IMPACT OF POLYCYSTIC OVARY SYNDROME ON CARDIOVASCULAR DISEASE IN OBESE FEMALE YOUTH

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INTRODUCTION:

- Current epidemiologic studies show approximately 17% of children in the United States are obese.[1] This is a serious public health concern as cardiovascular risk factors in childhood are correlated with increased cardiovascular disease (CVD) morbidity and mortality in adults.[2]
- The increasing rates of obesity-related PCOS are a major contributor to the earlier onset and rising incidence of type 2 diabetes, non-alcoholic fatty liver disease and CVD.[3-6]
- Polycystic ovary syndrome affects 6-10% of U.S. women, with an estimated economic burden of $4 billion, and is increasing in prevalence in parallel with the obesity epidemic.[7,8]
- Previous studies have evaluated endothelial function in young adult women with obesity and PCOS,[9-11] but little is known regarding whether vascular dysfunction is already present in youth with PCOS.
- We hypothesized there would be early evidence of CVD within our study population and girls with PCOS and obesity will have more evidence of early cardiovascular disease than girls with obesity alone.

STUDY OBJECTIVES:

I. Describe characteristics of early cardiovascular remodeling in female youth with obesity.
II. Identify if youth with PCOS and obesity demonstrate early physiologic signs of cardiovascular impairment beyond the impact of obesity alone.

METHODS AND MATERIALS:

- This was an analysis of participants in the National Institutes of Health (NIH) funded studies “Liver and Fat Regulation in Overweight Adolescent Girls” (APPLE) and “Post-Prandial Liver Glucose Metabolism in PCOS” (PLUM).
- 68 participants (44 youth with PCOS, and 24 obese controls without PCOS) were included in study analysis. Participant characteristics are shown in Table 1.
- Participants were admitted to Children’s Hospital Colorado for an inpatient 12-hour overnight monitored fast. The following day, participants underwent a 6-hour oral glucose tolerance test (OGTT), with serial blood draws conducted over 4 hours.
- EndoPAT-2000 was utilized to assess endothelial function in the form of the reactive hyperemia index (RHI) and a measure of peripheral arterial stiffness in the form of the augmentation index (AI).[12]
- Brachial artery distensibility (BAD), a measure of peripheral vascular stiffness, was measured via DynaPulse. Lower BAD represents worse arterial compliance.[13]
- Additional variables of interest collected during from these studies include age, ethnicity, medication history, systolic blood pressure (SBP), heart rate, habitual physical activity (METS), HbA1c, a fasting lipid panel, and blood glucose, insulin and free fatty acid (FFA) concentrations during the OGTT.
- Subgroup analysis categorized participants as either high cardiovascular risk (HCVR) or low cardiovascular risk (LCVR). HCVR was defined as falling in the worst tertile in ≥2 out of 3 measurements including RHI, AI and BAD within the study population. LCVR was defined as being in the healthiest tertile in ≥2 out of 3 of the same variables.
- Statistical analysis performed using Prism statistical software (version 8.2.1, Rochester, MI). Unpaired t-tests were used to compare patient characteristics if normally distributed, and a Welch’s t-test if not normally distributed. Level of significance was set at p=0.05.

Table 1: Participant Characteristics by PCOS Status

	PCOS	Obese Controls	p-Value
	n=44	n=24	
Age (years)	15.8 ± 1.0	15.9 ± 2.0	0.898
Ethnicity (N,%)			
Hispanic	24 (55%)	15 (62%)	
BMI (kg/m^2)	36.1 ± 6.3	34.5 ± 6.3	0.289
Vascular Measures			
SBP (mmHg)	128 ± 12	127 ± 10	0.766
DBP (mmHg)	68 ± 9	66 ± 7	0.573
RHI	2.17 ± 0.72	2.00 ± 0.60	0.343
AI %	-10.99 ± 9.28	-7.88 ± 10.94	0.226
BAD (mmHg^{-1})	5.41 ± 1.29	5.01 ± 1.82	0.301
Laboratory Measures			
HbA1c (%)	5.5 ± 0.3	5.2 ± 0.3	0.002**
TG (mg/dL)	127 ± 60	102 ± 35	0.065
LDL (mg/dL)	86 ± 28	75 ± 16	0.063
OGTT Measurements			
Mean OGTT Glucose (mg/dL)	128 ± 18	124 ± 16	0.445
Mean OGTT Insulin (µU/mL)	216 ± 133	156 ± 71	0.049*
Time to FFA nadir (min)	159 ± 29	165 ± 43	0.532
FFA nadir (mg/dL)	67 ± 29	51 ± 16	0.019*
Time to Peak Insulin (min)	76 ± 44	73 ± 45	0.792
Peak Insulin (µU/mL)	435 ± 284	267 ± 141	0.012*

Table 1: Data are given as mean ± SD or as a total n with percentage. * indicates p=0.049-0.01, ** p=0.009-0.001, ***p<0.001. Abbreviations: *PCOS* Polycystic Ovary Syndrome, *SBP* Systolic Blood Pressure, *DBP* Diastolic Blood Pressure, TG, Triglycerides, *LDL* Low Density Lipoprotein, *RHI* Reactive Hyperemic Index, *AI* Augmentation Index, *BAD* Brachial Artery Distensibility, *OGTT* Oral Glucose Tolerance Test, *FFA* Free Fatty Acids.

Figure 1: Systolic Blood Pressure by Risk Group

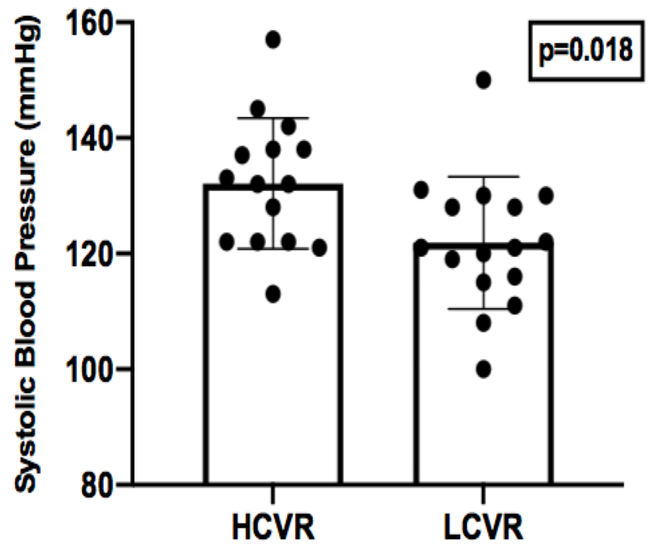

Figure 1. Box plot comparing the mean systolic blood pressure readings of participants in the HCVR group compared to the LCVR group. Abbreviations: *SBP* Systolic Blood Pressure, *HCVR* High Cardiovascular Risk, LCVR Low Cardiovascular Risk.

Table 2: Characteristics of High Cardiovascular Risk Participants Compared to Low Cardiovascular Risk

	HCVR	LCVR	p-Value
	n=15	n=16	
PCOS	12 (80%)	11 (69%)	
Control	3 (20%)	5 (31%)	
Age (years)	15.8 ± 1.0	15.9 ± 2.0	0.898
Ethnicity (N,%)			
Hispanic	9 (60%)	5 (31%)	
BMI (kg/m^2)	35.5 ± 4.6	34.2 ± 6.3	0.509
Vascular Measures			
SBP (mmHg)	132 ± 11	122 ± 11.5	0.018*
DBP (mmHg)	68 ± 8	66 ± 6	0.493
RHI	1.72 ± 0.47	2.50 ± 0.94	0.008**
AI %	-15.40 ± 7.71	-1.20 ± 8.35	<0.001***
BAD (mmHg^{-1})	4.95 ± 0.76	6.22 ± 0.98	<0.001***
Laboratory Measures			
HbA1c (%)	5.4 ± 0.3	5.4 ± 0.4	0.151
TG (mg/dL)	120 ± 58	105 ± 38	0.513
LDL (mg/dL)	74 ± 16	80 ± 15	0.273
OGTT Measurements			
Mean OGTT Glucose (mg/dL)	123 ± 17	120 ± 18	0.683
Mean OGTT Insulin (µU/mL)	214 ± 151	143 ± 74	0.106
Time to FFA nadir (min)	152 ± 33	176 ± 24	0.034*
FFA nadir (mg/dL)	63 ± 23	58 ± 23	0.545
Time to Peak Insulin (min)	77 ± 48	61 ± 40	0.337
Peak Insulin (µU/mL)	479 ± 341	269 ±146	0.034*

Table 2: Data are given as mean ± SD or as a total n with percentage. * indicates p=0.049-0.01, ** p=0.009-0.001, ***p<0.001. Abbreviations: *HCVR* High Cardiovascular Risk, LCVR Low Cardiovascular Risk, *SBP* Systolic Blood Pressure, *DBP* Diastolic Blood Pressure, TG, Triglycerides, *LDL* Low Density Lipoprotein, *RHI* Reactive Hyperemic Index, *AI* Augmentation Index, *BAD* Brachial Artery Distensibility, *OGTT* Oral Glucose Tolerance Test, *FFA* Free Fatty Acids.

Figure 2: OGTT Peak Insulin Concentration by Risk Group

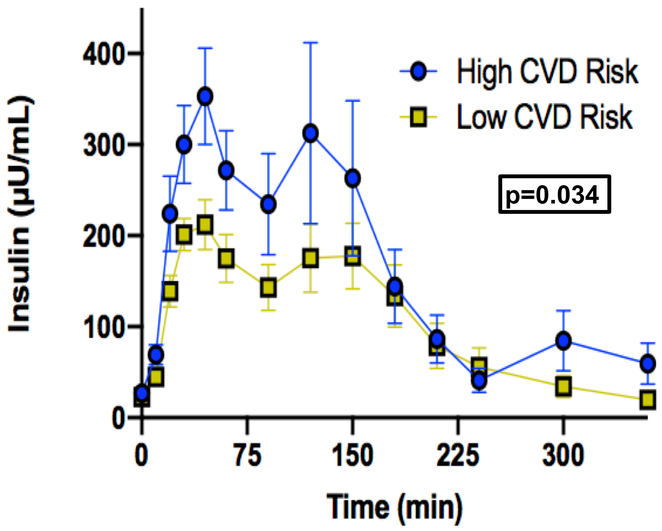

Figure 2. Line graph demonstrating serial t-tests of endogenous insulin values during an OGTT between participants in the HCVR group compared to the LCVR group. Abbreviations: *OGTT* Oral Glucose Tolerance Test, *HCVR* High Cardiovascular Risk, *LCVR* Low Cardiovascular Risk, *CVD* Cardiovascular Disease.

RESULTS:

COMPARISON OF PCOS TO OBESE CONTROLS

- 68 girls with obesity, consisting of 44 with PCOS (age 16.0±1.9 years; BMI 36.1±6.3 kg/m2) and 24 without PCOS (age 15.3±1.6 years; BMI 34.5±6.3 kg/m2) were enrolled8 (Table 1).
- Vascular measures including SBP, EndoPAT, and Dynapulse measures were similar between groups.
- During the OGTT, girls with PCOS had similar glucose values, but a higher mean (p=0.049) and peak (p=0.012) insulin concentration.
- Participants with PCOS had less suppression of FFA, with a higher FFA nadir (p=0.019).

COMPARISON OF HCVR TO LCVR GROUPS

- 15 participants were classified as HCVR (PCOS = 12, Obese Controls = 3) with 16 participants for LCVR (PCOS = 11, Obese Controls = 5) (see Table 2).
- Measures of dysglycemia were similar in these two groups based on HbA1c (p=0.151) and mean glucose during the OGTT (p=0.683).
- By design, measurements of endothelial dysfunction between the HCVR and LCVR cohorts including RHI, AI, and BAD were significantly different.
- SBP was significantly elevated in the HCVR group (p=0.018) (Figure 1).
- HCVR group had elevated peak insulin concentrations relative to LCVR (p<0.04) (Figure 2).

Conclusion:

PCOS in adolescents with obesity was not associated with vascular dysfunction or elevated SBP compared to similarly obese girls without PCOS. However, HCVR participants demonstrated hypertension and hyperinsulinemia relative to LCVR. This suggests vascular dysfunction can be observed as early as adolescence in girls with obesity. It should be noted our study population was largely Hispanic, which may limit generalizability to other populations. Additionally, EndoPAT and Dynapulse, while more economical than other methods, are not always considered the gold standard measures for endothelial dysfunction. Therefore, more subtle abnormalities may have been missed. Considering that women with PCOS have evidence of endothelial dysfunction in young adulthood, the teen years are the optimal time to intervene, and future studies to mitigate this risk are needed. Future projects should include measures such as brachial artery ultrasound for endothelial function. Also, peripheral measures may not reflect central arterial stiffness, and therefore future studies should also include additional central measures such as aortic MRI which is capable of detecting more subtle abnormalities.

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