METABOLIC PROFILE IN SONS OF WOMEN WITH POLYCYSTIC OVARY SYNDROME (PCOS)

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ABSTRACT

Context: PCOS is an endocrine–metabolic disorder with familial aggregation. It has been demonstrated that parents and brothers of PCOS women exhibit insulin resistance and related metabolic defects. However, metabolic phenotypes in sons of PCOS women have not been described. **Objective:** To assess the metabolic profiles in sons of women with PCOS during different stages of life: early infancy; childhood and adulthood. **Design:** Eighty sons of women with PCOS (PCOSS) and 56 of control women without hyperandrogenism (CS), matched for age were studied. In early infancy, glucose and insulin were determined in the basal sample. In children and adults, a 2 h OGTT was performed with measurements of glucose and insulin. Adiponectin, leptin, C-reactive protein, SHBG and serum lipids were determined in the basal sample during the three periods. **Results:** During early infancy, PCOSS showed higher weight than Cs ($p=0.038$). During childhood, weight, BMI, waist circumference, total cholesterol and LDL-cholesterol were higher in PCOSS ($p<0.05$), but after adjusting for BMI, these differences were non-significant. During adulthood, PCOSS exhibited higher weight, BMI and waist circumference ($p<0.05$). Fasting insulin, HOMA-IR, total cholesterol, LDL-cholesterol and 2 h insulin were also higher and ISI composite lower in PCOSs than in Cs ($p<0.05$). After adjusting for BMI, 2 h insulin and ISI composite remained different. **Conclusions:** The sons of PCOS women exhibit higher body weight from early infancy. In addition, insulin resistance became evident as the subjects got older, which may place them at risk for the development of type 2 diabetes and cardiovascular disease.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a familial endocrine-metabolic disorder, affecting approximately 5-8% of reproductive aged women (1-3), characterized by irregular menses, chronic anovulation, infertility and hyperandrogenism. Approximately 50% of the PCOS women are overweight or obese and most of them exhibit excess abdominal fat distribution (4,5). In addition, women with PCOS may also have other metabolic abnormalities such as insulin resistance (6,7), glucose intolerance, type 2 diabetes (4, 8-10) and an increased prevalence of lipid-related abnormalities (11-14).

In view of the high prevalence of affected individuals within families of PCOS women, a genetic basis for this syndrome has been suggested (15). This has been evaluated in different populations (16) through phenotypic and family aggregation studies. These studies have demonstrated that a significant number of female relatives are affected with this condition (17-24). However, the male phenotype of PCOS is not well defined, so it has been difficult to establish whether male relatives are also affected. Multiple possible phenotypes have been proposed including increased hair growth (15), abnormalities in male hair distribution such as premature male balding (18, 25), and metabolic abnormalities such as insulin resistance (26, 27). Insulin resistance appears to have a genetic basis, as the abnormality is perpetuated in tissue culture (26, 28). Therefore, it is possible that a proportion of the males in an affected family with PCOS might also manifest insulin resistance.

In previous studies, we demonstrated that parents and brothers of PCOS women exhibit insulin resistance and related metabolic defects more often than control subjects (29, 30).

Recently, Yildiz et al. (31) reported that first degree relatives of women with PCOS have more insulin resistance and glucose intolerance than control subjects. On the other hand, it has been proposed that PCOS has an environmental component and that intrauterine life, as an environmental factor, is implicated in the origin of PCOS (32, 33). Therefore, intrauterine life may affect the endocrine/metabolic function of a child born to a PCOS mother, independent of genetic inheritance and sex. However, no studies have evaluated the metabolic characteristics of sons of women with PCOS from the early stages of sexual development into adulthood, in order to establish whether metabolic abnormalities are present and if so, the stage of life at which they develop.

Therefore, the aim of the present study was to assess the metabolic profiles in sons of women with PCOS during three different stages of life: early infancy (2-3 months); childhood (4-7 years) and adulthood (18-30 years).

SUBJECTS AND METHODS

Subjects

We studied 80 boys (20 infants, 31 children and 29 adults) born to PCOS mothers (PCOS sons = $PCOS_S$). As a control group, we included 56 boys (20 infants, 17 children and 19 adults) born to mothers with regular menses and without hyperandrogenism (Control sons =Cs). The $PCOS_S$ and Cs were matched for age.

PCOS mothers were recruited from patients attending the Unit of Endocrinology and Reproductive Medicine at the University of Chile. This group of PCOS mothers is part of an unselected group of patients that has attended our clinic since they were diagnosed with PCOS. Diagnosis of PCOS was made according to the NIH consensus criteria (34). PCOS women were evaluated before pregnancy and they exhibited: chronic oligomenorrhea or amenorrhea, hirsutism, serum testosterone > 0.6 ng/ml and/or free androgen index (FAI) > 5.0, and androstenedione > 3.0 ng/ml. In addition, PCOS women showed the characteristic ovarian morphology of PCO on ultrasound, based on the criteria described by Adams et al. (35). PCOS women were normoglycemic, with varying degrees of hyperinsulinemia which were evaluated by an oral glucose tolerance test. All patients had an elevated waist-to-hip ratio, greater than 0.85. We excluded patients with hyperprolactinemia, androgen-secreting neoplasms, Cushing´s syndrome and late onset 21-hydroxylase deficiency, as well as thyroid disease.

All PCOS sons were born at term after spontaneous conceptions which led to singleton pregnancies. The prevalence of gestational diabetes for PCOS mothers, according to the World Health Organization criteria (36), was 17.5% and the incidence of pregnancy-induced hypertension was 13.6%. In addition, 57.5% of PCOS patients and 42.8 of control

mothers were primiparous.

As control mothers, we selected 56 women of similar socio-economic level as the PCOS patients, with a history of singleton pregnancies, regular 28- to 32-day menstrual cycles, absence of hirsutism and other manifestations of hyperandrogenism, and no history of infertility or pregnancy complications.

There were no siblings included in the groups studied.

The protocol was approved by the institutional review boards of the San Juan de Dios and San Borja Arriarán Hospitals, and the University of Chile. All parents and boys older than 8 years signed an informed consent before entering the study.

Study protocol

Infants and children were admitted with their mothers to the pediatric unit of our Clinical Research Center at approximately 08:30 h. We performed a complete physical examination on each boy, including anthropometric measurements (weight, height, waist, hip, BMI and BMI SDS calculated by the Growth Analyser Program using the USA Growth Charts BMI for age). Adult males were admitted to our Clinical Research Center at approximately 08:30 h, and we obtained a clinical history and performed a complete physical examination, including anthropometric measurements

In children and adults, after a 12 h overnight fast, an oral glucose tolerance test (1.75 g/kg,

up to a maximum of 75 g glucose in 250 ml water) was performed. In children, blood samples (5 ml) were obtained at baseline and 120 min after glucose administration. In adults, blood was withdrawn before and 30, 60, 90 and 120 min after the glucose load. In infants, a blood sample (3 ml) was obtained in the fasting state. Serum glucose and insulin were determined in each sample. Circulating concentrations of adiponectin, leptin, C-reactive protein (CRP), sex hormone binding globulin (SHBG) and serum lipids were determined in the fasting sample.

Assays

Serum glucose was determined by the glucose oxidase method (Photometric Instrument 4010; Roche, Basel, Switzerland). The intra-assay coefficient of variation of this method was < 2.0%. The lipid profile was determined by standard colorimetric assays (Photometric Instrument 4010; Roche, Basel, Switzerland). Serum low density lipoprotein cholesterol (LDL-C) concentration was calculated by Friedewald's formula [LDL-C= Total Cholesterol – HDL-Cholesterol-(Triglycerides/5)].

Serum adiponectin was assayed by radioimmunoassay (Linco-Research Inc., St Charles, Missouri, USA), with a sensitivity of 1.0 ng/ml and intra- and inter-assay coefficients of variation of 1.8 and 9.0 %, respectively. Leptin concentrations were measured by radioimmunoassay (Linco-Research Inc., St Charles, Missouri, USA), with a sensitivity of 0.5 ng/ml, and intra- and inter-assay coefficients of variation of 3.9% and 4.7%, respectively. CRP concentrations were determined by an ultrasensitive immunoturbidimetric assay (CRP Latex HS, Roche Diagnostics, Mannheim, Germany),

with a sensitivity of 0.03 mg/l and intra- and interassay coefficients of variation of 1.3 and 5.7%, respectively. Serum insulin was assayed by RIA (Diagnostic Systems Laboratories, Inc. Texas, USA). The intra- and inter-assay coefficients of variation were 5 and 8%, respectively. Sex hormone binding globulin (SHBG) was determined by radioimmunometric assay (DPC, Los Angeles, CA, USA), with intra- and inter-assay coefficients of variation of 3.8 and 7.9%, respectively.

Data analysis

The measurements derived from the oral glucose tolerance test included the following:

i) Serum fasting glucose, serum fasting insulin and homeostatic model assessment (HOMA-IR) (37)

ii) Serum 2 h glucose and insulin

iii) Whole body insulin sensitivity (ISI composite) (38).

iv) Serum lipid profile, total cholesterol (TC), triglycerides (TG), LDL cholesterol (LDL-C) and HDL cholesterol (HDL-C).

v) Serum adiponectin, leptin, CRP and SHBG

Statistical evaluation

Data are expressed as median and range. Normal distribution was assessed by the Kolmogorov-Smirnov test. Differences between study groups were assessed with the Student's t-test when data were normally distributed, or Mann-Whitney test when not normally distributed.. The effect of body weight or BMI on continuous variables was evaluated using multivariate analysis (multiple linear regression techniques). Spearman

correlations analysis was used to evaluate the relationship among the variables of interest. Statistical analysis was performed with STATA 7.0 package. A *p-value* of less than 0.05 was considered to be statistically significant.

RESULTS

The clinical characteristics of control mothers and PCOS mothers at the moment of the study and the clinical characteristics of the newborns are given in table 1. Control mothers were comparable in age with PCOS mothers in the three study periods. At the time when their sons were evaluated, PCOS mothers were more obese than control mothers of infants and children. Regarding pregnancy history, gravity and parity were similar between control mothers and PCOS mothers. BMI at term of pregnancy was significantly higher in PCOS mothers of children compared to control mothers. Gestational age and birthweight were similar between newborns of PCOS mothers and of control mothers in the three groups studied. There were no small for gestational age newborns (<2.0 SD of weight) in the PCOS groups or the control groups. However, a small number of large for gestational age children (>2.0 SD of weight) was observed only in the PCOS groups (2 in the infant group; 2 in the childhood group and 1 in the adult group). The correlation between the weight of the mothers at term of pregnancy and the weight of their sons at time of study was evaluated. A positive correlation between the weight of the PCOS mothers at term of pregnancy and the weight of the sons was observed during childhood ($r=0.440$, $p=0.02$) and adulthood ($r= 0.637$, $p=0.001$). Moreover during childhood, there was a positive correlation between BMI of the mothers and BMI of their sons in the PCOS group ($r=0.425$, $p=0.02$).

The clinical and metabolic characteristics during infancy in sons of PCOS women (PCOSs) and control women (Cs) are presented in Table 2. During early infancy, $PCOS_S$ showed a greater weight ($p=0.038$) and weight SDS ($p=0.031$) than Cs. Serum glucose, insulin, HOMA-IR and lipids were similar in both groups. Adiponectin, leptin, SHBG and CRP

protein serum concentration were also similar in both groups.

During childhood, weight (p=0.003), weight SDS (p=0.001), BMI (p<0.001), BMI SDS (p<0.001) and waist circumference (p=0.001) were higher in PCOSs compared to Cs. Total cholesterol (p=0.007) and LDL-cholesterol (p=0.022) were also higher in $PCOS_S$ compared to C_S, but after adjusting for BMI, these differences were non-significant (Table 3). Adiponectin, leptin, CRP serum concentration and SHBG were not different between groups.

During adulthood, $PCOS_S$ exhibited higher weight (p=0.022), BMI (p=0.046) and waist circumference (p=0.028) than C_S. Fasting insulin (p=0.030), HOMA-IR (p=0.034), total cholesterol (p=0.043), LDL-cholesterol (p=0.034) and 2 h insulin (p=0.006) were also significantly higher. ISI composite was significantly lower than in C_S (p=0.003). After adjusting for BMI, only 2-h insulin and ISI composite remained significantly different (Table 4). Adiponectin, leptin and CRP serum concentration were not different between groups. SHBG serum concentrations tended to be lower in $PCOS_S$ compared C_S (p=0.067).

In a simple linear regression analysis, BMI was positively correlated with leptin (r=0.749, p=0.001), 2 h insulin (r= 0.531, p=0.002) and TG (r= 0.409, p=0.02) in PCOSs during childhood. In addition, BMI was positively correlated with leptin (r=0.822, p=0.001), 2 h insulin (r= 0.711, p=0.001), HOMA-IR (r= 0.733, p=0.01) and TG (r= 0.453, p=0.01) in PCOSs during adulthood. BMI was inversely correlated with ISI composite (r= -0.524, p=0.004) in PCOSs during adulthood.

DISCUSSION

In this study we evaluated metabolic parameters during different stages of life in sons of women with PCOS. We observed that PCOS sons exhibited a higher body weight than control sons at all stages. In addition, insulin resistance independent of body weight became evident during adulthood.

In the present study PCOS sons exhibited a higher body weight than control sons. During early infancy and childhood, PCOS sons showed higher weight and weight SDS than control sons, but no other metabolic changes were observed after the data were corrected by BMI. Finally during adulthood, insulin resistance was present independent of body weight, indicating that sons of PCOS women showed an abnormal metabolic profile which was more evident as the subjects became older.

Interestingly, an increased body weight during infancy was the earliest sign that was observed in our PCOSs, and persisted during the different stages of life. This may represent an important finding that may underscore the crucial role of early excess weight gain in the development of metabolic changes in these boys. As mentioned previously, approximately 50% of the PCOS women are overweight or obese and most of them exhibit an abdominal phenotype (4, 5). It has been proposed that obesity may play a pathogenetic role in the development of this syndrome in susceptible individuals (4, 39, 40). It is possible that a similar phenomenon occurs in the sons of PCOS women.

The origin of obesity in these boys is probably the consequence of several factors, which include genetic susceptibility, environmental factors and eating habits. In this regard, it is

interesting to point out that PCOS mothers were more obese than control mothers at the time when these boys were evaluated. In addition, we have demonstrated that during pregnancy, PCOS mothers are more obese and exhibit an altered metabolic profile with high insulin and low adiponectin levels (41). Moreover, in the present study a positive correlation between the weight of the PCOS mother at term of pregnancy and the weight of theirs sons was observed in children and adults Therefore, prenatal environmental factors and/or abnormal eating habits of the mother may be important for promoting weight gain. On the other hand, sisters of PCOS patients have higher BMI than sisters of normal women, suggesting a genetic component for PCOS-associated obesity in these subjects (22).

Considering that numerous studies confirm that childhood obesity is associated with insulin resistance, hyperinsulinemia and an increased risk of developing diabetes, PCOS sons constitute a high risk group for metabolic abnormalities. Interventions aimed at reducing body fat through dietary modifications and exercise are likely to improve insulin resistance, reducing the risk of developing type 2 diabetes and cardiovascular disease, similar to what has been proposed for women with PCOS (42).

Several studies have reported a high prevalence of insulin resistance in PCOS women. Few studies, however, have systematically examined possible metabolic abnormalities in male relatives of PCOS women, and none have included a concurrently-studied control group. The present study demonstrates for the first time that adult sons of women with PCOS exhibit insulin resistance according to ISI composite values, independent of body weight. Several methods have been proposed to evaluate insulin sensitivity from data obtained by the oral glucose tolerance test. Most of them rely on the ratio of plasma glucose to insulin

concentrations during the OGTT. In the present study, we chose two methods, HOMA-IR (37) and ISI composite (38). Fasting plasma glucose, fasting plasma insulin and HOMA-IR-index are poor predictors of insulin resistance and glucose intolerance in young subjects, or in studies where a small number of subjects are included (43, 44). In the case of the ISI composite, basal and post-stimulated values of glucose and insulin are integrated, differing from HOMA-IR which only considers the fasting values of glucose and insulin. Therefore, ISI composite offers more advantages than HOMA-IR and is a better method to assess individual insulin resistance in young subjects (45). After the data were adjusted by BMI, ISI composite was the only measurement of insulin resistance which persisted significantly different between control and PCOS sons during adulthood. However, we were not able to assess insulin resistance by more sensitive methods, in order to establish whether insulin resistance is present since childhood, because multiple blood sampling at this age was not possible.

The presence of insulin resistance in adult sons of PCOS women is a novel finding, which suggests that insulin resistance may constitute part of the male PCOS phenotype, as previously proposed (27). Our findings confirm the results of Norman et al. (26), who proposed that hyperinsulinemia may be an important marker of the condition in family members of PCOS patients. IR is central to the pathogenesis of both type 2 diabetes and PCOS, with a strong genetic basis and important implications for the management of both disorders. IR and hyperinsulinemia are common precursors of IGT and type 2 diabetes (46, 47). In this context, the presence of insulin resistance in early adulthood sons of women with PCOS could be the first step in the development of type 2 diabetes. Therefore, its

detection and the employment of therapeutic tools might be useful for the prevention of this disorder.

It is difficult, however, to establish whether insulin resistance in PCOS sons is a genetic trait, the result of fetal programming or both. There are relatively few studies studying this hypothesis in males. Recently, we have demonstrated that female sheep treated prenatally with testosterone exhibited reduced birth weight and impaired insulin sensitivity in early postnatal life (48). In adult male rhesus monkeys treated prenatally with testosterone, a similar phenomenon was observed (49). On the other hand in humans, we demonstrated a significant increase in androgen concentrations during pregnancy in PCOS women, suggesting that these androgens could provide a potential source of androgen excess for the fetus (50). In sum, it is possible that prenatal androgen excess may influence insulin sensitivity in the offspring of PCOS mothers, which may act in concert with an inherited genetic predisposition for a reduced insulin sensitivity in these patients.

Other metabolic variables measured in the present study, such as leptin, adiponectin, CRP and SHBG were similar in both groups. Recently, we observed that normal weight prepubertal daughters of PCOS women showed significantly lower concentrations of adiponectin and higher levels of post-stimulated insulin compared to control daughters (51). Normal weight pubertal PCOS daughters exhibited higher levels of triglycerides and post-stimulated insulin and lower levels of SHBG compared to controls, suggesting that some metabolic features of PCOS are also present in these girls (51). However, in comparison with the data of the present study, some interesting differences were observed. The boys were relatively more obese than the girls, and surrogate markers of insulin resistance such

as circulating concentrations of adiponectin and SHBG were affected in girls, but not in boys. It is possible that gender differences and body weight may partly explain these differences. However, based on our studies, we should point out that both daughters and sons of PCOS women appear to constitute high risk groups for possible metabolic derangements.

In conclusion, our results suggest that some of the metabolic alterations described in PCOS women are present in their sons. In addition, sons of PCOS women exhibit higher body weight since early life. In addition, insulin resistance became evident as the subjects got older. We propose that insulin resistance may be part of the male PCOS phenotype, and that this metabolic feature should be investigated in males born to PCOS mothers.

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Table 1.- Clinical characteristics of control mothers and PCOS mothers (PCOS) at the moment of the study and clinical characteristics of the newborns.

	Infancy		**Childhood**		**Adulthood**	
	Control mothers (n=20)	**PCOS mothers (n=20)**	**Control mothers (n=17)**	**PCOS mothers (n=31)**	**Control mothers (n=19)**	**PCOS mothers (n=29)**
Age at study (years)	28.0 (22.0 – 38.0)	31.0 (21.0 – 38.0)	32.0 (26.0 – 46.9)	33.0 (23.0 – 46.0)	49.0 (43.0 – 64.0)	51.0 (45.0 – 59.0)
BMI at study (Kg/m^2)	28.3 (21.1 – 33.6)	30.6 (23.3 – 42.0)*	24.2 (20.5 – 25.8)	30.1 (21.2 – 31.6)*	25.4 (22.3 – 26.4)	25.2 (21.8 – 33.3)
Gestations (n)	1.0 (1.0 – 3.0)	1.0 (1.0 – 4.0)	2.0 (1.0 – 4.0)	1.0 (1.0 – 4.0)	3.0 (1.0 – 4.0)	3.0 (2.0 – 4.0)
Parities (n)	1.0 (1.0 – 3.0)	1.0 (1.0 – 4.0)	2.0 (1.0 – 4.0)	1.0 (1.0 – 4.0)	3.0 (1.0 – 4.0)	3.0 (2.0 – 4.0)
Weight at term of pregnancy (Kg)	77.0 (60.0 – 90.0)	79.5 (63.0 – 115.8)	68.0 (57.0 – 76.0)	86.0 (67.0 – 120.0)*	70.0 (65.0 – 75.0)	71.0 (66.0 – 89.0)
Birthweight (Kg)	3.5 (2.7 – 4.1)	3.7 (2.6 – 4.3)	3.3 (3.0 – 3.5)	3.5 (3.1 – 4.4)	3.5 (3.1 – 4.1)	3.4 (3.0 – 4.2)
Gestational age (weeks)	39.0 (37.0 – 41.0)	39.0 (38.0 – 41.0)	38.0 (37.0 – 41.0)	40.0 (37.0 – 40.0)	40.0 (38.0 – 40.0)	39.5 (38.0 – 40.0)
SDS weight at birth	0.3 (-1.8 – 1.6)	0.7 (-1.7 –2.2)	-0.2 (-0.9 – 0.7)	0.4 (-1.4 –2.7)*	0.1 (-1.2 – 1.9)	-0.1 (-1.9 –2.4)

Values are median and range
*$p<0.05$ between control mothers and PCOS mothers

Table 2.- Clinical and metabolic characteristics during infancy in control sons (Cs) and PCOS sons (PCOSs)

	Cs (n=20)	**PCOSs (n=20)**	***P*-unadjusted**	****P*-adjusted**
Age (months)	2.0 (2.0 – 3.0)	2.0 (2.0 – 3.0)	0.582	-
Weight (kg)	5.6 (5.0 – 7.5)	6.1 (4.9 – 8.4)	0.038	-
Height (cm)	58.3 (56.0 – 61.0)	59.5 (53.0 – 67.0)	0.273	-
Weight SDS	0.3 (-0.8 – 2.0)	0.5 (-0.9 – 3.0)	0.031	-
Fasting				
Glucose (mg/dl)	100.0 (88.0 – 119.0)	102.5 (87.0 – 117.0)	0.577	0.691
Insulin (μIU/ml)	4.7 (4.0 – 14.7)	5.3 (4.0 – 24.4)	0.091	0.103
HOMA-IR	1.2 (0.9 – 4.0)	1.4 (0.9 – 6.7)	0.110	0.126
Triglycerides (mg/dl)	149.0 (75.0 – 258.0)	121.5 (70.0 – 239.0)	0.208	0.357
Cholesterol (mg/dl)	155.7 (89.0 – 224.0)	145.1 (103.0 – 183.0)	0.072	0.152
HDL-Cholesterol (mg/dl)	51.6 (35.6 – 67.5)	55.1 (33.6 – 68.1)	0.110	0.184
LDL-Cholesterol (mg/dl)	66.6 (20.3 – 152.1)	57.8 (9.9 – 101.7)	0.110	0.184
SHBG (nmol/l)	113.9 (48.3 – 173.2)	95.6 (30.3 – 164.3)	0.115	0.117
Adiponectin (ug/ml)	57.4 (49.9 – 69.8)	58.1 (34.9 – 74.4)	0.540	0.836
Leptin (ng/ml)	7.4 (1.6 – 15.0)	8.1 (2.6 – 19.3)	0.470	0.233
C-Reactive protein (mg/ml)	0.4 (0.3 – 8.9)	0.3 (0.3 – 10.8)	0.936	0.237

Values are median and range.
*p-values were adjusted by weight

Table 3.- Clinical and metabolic characteristics during childhood in control sons (Cs) and PCOS sons (PCOSs)

	Cs (n=17)	**PCOSs (n=31)**	***P*-unadjusted**	****P*-adjusted**
Age (years)	5.1 (4.0 – 7.0)	6.0 (4.0 – 7.5)	0.340	-
Weight (kg)	19.4 (14.5 – 24.0)	23.0 (14.3 – 38.7)	0.003	-
Height (cm)	111.0 (97.0 – 125.0)	116.0 (96.0 – 132.0)	0.129	-
BMI (kg/m^2)	15.1 (13.8 – 18.8)	17.4 (14.9 – 24.7)	<0.001	-
Weight SDS	-0.3 (-1.6 – 1.6)	1.0 (-1.3 – 2.8)	0.001	-
BMI SDS	-0.2 (-1.9 – 2.1)	1.2 (-0.7 – 2.9)	<0.001	-
Waist circumference (cm)	51.0 (46.0 – 61.5)	57.5 (47.0 – 70.0)	0.001	0.219
Fasting				
Glucose (mg/dl)	85.0 (64.0 – 109.2)	90.2 (59.0 – 115.0)	0.157	0529
Insulin (μIU/ml)	5.4 (4.0 – 12.3)	5.8 (4.0 – 18.0)	0.488	0.498
HOMA-IR	1.0 (0.5 – 2.6)	1.3 (0.7 – 4.3)	0.335	0.426
Triglycerides (mg/dl)	86.0 (59.0 – 130.0)	101.0 (63.0 – 174.0)	0.340	0.492
Cholesterol (mg/dl)	155.0 (110.0 – 199.0)	171.0 (129.0 – 262.0)	0.007	0.153
HDL-Cholesterol (mg/dl)	41.5 (31.6 – 73.6)	44.2 (29.8 – 58.3)	0.253	0.310
LDL-Cholesterol (mg/dl)	94.0 (60.4 – 142.5)	106.8 (52.6 – 224.3)	0.022	0.321
SHBG (nmol/l)	97.5 (59.1 – 128.1)	87.3 (53.9 – 129.8)	0.527	0.563
Adiponectin (ug/ml)	22.1 (13.9 – 39.0)	21.8 (9.3 – 61.1)	0.397	0.429
Leptin (ng/ml)	3.4 (0.7 – 9.1)	4.3 (0.9 – 10.1)	0.123	0.143
C-Reactive protein (mg/ml)	0.3 (0.3 – 7.0)	0.3 (0.3 – 5.8)	0.551	0.584
2-h				
Glucose (mg/dl)	91.4 (65.0 – 121.0)	100.5 (69.0 – 139.0)	0.051	0.285
Insulin (μIU/ml)	8.6 (4.0 – 47.3)	19.7 (4.0 – 61.1)	0.224	0.483

Values are median and range.
*p-values were adjusted by BMI

Table 4.- Clinical and metabolic characteristics during adulthood in control sons (Cs) and PCOS sons (PCOSs)

	Cs (n=19)	**PCOSs (n=29)**	***P*-unadjusted**	****P*-adjusted**
Age (years)	22.0 (19.0 – 29.0)	22.0 (18.0 – 29.0)	0.597	-
Weight (kg)	72.5 (54.0 – 86.0)	78.0 (56.2 – 139.0)	0.022	-
Height (cm)	175.0 (165.0 – 184.0)	176.0 (163.0 – 190.0)	0.399	-
BMI (kg/m^2)	22.9 (19.4 – 29.1)	25.1 (20.0 – 45.4)	0.046	-
Waist circumference (cm)	82.0 (71.0 – 95.0)	87.0 (65.0 – 129.0)	0.028	0.222
Fasting				
Glucose (mg/dl)	86.3 (65.6 – 108.6)	85.4 (65.9 – 105.4)	0.945	0.696
Insulin (μIU/ml)	7.0 (4.0 – 49.8)	10.4 (4.0 – 59.4)	0.030	0.560
HOMA-IR	1.3 (0.8 – 13.4)	2.3 (0.7 – 14.5)	0.034	0.729
Triglycerides (mg/dl)	117.5 (69.0 – 345.0)	112.0 (69.0 – 340.0)	0.663	0.367
Cholesterol (mg/dl)	163.0 (106.0 – 208.0)	182.0 (102.0 – 240.0)	0.043	0.148
HDL-Cholesterol (mg/dl)	41.9 (28.7 – 64.1)	41.3 (29.1 – 64.9)	0.548	0.399
LDL-Cholesterol (mg/dl)	97.2 (84.1 – 185.5)	114.5 (39.6 – 169.2)	0.034	0.108
SHBG (nmol/l)	26.3 (13.3 – 46.8)	23.1 (10.2 – 44.7)	0.067	0.121
Adiponectin (ug/ml)	10.5 (5.1 – 15.7)	11.5 (2.1 – 36.8)	0.194	0.121
Leptin (ng/ml)	3.2 (2.4 – 7.7)	6.1 (1.0 – 56.8)	0.364	0.317
C-Reactive protein (mg/ml)	0.7 (0.3 – 11.7)	0.7 (0.3 – 9.2)	0.513	0.237
2-h				
Glucose (mg/dl)	79.6 (54.9 – 105.5)	89.2 (57.0 – 155.0)	0.058	0.210
Insulin (μIU/ml)	18.2 (4.0 – 63.0)	55.3 (24.0 – 394.2)	0.006	0.043
ISI composite	8.3 (2.1 – 17.0)	4.6 (0.7 – 10.3)	0.003	0.010

Values are median and range.
*p-values were adjusted by BMI