. As expected, all PCOS subjects as a group exhibited higher serum testosterone when compared to all C as a group ($P< 0.001$).

Four percent (3 of 74) of PCOS had glucose dysfunction including impaired fasting G (IFG) (2.7%) and diabetes (1.3%). Similar to PCOS, 3% of C had IFG (3 of 82) but none had

diabetes. Impaired glucose tolerance (IGT) occurred in 15% of PCOS and 1.4 % of C ($P < 0.003$). $Time_I$ occurred, on average, 12 minutes later in SO-PCOS when compared to NW-PCOS and 13 minutes later than SO-C. $Time_G$ occurred, on average, 5 minutes later in SO-PCOS when compared to NW- PCOS and 7 minutes later than SO-C (p=NS) (Figure 1).

In all PCOS subjects, higher testosterone levels was associated with higher BMI (p=0.0141), I_0 (p=0.018), ΔI (p=0.0083), HOMA-IR (p=0.036), and DBP (p=0.015), and lower Sglo (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)—Table 2 shows the results from multivariable general linear models. Severe obesity was associated with higher SBP (difference in means 11.73 ±2.54 mmHg, p<0.001 and 6.29±2.87 mmHg, p=0.031) and DBP (difference in means 10.47 ±2.09 mmHg p<0.0001 and 5.55 ±2.39 mmHg, 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 has a significant impact on indices of insulin sensitivity/resistance (Table 2)—Table 2 shows the results from multivariable general linear models. As expected SO 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 and NW-C and OO-PCOS and OO-C subjects. PCOS status did not affect indices of insulin sensitivity/resistance.

BMI and PCOS status have a significant impact on indices of post-glucose load (Table 3 and Figure 2)—Table 3 shows the results from multivariable general linear models. As expected NW- PCOS and OO-PCOS subjects had lower risk of having abnormal post- glucose load indices determined by an OGTT than did those with SO-PCOS. 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 control 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 C subjects for 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 significant impact on glucose effectiveness (Figure 3)—Figure 2 shows the results from multivariable general linear model, for each unit

increase in BMI, Sglo decreased on average by 0.09 for both PCOS and control group ($p<0.0001$). That relationship is exacerbated in the SO- PCOS and SO-C group in which Sglo decreased on average by 2.27 when compared to NW PCOS and NW-C subjects ($p=0.001$).

Interestingly, PCOS status had a significant relationship with Sglo when BMI is > 36 kg/m^2. The combination of PCOS and a BMI > 36 kg/m^2 explained 88% of the variance in Sglo ($r^2 = 0.88$; $P <0.0001$). This hyperbolic relationship demonstrated that Sglo was significantly lower in PCOS as compared to C when BMI is greater than 36 kg/m^2 consistent with the premise of declining Sglo in SO-PCOS.

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 Sglo. This study suggests that SO-PCOS are metabolically different than OO- PCOS 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 non obese subjects with PCOS, again suggesting that PCOS is an independent risk factor for the development 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 mins 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 also has 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, 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 adolescent and young adult is mainly associated with severe obese 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 increased risk of development of T2DM, 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 $G_{AU.}$, In addition SO was associated with a later I peak in response to an OGTT when compared to other PCOS groups. SO-PCOS also have a decreased capacity for glucose to enhance its own cellular uptake and to suppress endogenous glucose production, as determined by Sgl_0. The hyperbolic relationship between BMI and Sgl_0 exists in both C and PCOS subjects; however, despite this similarity, PCOS have lower Sglo when their BMI is > 36kg/m^2 compared to their respective controls (Figure 3). This observation suggests that the combination of SO and PCOS both independently and in combination, increases the risk for disturbances in G metabolism. This is extremely important because decreased G effectiveness similarly to a delayed in insulin release has been associated with the development of impaired glucose tolerance or T2DM in various populations [30, 31]. Thus, degree of obesity, altered Sglo, delayed I peak in response to a G 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 G metabolism using an OGTT. Although our program represents a single center, our population is ethnically diverse and demonstrated that ethnicity did not impact indices of G and I dynamics.

Limitations of our study include the use of OGTT-derived indices as surrogate method of determining G and I dynamics rather than an IVGTT. 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 I sensitivity and/or secretion.

Other studies have suggested that the presence of abnormal OGTT and diabetes is present in 30–40% of PCOS women and adolescents as well [11, 22, 33–36]. In our study, only one 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 and controls are mainly dependent on 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 insulin sensitivity and insulin secretion was not identified in NW PCOS subjects; alterations in glucose response to an OGTT decreased activity of glucose per se on its own uptake under and delayed insulin secretion was observed in SO-PCOS. 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 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.

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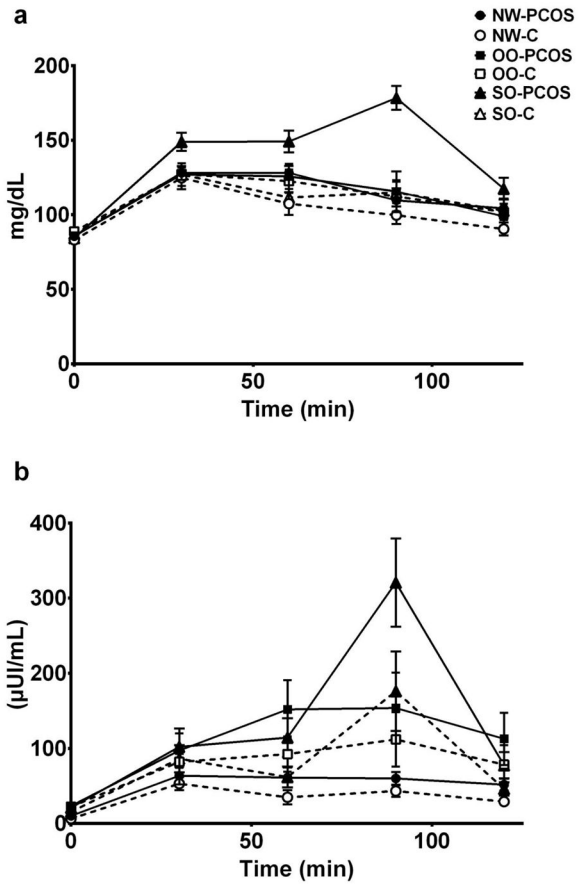

Figure 1.
Glucose and (b) insulin response during and OGTT in PCOS and C subjects.

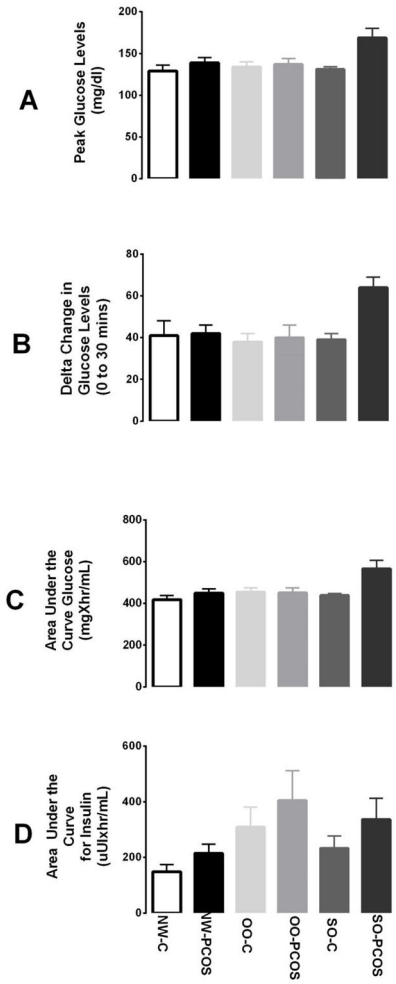

Figure 2.

Post Meal Indices of Carbohydrate Metabolism in PCOS and C divided into 6 groups based on their BMI-Normal weight (NW) PCOS and control: BMI < 25 kg/m^2; overweight/obese (OO) PCOS and C: BMI 25 – < 40 kg/m^2; severely obese (SO) PCOS and C: BMI ≥ 40 kg/m^2. All data presented as mean ± SE for indices of $Peak_G$ (A), ΔG (B), G_{AUC} (C) and I_{AUC} (D). Multivariable analyses described in Table 3 represent the statistical differences between individual categories.

Term	Estimate	SE	t-Ratio	Prob > [t]
Intercept	4.402	0.20	21.33	<0.0001
BMI	-0.085	0.005	-16.65	<0.0001
(BMI-36.76) X (BMI-36.76)	0.0027	0.0002	9.25	<0.0001
(BMI-36.76)XPCOS (yes=1, no=0)[1-0]	-0.018	0.0071	-2.54	0.001

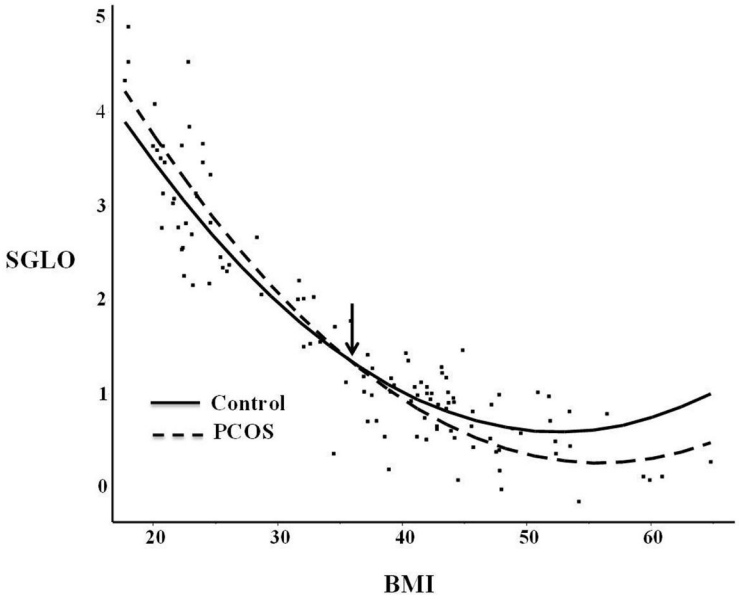

Figure 3.

Hyperbolic relationship between Sglo and BMI in adolescent subjects with PCOS (open line) and control (closed line). PCOS subjects have lower SgI_0 when BMI is greater than 36 (arrow) when compared to control subjects (P = 0.01). BMI = body mass index. Table represents the results of a multivariate linear regression analysis all variables entered into the model included those with a P < 0.15 in univariant analysis: BMI and the diagnosis of PCOS

Table 1

Clinical Characteristics of PCOS and C

All data presented as mean ±SE (range). Data points which are significantly different from PCOS and C are denoted by different letters (AB) ($P < 0.001$).

	Control (82)	PCOS (74)
Age (yr)	16.2±0.24	16.2±0.5
BMI (kg/m^2)	21.6±0.4	33.8±1.0
Menarche (yr)	11.8±0.3	11.9±0.2
Post menarche (yr)	4.2±0.2	4.6±0.2
Ethnicity	30W, 30H, 8B, 11A, 3O	26W, 32H, 3B, 10A, 3O
Diastolic BP (mmHg)	71±1	70±1
Systolic BP (mmHg)	115±1	112±1
Fasting Glycemia-(G_0)(mg/dL)	86±0.9	86±1.9
Fasting Insulin levels-(I_0) (uUI/mL)	15.9±1.7	18.1±1.7
HgbA1c	5.3±0.1	5.3±0.1
FSH Levels (uUI/mL)	5.3±0.3	5.4±0.2
LH Levels (uUI/mL)	8.5±1.4	10.1±0.7
Testosterone (ng/dL)	28.7±2.5^B	26.5±2.4^A

Table 2

Multiple Regression Model Showing the Effect of BMI on Fasting and Post OGTT Indices of Carbohydrate Metabolism and Blood Pressure in PCOS and C divided into 6 groups based on their BMI-1)

Normal weight (NW): BMI < 25kg/m^2; B) overweight/obese (OO) BMI 25 – < 40 kg/m^2; C) severely obese (SO) BMI ≥ 40 kg/m^2. Parameter estimates from the multiple regression model are reported as SE, p-value and 95% confidence intervals.

Outcome	Parameter	Estimate	SE	t Value	Pr > |t|	95% CI	
HOMA-IR	**Intercept**	3.61	0.45	8.00	<.0001	2.71	4.50
	PCOS+	0.85	0.54	1.58	0.117	−0.21	1.91
	BMI- NW vs SO	−2.27	0.67	−3.39	**0.001**	−3.59	−0.95
	BMI- OO vs SO	0.96	0.62	1.56	0.120	−0.25	2.18
DI (1/(mmol/L)$^{2\ X}$ (pmol/L)^2 * (uUI/mL))	**Intercept**	12.58	3.40	3.70	0.000	5.84	19.32
	PCOS+	−8.03	4.35	−1.85	0.067	−16.64	0.58
	BMI- NW vs SO	7.61	5.21	1.46	0.147	−2.72	17.94
	BMI- OO vs SO	−2.99	5.14	−0.58	0.563	−13.18	7.21
Matsuda Index (ISI) ^(1/(mmol/L)$^{2\ X}$ (pmol/L)^2)	**Intercept**	6.71	1.41	4.75	<.0001	3.91	9.50
	PCOS+	−2.52	1.81	−1.39	0.168	−6.11	1.08
	BMI- NW vs SO	6.63	2.22	2.99	**0.003**	2.23	11.03
	BMI- OO vs SO	−0.08	2.15	−0.04	0.970	−4.34	4.18
SBP	**Intercept**	118.90	1.56	76.20	<.0001	115.80	122.00
	PCOS+	−1.55	2.15	−0.72	0.474	−5.82	2.73
	BMI- NW vs SO	−11.73	2.51	−4.68	**<.0001**	−16.71	−6.75
	BMI- OO vs SO	−6.29	2.87	−2.19	**0.031**	−11.99	−0.58
DBP	**Intercept**	74.24	1.30	57.15	<.0001	71.66	76.82
	PCOS+	0.58	1.79	0.32	0.749	−2.98	4.13
	BMI- NW vs SO	−10.47	2.09	−5.01	**<.0001**	−14.61	−6.32
	BMI- OO vs SO	−5.55	2.39	−2.32	**0.022**	−10.30	−0.80

Table 3

Multiple Regression Model Showing the Effect of BMI and PCOS on Post OGTT Indices of Carbohydrate Metabolism in PCOS and C divided into 6 groups based on their BMI-1)

Normal weight (NW): BMI < 25 kg/m^2; B) overweight/obese (OO) BMI 25 – < 40 kg/m^2; C) severely obese (SO) BMI ≥ 40 kg/m^2. Parameter estimates from the multiple regression model are reported as SE, p-value and 95% confidence intervals.

Outcome	Parameter	Estimate	SE	t Value	Pr > |t|	95% CI	
Peak $_G$ (mg/dL)	**Intercept**	131.08	4.29	30.54	<.0001	122.58	139.58
	PCOS+	28.83	7.26	3.97	**0.0001**	14.46	43.20
	BMI- NW vs SO	−0.26	9.15	−0.03	0.978	−18.38	17.86
	BMI- OO vs SO	3.51	7.79	0.45	0.653	−11.92	18.94
	PCOS+*BMI_NW vs SO	−18.54	12.48	−1.49	0.140	−43.26	6.18
	PCOS+*BMI_OO vs SO	−26.36	11.71	−2.25	**0.026**	−49.55	−3.16
ΔG (0–30 min)	**Intercept**	39.45	3.74	10.56	<.0001	32.05	46.84
	PCOS+	25.50	6.36	4.01	**0.0001**	12.90	38.10
	BMI- NW vs SO	2.22	7.02	0.32	0.753	−11.69	16.12
	BMI- OO vs SO	−0.98	6.72	−0.15	0.885	−14.28	12.33
	PCOS+*BMI_NW vs SO	−24.82	10.12	−2.45	**0.016**	−44.85	−4.79
	PCOS+*BMI_OO vs SO	−23.33	10.14	−2.30	**0.023**	−43.41	−3.24
G_{AUC} (mgXhr/dL)	**Intercept**	439.10	15.13	29.02	<.0001	409.13	469.07
	PCOS+	92.01	25.51	3.61	**0.001**	41.49	142.52
	BMI- NW vs SO	−74.90	27.62	−2.71	**0.008**	−129.61	−20.19
	BMI- OO vs SO	16.43	26.46	0.62	0.536	−35.98	68.84
	PCOS+*BMI_NW vs SO	−16.28	39.82	−0.41	0.683	−95.14	62.58
	PCOS+*BMI_OO vs SO	−95.69	40.28	−2.38	**0.019**	−175.47	−15.91
I_{AUC} (uUIXhr/mL)	**Intercept**	237.86	41.56	5.72	<.0001	155.57	320.14
	PCOS+	103.94	51.50	2.02	**0.046**	1.97	205.92
	BMI- NW vs SO	−122.54	61.34	−2.00	**0.048**	−243.99	−1.08
	BMI- OO vs SO	67.61	61.75	1.09	0.276	−54.66	189.88