Obese Adolescent Girls with Polycystic Ovary Syndrome (PCOS) Have More Severe Insulin Resistance Measured by HOMA-IR Score than Obese Girls without PCOS

Pairunyar Sawathiparnich MD*, Linda Weerakulwattana BSC, MSC*,
Jeerunda Santiprabhob MD*, Supawadee Likitmaskul MD*

*Division of Pediatric Endocrinology, Department of Pediatrics,
Faculty of Medicine Siriraj Hospital

The prevalence of obesity in Thai children is increasing. These individuals are at increased risks of metabolic syndrome that includes insulin resistance, type 2 diabetes mellitus (T2DM), polycystic ovary syndrome (PCOS), dyslipidemia and hypertension. PCOS has been known to be associated with insulin resistance.

Objectives: *To compare the insulin sensitivity between obese adolescent girls with PCOS and those without PCOS.*

Material and Method: *We reviewed demographic and hormonal data of 6 obese adolescent girls with PCOS and compared with 6 age, weight and BMI-matched non-PCOS controls. Each subject underwent an oral glucose tolerance test.*

Results: *Homeostasis model assessment of insulin resistance score (HOMA-IR score) in obese adolescent girls with PCOS was significantly higher than in girls without PCOS with median and range as follows (16.5 [3.8, 21.8] vs. 4.1 [3.3, 6.9], p=0.04).*

Our study demonstrates that obese adolescent girls with PCOS have more severe insulin resistance measured by HOMA-IR score than girls without PCOS independent of the degree of obesity. Since insulin resistance is a metabolic precursor of future cardiovascular diseases, obese adolescent girls with PCOS might be at greater risk of developing cardiovascular disease in later adulthood than their non-PCOS counterparts.

Keywords : *Polycystic ovary syndrome, Obesity, Insulin resistance*

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The prevalence of obesity and T2DM in children is increasing worldwide including in Thailand[1-2]. The prevalence of obesity in Thai children aged 6-12 years has increased from 5.8 % in 1990 to 13.3% in 1996[2]. Moreover, T2DM has been diagnosed among Thai children and adolescents with new-onset DM with increasing frequency, from 5% in 1986-1995 to 17.9% in 1996-1999[3].

Correspondence to: Sawathiparnich P, Division of Pediatric Endocrinology, HRH Princess Mahachakri Building, 9th floor Department of Pediatrics, Faculty of Medicine Siriraj Hospital. 2 Prannok Road Bangkok, 10700 Thailand. Phone: 02419-7000 ext. 5676, Fax: 02419-7000 ext. 5676 E-mail: pairnyr@yahoo.com

Moreover, obese women are more likely to develop other features of metabolic syndrome, including insulin resistance, T2DM, dyslipidemia, hypertension and polycystic ovary syndrome (PCOS).

PCOS, characterized by chronic anovulation and hyperandrogenism, is the most common endocrine disorder in reproductive-aged women[4]. The etiology of PCOS remains unclear and may be multifactorial. One of the several factors involve in the pathogenesis of PCOS is insulin resistance[5]. Improvement of hyperandrogenism and induction of ovulation in women with PCOS by insulin-sensitizing drugs

suggest that insulin resistance might play an important role in the pathogenesis of PCOS[6-7]. Palmert et al reported that 33 % of adolescent girls with PCOS had impaired glucose tolerance (IGT) and 3.7 % had T2DM[8]. These data suggest that PCOS may be an important risk factor of glucose intolerance and diabetes mellitus in adolescent girls.

The purpose of our study was to compare the insulin sensitivity between obese adolescent girls with PCOS and girls without PCOS.

Material and Method

We retrospectively reviewed demographic and hormonal data of six obese adolescent girls with PCOS who attended our Pediatric Endocrinology Clinic from 1999 to 2004. Their data were compared with the data of six age, weight and BMI-matched non-PCOS controls.

The diagnosis of PCOS is based upon the NIH 1990 criteria which included 1) oligomenorrhea or amenorrhea 2) presence of signs of androgen excess or hyperandrogenemia 3) exclusion of other diseases such as prolactinoma, hypothyroidism, adrenal tumor or late-onset congenital adrenal hyperplasia[9].

Family history of T2DM in the first or second-degree relatives was obtained. Weight, height and blood pressures after 15 minutes rest were measured. Body mass index (BMI) was calculated in kg/m^2. Each girl underwent an oral glucose tolerance test. Fasting lipid profiles were measured. Criteria for the diagnosis of diabetes mellitus and impaired glucose tolerance (IGT) was based on the 2004 clinical practice recommendation by the American Diabetes Association[10].

Serum glucose concentrations were determined by enzymatic assay. Serum insulin concentrations were measured by immunoassay. The cross-reactivity with proinsulin was less than 0.05 %.

The differences in HOMA-IR score between the two groups were determined using Mann-Whitney U test (SPSS 11.00, Chicago, IL). Data are presented as median (min, max). The difference is statistically significant if p value is less than 0.05. HOMA-IR score was calculated by standard method described previously[11]. Due to the small numbers of our subjects, we could not compare the difference of fasting serum glucose, fasting serum glucose/insulin ratio, 2-hour serum glucose and serum insulin levels, serum cholesterol, TG, HDL and LDL levels between the two groups.

Results

All subject characteristics (Table 1)

All subjects were obese (BMI of 27.6 to 51.5 kg/m^2). Most subjects (92%) had family history of T2DM. Acanthosis negricans was present in all subjects. Hyperinsulinemia (fasting serum insulin $\geq$ 15 uU/ml) was evident in each subject. 11 of 12 girls had hypercholesterolemia (serum cholesterol > 170 mg/dl).

Subject characteristics in each group (Table 2.)

There was no significant difference between the age, weight, BMI, systolic and diastolic blood pressures of the two groups. 3 of 6 (50%) girls with PCOS were diagnosed with T2DM, while 3 of 6 (50%) non-PCOS girls had impaired glucose tolerance (IGT).

Calculated HOMA-IR scores in obese girls with PCOS were significantly higher than in girls without PCOS with median and range as follows; (16.5 [3.8, 21.8] vs. 4.1 [3.3, 6.9], p=0.04). Fasting serum insulin levels in obese girls with PCOS seemed to be higher than in girls without PCOS (p=0.06).

Table 1. Clinical characteristics of the study population

Clinical and biochemical parameters	Median (Min, Max) (N=12)
Age (yrs)	14.3 (11.6, 18)
Weight (kgs)	88.3 (62.8, 170.4)
BMI (kg/m^2)	36.3 (27.6, 51.5)
SBP(mmHg)	120 (110, 156)
DBP (mmHg)	70 (56, 88)
Acanthosis negricans	12 in 12 (100%)
Family Hx of type 2 DM	11 in 12 (92%)

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure

Table 2. Clinical and metabolic characteristics in the separate group of subjects

Clinical and biochemical parameters	Girls with PCOS (N=6)	Girls without PCOS (N=6)	p value
Age (years)	14.1 (11.6, 18)	14.5 (10, 13)	0.5
Weight (kgs)	93.1 (62.8, 125.2)	85.8 (69.8, 120.3)	0.7
BMI (kg/m^2)	37.4 (29, 43)	34.2 (27.6, 51.5)	0.9
SBP(mmHg)	120 (110,156)	124 (110, 140)	0.9
DBP (mmHg)	60 (56, 82)	73 (63, 88)	0.4
Acanthosis negricans	6/6 (100%)	6/6 (100%)	
Family Hx of T2DM	5/6 (83%)	6/6 (100%)	
Presence of T2DM	3/6 (50%)	0/6 (0%)	
IGT	0/6 (0%)	3/6 (50%)	
NGT	3/6 (50%)	3/6 (50%)	
Fasting insulin level (uU/ml)	58.3 (17.2, 79)	21.3 (15.2, 33.9)	0.06
Fasting serum glucose (mg/dl)	90.5 (86, 145)	83 (75, 100)	N/A
Fasting glucose: insulin ratio	2.4 (1.14, 4.94)	4.4 (2.45, 6.05)	N/A
2 hour insulin level (uU/ml)	180.4 (99.6, 468.9)	151.1 (59.1, 199.7)	N/A
2 hr serum glucose (mg/dl)	172 (120, 332)	137 (111, 172)	N/A
HOMA-IR SCORE	16.5 (3.8, 21.8)	4.1 (3.3, 6.9)	*0.04
Cholesterol (mg/dl)	194.5 (177, 223)	197 (108, 259)	N/A
TG (mg/dl)	96 (80, 265)	87.5 (55, 132)	N/A
HDL (mg/dl)	43.5 (34, 57)	49.5 (28, 79)	N/A
LDL (mg/dl)	115.5 (107, 177)	100 (50, 206)	N/A

SBP, systolic blood pressure; DBP, diastolic blood pressure
IGT, impaired glucose tolerance; NGT, normal glucose tolerance
Data are presented as median (min, max), * significant at $p < 0.05$

Discussion

Our study indicates that obese adolescent girls with PCOS have higher insulin resistance measured by HOMA-IR score than girls without PCOS independent of age, weight and body mass index (BMI). Since insulin resistance is strongly associated with increased risks of T2DM and cardiovascular diseases, our study suggests that obese adolescent girls with PCOS might be at higher risks of developing T2DM and cardiovascular diseases in adulthood compared to obese non-PCOS adolescent girls.

In our study, insulin sensitivity (S_i) as measured by HOMA-IR score in obese adolescent girls with and without PCOS was found to differ significantly. There are currently several studies to substantiate the association between PCOS and insulin resistance. Lewy et al previously reported that obese adolescent girls with PCOS (mean age 12 years olds, BMI 33 kg/m^2) had higher insulin resistance as measured by hyperinsulinemic-euglycemic clamp than those who were matched for age, percent body fat and abdominal fat without PCOS[12]. Moreover, Toprak et al previously reported that insulin resistance in non-obese women with PCOS was also higher than in healthy control subjects matched for age and weight[13]. Palmert et al reported that approximately 33 % of obese adolescent girls with PCOS had IGT and 3.7 % had T2DM. In adult women with PCOS, abnormal glucose tolerance was present among 30-40% of both lean and obese women[14].

There are two potential limitations to the present study. First, the fact that 50% of girls with PCOS had T2DM and 50% of girls without PCOS had IGT raises the possibility that abnormal glucose tolerance influences the insulin sensitivity. Secondly, the subject numbers of our study were too small to evaluate the difference of other measurements of insulin sensitivity such as fasting serum glucose: insulin ratio and fasting serum insulin between obese girls with and without PCOS.

A larger study is needed to evaluate the relationship between PCOS and serum lipid profiles.

Robinson et al previously reported that low HDL and high triglyceride levels were associated with insulin resistance rather than the presence of PCOS[15].

Since insulin resistance is severely pronounced in obese adolescent girls with PCOS, improvement of insulin sensitivity via weight loss and lifestyle modification either with or without metformin should be strongly encouraged in these girls. Previous studies have shown that even 10-20% weight loss could improve menstrual irregularities, acne and hirsutism in obese patients[16]. Metformin, the only FDA-approved oral hypoglycemic agent for treating T2DM in children and adolescents has recently been evaluated for its ability to improve PCOS**.** Treatment of PCOS with metformin in adolescent girls has been shown to improve hirsutism, hyperinsulinemia, hyperandrogenemia, dyslipidemia and menstrual cycles in various studies[17]. However, to date, there is no consensus regarding the use of metformin in adolescent girls with PCOS.

In conclusion, the present study demonstrates that obese adolescent girls have more severe insulin resistance measured by HOMA-IR score than in girls without PCOS independent of age, weight and BMI. Since insulin resistance is a metabolic predictor of future T2DM and cardiovascular disease (CVD), early intervention with lifestyle modification by diet and exercise is warranted in obese adolescent girls with PCOS. Moreover, early identification and treatment of common co-morbidities found in obese adolescent girls with PCOS such as dyslipidemia, T2DM and hypertension are needed to decrease risks of cardiovascular disease in later adulthood.

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References

1. Ogden CL, Flegal KM, Carroll MD, Johnson CL. Prevalence and trends in overweight among US children and adolescents, 1999-2000. JAMA 2002;288:1772-3.
2. Ruangdarakanon N. Health status in school children aged 6-12 years. Department of Health Survey. Bangkok: Ministry of Public Health, 1996:38-61.
3. Likitmaskul S, Kiattisakthavee P, Chaichanwatanakul K, Punnakanta K, Angsusingha K, Tuchinda C. Increasing prevalence of type 2 diabetes mellitus in Thai children and adolescents associated with increasing prevalence of obesity. J Ped Endocrinol Metab 2003;16:71-7.
4. Franks S. Medical progress article: polycystic ovary syndrome. N Engl J Med 1995:333;853-61.
5. Dunaif A. Insulin resistance and the polycystic ovary syndrome: mechanisms and implications for pathogenesis. Endocr Rev 1997;18:774-800.
6. Nestler JE, Jakubowicz DJ, Evans WS, Pasquali R. Effects of metformin on spontaneous and clomiphene-induced ovulation in the polycystic ovary syndrome. N Engl J Med 1998;338: 1876-80.
7. DeLeo V, la Marca A, Ditto A, Morgante G, Cianci A. Effects of metformin on gonadotropin-induced ovulation in women with polycystic ovary syndrome. Fertil Steril 1999;72:282-5.
8. 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;87:1017-23.
9. Zawadzki JK, Dunaif A. Diagnostic criteria for polycystic ovary syndrome: towards a rational approach. In: Dunaif A, Given JR, Haseltine F, Merriam GR, eds. Polycystic ovary syndrome. Boston (MA): Blackwell Scientific Publications; 1992:377-84.
10. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2004;27 (Supply 1):S5-S10.
11. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28: 412-9.
12. Lewy VD, Danadian K, Witchel SF, Arslanian S. Early metabolic abnormalities in adolescent girls with polycystic ovarian syndrome. J Pediatr 2001;138:38-44.
13. Toprak S, Yonem A, Cakir B, Guler S, Azal O, Ozata M, et al. Insulin resistance in nonobese patients with polycystic ovary syndrome. Horm Res 2001;55:65-70.
14. Legro RS, Kunselman 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;84:165-9.

15. Robinson S, Henderson AD, Gelding SV, Kiddy D, Niththyananthan R, Bush A, et al. Dyslipidaemia is associated with insulin resistance in women with polycystic ovaries. Clin Endocrinol 1996;44:277-84.
16. Holte J, Bergh T, Berne C, Wide L, Lithell H. Restored insulin sensitivity but persistently increased early insulin secretion after weight loss in obese women with polycystic ovary syndrome. J Clin Endocrinol Metab 1995; 80: 2586-93.
17. Nestler JE, Jakubowicz DJ. Decreases in ovarian cytochrome P450C17-alpha activity and serum free testosterone after reduction of insulin secretion in polycystic ovary syndrome. N Engl J Med 1996;335:617-23.

เด็กหญิงวัยรุ่นที่อ้วนและเป็น Polycystic ovary syndrome (PCOS) มีภาวะดื้ออินซูลิน (วัดโดย HOMA-IR score) รุนแรงกว่าเด็กหญิงวัยรุ่นที่อ้วนแต่ไม่เป็น PCOS

ไพรัลยา สวัสดิ์พานิช, ลินดา วีรกุลวัฒนา, จีรันดา สันติประภพ, สุภาวดี ลิขิตมาศกุล

อุบัติการณ์ของโรคอ้วนในเด็กไทยกำลังเพิ่มขึ้น เด็กเหล่านี้มีความเสี่ยงสูงต่อการเกิดกลุ่มอาการเมตาบอลิก ได้แก่ ภาวะดื้ออินซูลิน เบาหวานชนิดที่ 2 ไขมันในเลือดสูง ความดันโลหิตสูง polycystic ovary syndrome (PCOS) เป็นอีกภาวะหนึ่งที่สัมพันธ์กับภาวะดื้ออินซูลิน

จุดประสงค์การศึกษา: *เพื่อเปรียบเทียบภาวะดื้ออินซูลินระหว่างเด็กหญิงวัยรุ่นที่อ้วนและเป็น PCOS กับเด็กหญิงวัยรุ่นที่อ้วนแต่ไม่เป็น PCOS*

วัตถุประสงค์: *เป็นการเปรียบเทียบลักษณะทางคลินิกและภาวะดื้ออินซูลินในเด็กหญิงวัยรุ่นที่อ้วนและเป็น PCOS 6 คน กับเด็กหญิงวัยรุ่นที่อ้วนแต่ไม่เป็น PCOS 6 คน ที่มีอายุ น้ำหนัก และดัชนีมวลกายใกล้เคียงกัน ผู้เข้าร่วมการศึกษาแต่ละคนได้รับการทดสอบการเผาผลาญน้ำตาล (OGTT)*

ผลการศึกษา: *ภาวะดื้ออินซูลิน (วัดโดย HOMA - IR score) ในเด็กหญิงวัยรุ่นที่อ้วนและเป็น PCOS มีค่าสูงกว่าเด็กหญิงวัยรุ่นที่อ้วนแต่ไม่เป็น PCOS อย่างมีนัยสำคัญ (16.5 [3.8, 21.8] vs. 4.1 [3.3, 6.9], p=0.04) เด็กหญิงวัยรุ่นที่อ้วนและเป็น PCOS มีแนวโน้มที่ระดับอินซูลินในเลือดหลังงดน้ำและอาหารสูงกว่าเด็กหญิงวัยรุ่นที่อ้วนแต่ไม่เป็น PCOS*

การศึกษาแสดงว่าเด็กหญิงวัยรุ่นที่อ้วนและเป็น PCOS มีภาวะดื้ออินซูลิน (วัดโดย HOMA-IR score) รุนแรงกว่าเด็กหญิงวัยรุ่นที่อ้วนแต่ไม่เป็น PCOS โดยความแตกต่างนี้ไม่ขึ้นกับความรุนแรงของความอ้วน เนื่องจากภาวะดื้ออินซูลินเป็นตัวพยากรณ์การเกิดโรคหลอดเลือดและหัวใจในอนาคต เด็กหญิงวัยรุ่นที่อ้วนและเป็น PCOS อาจมีความเสี่ยงสูงขึ้นต่อการเกิดโรคหัวใจและหลอดเลือดในอนาคต เมื่อเปรียบเทียบกับเด็กหญิงวัยรุ่นที่อ้วนแต่ไม่เป็น PCOS