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Relationship of serum adipocyte-derived proteins with insulin sensitivity and reproductive features in pre-pubertal and pubertal daughters of polycystic ovary syndrome women

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ABSTRACT

Objective: To evaluate in a cross-sectional study adiponectin and leptin levels in prepubertal and pubertal daughters of women with PCOS and their relationship to insulin sensitivity and reproductive features.
Study design: We studied 92 daughters of PCOS women (PCOSd) and 76 daughters of control women (Cd) matched by age and body mass index SD scores and distributed according to breast Tanner stage: prepuberty (Tanner 1), early puberty (Tanner 2–3) or late puberty (Tanner 4–5). In all girls an oral glucose tolerance test was performed. Leptin, adiponectin, sex steroids, SHBG, glucose, insulin and lipid profile were determined. Leptin–adiponectin ratio, free androgen index and insulin sensitivity (HOMA-IR and ISI composite) were then calculated.
Results: Prepubertal PCOSd showed lower serum adiponectin compared to Cd ($p = 0.028$), whereas during puberty no differences were observed between the groups. Leptin concentrations were similar in both groups in all Tanner stages. In addition, in PCOSd during early puberty, adiponectin showed a negative correlation with testosterone and leptin showed a negative correlation with ISI composite, which were independent of BMI SDS ($r = -0.39$; $p = 0.02$ and $r = -0.42$; $p = 0.01$).
Conclusion: These observations suggest that during the prepubertal period PCOSd exhibit abnormal adiponectin levels, independently of BMI. Moreover, leptin and adiponectin may be related to metabolic and reproductive abnormalities observed in PCOSd during the early stages of sexual development.

1. Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder in women of reproductive age, which is characterized mainly by the presence of hyperandrogenism, chronic anovulation and polycystic ovaries. Moreover, these women frequently exhibit insulin resistance, which plays a key role in the pathogenesis of this syndrome [1]. We have observed that during childhood, daughters of women with PCOS showed elevated post-stimulated insulin concentrations and lower adiponectin concentrations compared to control girls [2]. In addition, these girls exhibited an increased ovarian volume from childhood to the end of puberty and elevated testosterone levels during late puberty [3].

Pubertal development is accompanied by an increase in fat mass and changes in regional fat distribution and in the serum concentrations of adipokines. All these changes are closely related to the modifications in the insulin sensitivity observed in this period of life [4,5]. For instance, adiponectin is negatively associated with insulin resistance and visceral fat mass in girls, independent of BMI [6]. Another important molecule secreted by the adipose tissue is leptin, which is directly related with insulin resistance and subcutaneous fat mass [4,7].

It has been suggested that changes in the distribution and/or dysfunction of adipose tissue have a central role in the pathogenesis of insulin resistance. In this regard, the ratio of plasma leptin and adiponectin could reflect these disturbances. The leptin–adiponectin ratio has shown a better association with insulin sensitivity, measured by a hyperinsulinemic clamp in a large cohort of European individuals, than either leptin or adiponectin alone [8].

On the other hand, adiponectin and mainly leptin could interact at different levels with the hypothalamic–pituitary–ovarian axis, modulating its functions [9]. Therefore, these adipokines could directly affect reproductive function in PCOS daughters during

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puberty. In addition, since insulin resistance is an early feature of PCOS [10], and plays a pivotal role in the pathogenesis of PCOS, adipokines regulating insulin sensitivity may influence the development of reproductive abnormalities observed in this syndrome.

Based on our previous finding that daughters of PCOS women have decreased serum adiponectin concentrations and some reproductive alterations [2,3], in the present study we explored the relationship between leptin and adiponectin concentrations, insulin sensitivity and testosterone levels in prepubertal and pubertal daughters of women with PCOS.

2. Material and methods

2.1. Subjects

We studied 92 daughters of PCOS women (PCOSd) and 76 daughters of control women (Cd) matched by age and body mass index SD scores and distributed according to breast Tanner stage. Pubertal stage was classified as prepuberty (Tanner stage 1), early puberty (Tanner stage 2–3) or late puberty (Tanner stage 4–5). All girls were born at term from singleton pregnancies. The girls included in the study were not taking oral contraceptives or any other medication.

PCOS mothers were recruited from patients attending the Unit of Endocrinology and Reproductive Medicine, University of Chile. PCOS was diagnosed according to the National Institutes of Health criteria [11]. PCOS mothers were evaluated before pregnancy and they exhibited: chronic oligomenorrhea or amenorrhea, hirsutism, serum testosterone concentration $\geq$0.6 ng/ml, free androgen index (FAI) >5.0, and/or androstenedione concentration $\geq$3.0 ng/ml. Moreover, PCOS women showed the characteristic ovarian morphology of polycystic ovaries on ultrasound, based on the criteria described by Adams et al. [12].

As control mothers, we selected women comparable in age and socio-economic level, who had a history of regular 28- to 32-day menstrual cycles, absence of hirsutism and other manifestations of hyperandrogenism, and no history of infertility or pregnancy complications.

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 signed informed consents, and girls gave their assent before entering the study.

2.2. Study protocol

We performed a complete physical examination and pubertal development assessment, according to Marshall and Tanner, on each girl [13]. Pubertal onset was defined as having reached Tanner stage 2. Anthropometric measurements included: weight, height, waist, hip and BMI. Waist circumference (WC) was defined as the narrowest circumference between the inferior costal margin and the iliac crest in the standing position. The hip circumference measurement was obtained at the maximum perimeters at the level of the femoral trochanters. Standard deviation scores were calculated for height, weight and BMI using current National Center for Health Statistics (NCHS) standard curves. These growth curves have been shown to be applicable to contemporary Chilean populations [14]. Obesity was defined as a BMI Standard Deviation Score (SDS) >2.0. Blood pressure (BP) was measured using a standard mercury sphygmomanometer in the supine position, using the right arm after the subject had rested quietly for 5 min. The presence of metabolic syndrome was diagnosed according to International Diabetes Federation (IDF) criteria for children aged 10 years or older [15]: presence of WC >90th percentile for age and sex [16], and presence of two or more of the following findings: triglycerides (TG) >150 mg/dL; HDL-cholesterol <40 mg/dL; systolic blood pressure >130 mmHg, diastolic >85 mmHg; and plasma glucose >100 mg/dL or known type 2 diabetes.

Gynecological age was defined as the number of years past menarche at the moment of the study. Menstrual regularity was not considered in the data analysis, because irregular menses are highly frequent during the first years after the menarche.

In both groups of girls, we performed an oral glucose tolerance test (1.75 g of glucose/kg body weight, up to a maximum of 75 g glucose in 250 ml water) after a 12-h overnight fast. Blood samples (5 ml) were drawn before and 30, 60, 90 and 120 min after the glucose load. Serum glucose and insulin concentrations were determined in each sample. In post-menarcheal girls, the test was performed during the follicular phase (day 3–8). Insulin resistance was estimated by the Homeostasis Model Assessment (HOMA-IR) and by the insulin sensitivity composite index (ISI composite) [17,18]. Circulating concentrations of adiponectin, leptin, sex hormone binding globulin (SHBG), testosterone, estradiol and lipid profile were determined in the fasting sample. The leptin–adiponectin ratio (LAR) was calculated. The FAI was calculated as the ratio of serum testosterone/SHBG $\times$ 100.

2.3. Assays

Serum adiponectin and leptin concentration were assayed by radioimmunoassay (Linco-Research Inc., St Charles, Missouri, USA) with a sensitivity of 1.0 ng/ml and 0.5 ng/ml, respectively. The intra- and inter-assay coefficients of variation were 1.8 and 9.0% for adiponectin and 3.9 and 4.7% for leptin. Serum insulin and testosterone were assayed by RIA (Diagnostic Systems Laboratories, Inc., Texas, USA) with a sensitivity of 3.0 μIU/ml and 0.1 ng/ml, respectively. The intra- and inter-assay coefficients of variation were 5 and 8% for insulin and 7.0 and 11.0% for testosterone. Testosterone RIA was validated against liquid chromatography and tandem mass spectrometry [3]. Estradiol was determined by electrochemiluminiscence (Roche, Basel, Switzerland). Assay sensitivity was 5.0 pg/ml. Intra- and inter-assay coefficients of variation were 2.7 and 5.0%, 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.

Serum glucose and lipid profile were determined by standard colorimetric assays (Photometric Instrument 4010; Roche, Basel, Switzerland). The intra-assay coefficient of variation of these methods was <2.0%. Low-density lipoprotein cholesterol (LDL-C) concentration was calculated as: LDL-C = total cholesterol − HDL-cholesterol − (triglycerides/5).

2.4. Statistical evaluation

Data are expressed as mean and standard error of the mean (SEM). 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 the Mann–Whitney test when not normally distributed. Multiple regression techniques were performed to assess a possible confounding effect of BMI SDS. Associations among continuous variables were determined using the Spearman correlation coefficients test and controlled by BMI SDS. A *p*-value of less than 0.05 was considered statistically significant.

3. Results

3.1. Clinical characteristics

Clinical characteristics in Cd and PCOSd are shown in Table 1. Prepubertal and pubertal girls of both groups were comparable in

Table 1
Clinical and anthropometric characteristics of control daughters (Cd) and PCOS daughters (PCOSd) according to the Tanner stage.

	Tanner I		Tanner II–III		Tanner IV–V	
	Cd ($n=18$)	PCOSd ($n=16$)	Cd ($n=28$)	PCOSd ($n=41$)	Cd ($n=30$)	PCOSd ($n=35$)
Age (years)	8.7 ± 0.3	8.7 ± 0.3	10.7 ± 0.2	10.4 ± 0.2	12.4 ± 0.2	12.8 ± 0.3
Weight SDS	0.5 ± 0.2	0.4 ± 0.3	0.6 ± 0.2	0.5 ± 0.1	0.7 ± 0.1	0.6 ± 0.1
Height SDS	−0.3 ± 0.2	−0.4 ± 0.3	0.0 ± 0.1	0.0 ± 0.1	0.1 ± 0.1	−0.2 ± 0.1
BMI SDS	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.1
WC (cm)	61.5 ± 1.3	62.4 ± 2.3	68.4 ± 1.5	66.2 ± 1.3	69.4 ± 1.1	70.5 ± 1.4
WHR	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.8 ± 0.1	0.8 ± 0.1
Onset of puberty (years)	NA	NA	9.7 ± 0.2	9.4 ± 0.2	9.9 ± 0.2	9.6 ± 0.3
Gynecological age (years)	NA	NA	0.6	0.2	1.5 ± 0.3	2.3 ± 0.5
Menarche (%)	0	0	3.5	2.4	56.7	62.9

Values are mean ± SEM. BMI: body mass index. WC: waist circumference. NA: not applicable.

BMI SDS, waist circumference and waist to hip ratio (WHR) at each Tanner stage. The age of onset of puberty and gynecological age were similar in both groups. Moreover, the age of menarche did not differ between groups. In addition, prevalence of obesity was comparable between Cd and PCOSd (1.6% vs. 6.6%, $p = 0.09$). In girls younger than 10 years old, only two PCOSd (7.1%) showed a WC higher than 90th percentile. In girls between 10 and 16 years old, 3.9% of Cd and 4.7% of PCOSd ($p = 0.607$) had a WC higher than 90th percentile. No girls in the Cd or PCOSd groups showed elevated BP. Low HDL-C was observed in 51.0% of Cd and 45.3% of PCOSd ($p = 0.338$). Elevated TG levels were similar in both groups (23.5% of Cd and 25% of PCOSd; $p = 0.516$). Fasting glucose levels $\geq$100 mg/dl were observed in 7.8% of Cd and 4.7% of PCOSd. Metabolic syndrome was observed in only one Cd. No differences in lipid levels were observed in any Tanner stage.

3.2. Insulin sensitivity

Girls of both groups showed similar fasting serum glucose and insulin concentrations at any Tanner stage (Table 2), and consequently no differences in HOMA-IR index were found. However, 2-h serum insulin concentrations were higher in PCOSd compared to Cd in all Tanner stages. When insulin sensitivity (by ISI composite) was compared, only late pubertal-PCOSd showed decreased insulin sensitivity compared to Cd ($p = 0.04$) (Table 2).

3.3. Serum steroid concentrations and free androgen index

Serum testosterone concentrations were not different between Cd and PCOSd during the prepubertal and early pubertal periods (Table 2). However, late-pubertal PCOSd showed increased serum testosterone concentrations, lower SHBG concentrations and higher FAI when compared with Cd ($p < 0.05$). Serum estradiol concentrations were similar between groups in all Tanner stages.

3.4. Serum adiponectin and leptin concentrations

Serum adiponectin and leptin concentrations and their ratio are illustrated in Fig. 1. Adiponectin levels were significantly lower in PCOSd compared to Cd during the prepubertal period (15.4 ± 1.6 μg/ml vs. 19.5 ± 0.8 μg/ml; $p = 0.028$). These differences remained significant after data were adjusted for BMI SDS. In early and late puberty, adiponectin concentrations were similar between PCOSd and Cd. On the other hand, serum leptin concentrations were similar between PCOSd and Cd during all Tanner stages.

During the prepubertal period there was a trend to higher LAR in PCOSd compared to Cd (1.0 ± 0.3 vs. 0.6 ± 0.3; $p = 0.07$). During puberty, LAR was comparable between groups.

3.5. Association of adiponectin and leptin serum concentrations with steroid concentrations

In PCOSd, serum testosterone concentration was inversely related with serum adiponectin concentration during early puberty ($r = -0.41$; $p = 0.01$) (Fig. 2). After data were adjusted by BMI SDS this relationship remained significant ($r = -0.39$; $p = 0.02$). In Cd a direct correlation between serum testosterone and serum leptin concentrations was observed in prepubertal girls ($r = 0.50$; $p = 0.03$). This relationship was not observed when data

Table 2
Serum biochemical characteristics of control daughters (Cd) and PCOS daughters (PCOSd) according to the Tanner stage.

	Tanner I		Tanner II–III		Tanner IV–V	
	Cd ($n=18$)	PCOSd ($n=16$)	Cd ($n=28$)	PCOSd ($n=41$)	Cd ($n=30$)	PCOSd ($n=35$)
Fasting						
Glucose (mg/dl)	84.6 ± 2.5	88.0 ± 2.6	88.3 ± 1.9	83.0 ± 1.8	86.1 ± 1.6	84.6 ± 1.8
Insulin (μIU/ml)	9.1 ± 0.9	9.8 ± 1.5	12.3 ± 1.6	12.3 ± 1.2	14.4 ± 1.6	13.7 ± 1.2
HOMA-IR	1.9 ± 0.2	2.2 ± 0.4	2.7 ± 0.4	2.5 ± 0.2	3.1 ± 0.4	2.9 ± 0.3
Triglycerides (mg/dl)	113.9 ± 6.3	135.9 ± 15.8	119.4 ± 9.0	117.1 ± 7.2	124.8 ± 8.2	125.7 ± 10.0
Cholesterol (mg/dl)	180.2 ± 7.7	166.5 ± 7.6	155.6 ± 4.6	161.5 ± 4.5	154.7 ± 5.8	148.4 ± 4.6
HDL-cholesterol (mg/dl)	44.3 ± 2.0	46.1 ± 3.3	41.7 ± 1.7	43.4 ± 1.6	41.2 ± 1.3	43.3 ± 1.7
LDL-cholesterol (mg/dl)	158.7 ± 7.6	147.6 ± 8.8	139.8 ± 5.3	141.6 ± 4.7	141.4 ± 6.2	130.2 ± 5.8
Testosterone (ng/dl)	24.3 ± 3.9	24.5 ± 3.7	37.0 ± 3.6	36.5 ± 3.2	42.7 ± 3.3	68.0 ± 8.1*
Estradiol (pg/ml)	7.9 ± 1.6	7.8 ± 1.2	25.5 ± 4.2	23.9 ± 1.3	42.3 ± 3.9	35.8 ± 3.2
SHBG (nmol/L)	63.2 ± 8.6	63.0 ± 8.1	60.9 ± 6.1	61.0 ± 5.1	61.7 ± 4.5	44.3 ± 4.9*
FAI	2.3 ± 0.6	1.7 ± 0.3	3.4 ± 0.8	2.7 ± 0.5	2.7 ± 0.3	8.8 ± 1.9*
2-h						
Glucose (mg/dl)	95.7 ± 4.5	103.8 ± 3.5	99.6 ± 3.1	100.0 ± 3.0	96.7 ± 3.2	102.4 ± 4.1
Insulin (μIU/ml)	35.9 ± 4.8	50.7 ± 10.1*	48.7 ± 4.5	79.4 ± 9.6*	46.5 ± 4.7	81.7 ± 8.0*
ISI composite	7.3 ± 0.7	6.7 ± 0.9	5.8 ± 0.6	5.6 ± 0.5	6.0 ± 0.9	4.2 ± 0.3*

Values are mean ± SEM. SHBG: sex hormone binding globulin. FAI: free androgen index.
* $p < 0.05$ between Cd and PCOSd.

were adjusted by BMI SDS. Moreover, LAR was positively correlated with testosterone concentrations during early puberty in PCOSd, which remained significant after controlling by BMI SDS ($r = 0.35$; $p = 0.04$) (Fig. 2).

3.6. Association of adiponectin and leptin serum concentrations with insulin sensitivity

Serum leptin concentration was inversely related with insulin sensitivity (by ISI composite) in PCOSd in all Tanner stages (Fig. 2). After the data were adjusted by BMI SDS, only the correlation between leptin and ISI composite in early puberty remained significant ($r = -0.42$; $p = 0.01$). Moreover, LAR showed a negative correlation with ISI composite in all Tanner stages in PCOSd. However, these parameters were not statistically significant after controlling by BMI SDS. In Cd, no correlations between LAR and ISI composite were observed.

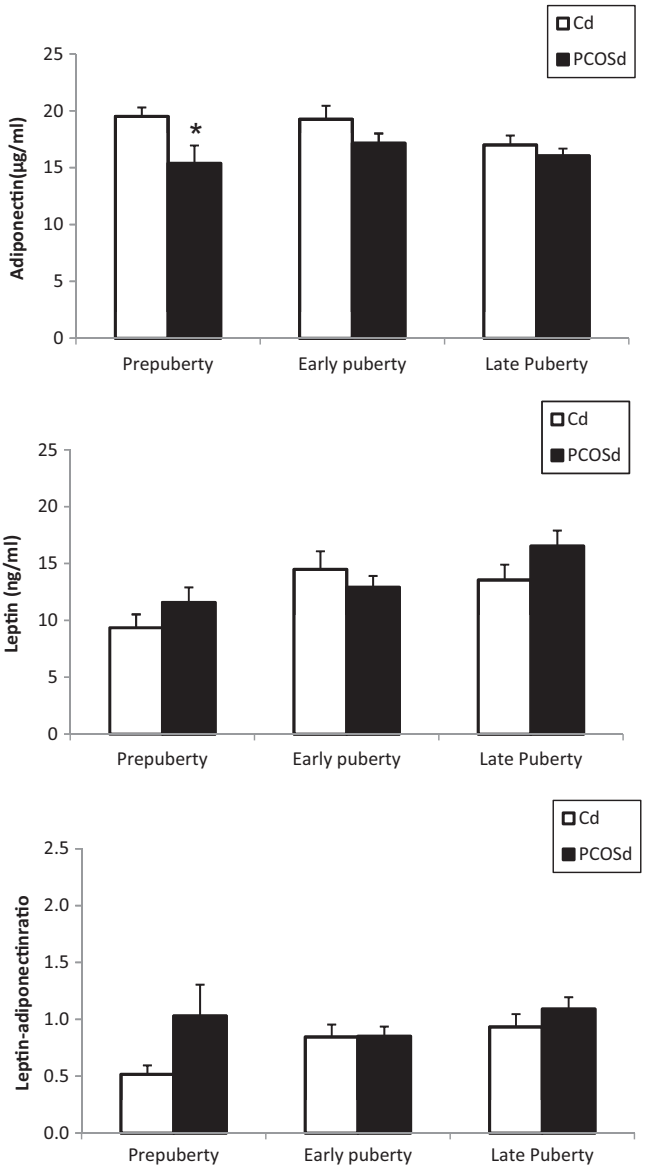

Fig. 1. Adiponectin and leptin serum concentrations and leptin–adiponectin ratio according to the Tanner stage in control daughters (Cd) and PCOS daughters (PCOSd). Values are expressed as mean ± SEM. $^{*}p < 0.05$.

4. Comments

In the present study, we expand in a BMI and Tanner stage matched study, our previous observations about adiponectin and leptin concentrations during pubertal age in daughters of PCOS women [2]. Moreover, we provide more information about the role of these adipocytokines in the development of endocrine and metabolic derangements in daughters of women with PCOS during the early stages of sexual development.

We have confirmed our previous observation that adiponectin is lower in the prepubertal period in PCOS daughters. These lower adiponectin levels were not associated with any anthropometric parameter, dyslipidemia or a higher prevalence of metabolic syndrome. Nevertheless, we observed that PCOS daughters exhibit higher insulin levels after the glucose load during the prepubertal period, which could lead to decreased adiponectin levels. In this regard, it has been demonstrated that hyperinsulinemia can induce low adiponectin secretion by adipocytes [19]. It is interesting to note that prepubertal girls born small for gestational age, at 6–8 years old exhibit lower adiponectin levels and higher concentrations of dehydroepiandrosterone sulfate, which are associated with an increase in insulin levels and the accumulation of visceral fat mass [20]. Interestingly, we have described similar findings in our cohort of PCOS daughters [21]. However, whether the lower adiponectin levels observed in these girls is a consequence or the cause of hypersinsulinaemia cannot be determined from the present study.

We did not find differences in adiponectin levels during early and late puberty. In this regard, there is controversial information about adiponectin levels in adolescents with PCOS. Early observations showed lower adiponectin levels only in obese PCOS adolescent [22]. However, that study was performed with a small sample size and without an obese control group. Recently, Yasar et al. reported lower adiponectin levels in teenage PCOS girls independent of BMI [23]. In our study, the BMI effects were excluded by matching BMI between control and PCOS daughters in all Tanner stages.

Based on a our previous observation and the values reported by Pinhas-Hamiel et al., in adolescents with PCOS [2,22] we would need 36 cases to provide a 0.8 of power; assuming a standard deviation of 6.0 μg/ml with a difference of 20% in order to find differences in adiponectin levels between our two study groups. Thus, the present study has a reasonable power to analyze the differences between both groups in terms of adiponectin levels.

Leptin concentrations were similar between PCOS and control daughters in all Tanner stages. This observation is in agreement with data reported in PCOS adolescents, who exhibit leptin levels comparable to control girls matched by BMI [24]. It has been proposed that leptin is a physiological link between adiposity and the start of sexual maturation [9]. In this regard, it has been described that leptin levels are associated with the age of menarche [25]. In our study, leptin concentrations showed a similar pattern of increase during puberty in both groups, and the age of menarche was not different between control and PCOS daughters. On the other hand, leptin levels are associated with subcutaneous adipose tissue [4]. Therefore, it is possible to suggest that in our study the body fat was not different between both groups. However, more accurate measurements of fat mass are needed to confirm this asseveration. Interestingly, leptin concentrations were inversely related to insulin sensitivity in daughters of PCOS women in all Tanner stages, which could indicate that in these girls, the changes in insulin sensitivity could be associated with variations in the amount of fat mass, independent of the Tanner stages, as previously described [7].

During early puberty, we observed a negative correlation between adiponectin and testosterone serum concentrations and

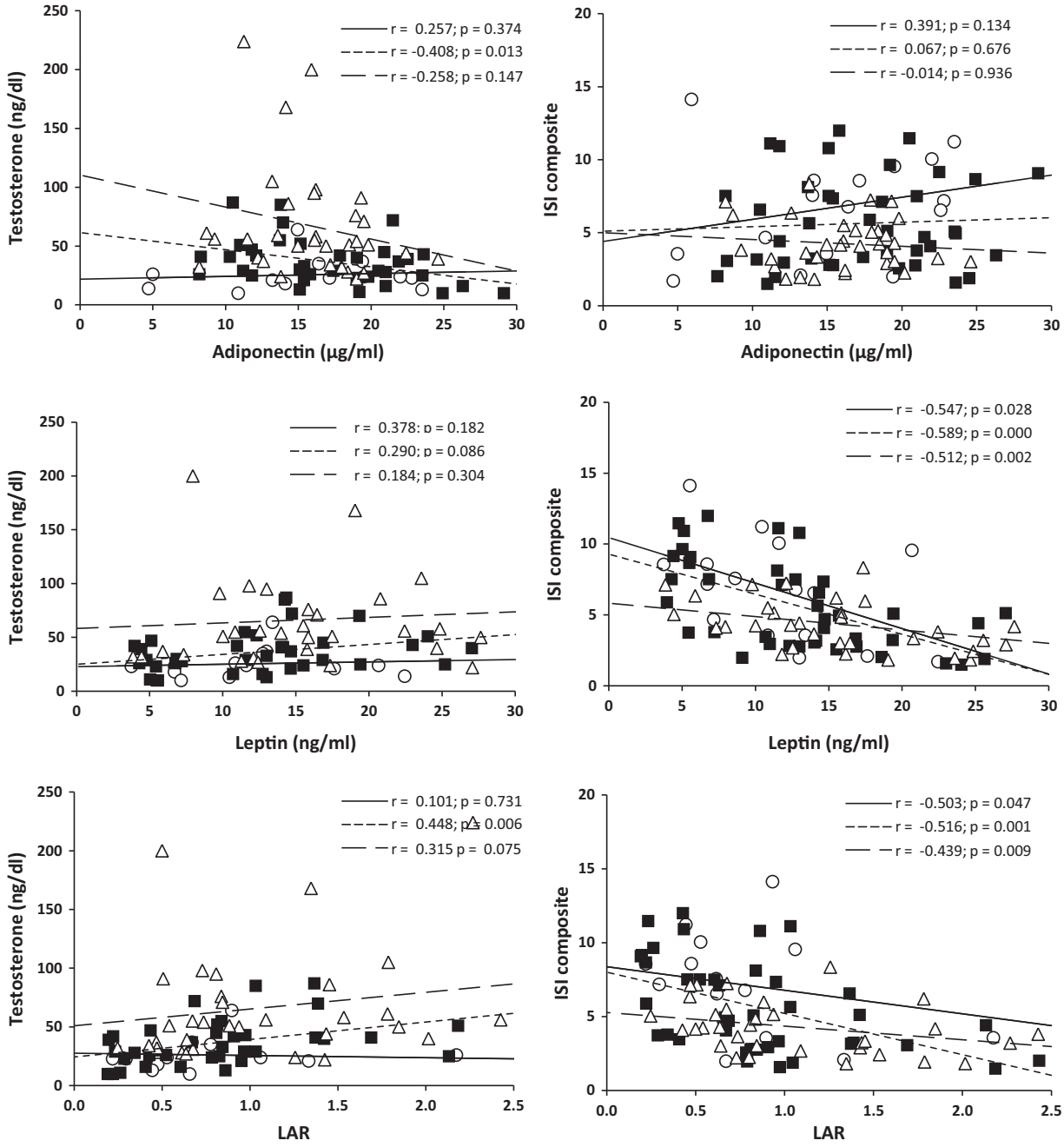

Fig. 2. Spearman's correlation between the concentrations of adiponectin and leptin, leptin–adiponectin ratio, testosterone serum concentrations and ISI composite in PCOS daughters (PCOSd) according to the Tanner stage. (○) prepuberty; (■) early puberty; (△) late puberty. The lines represent the correlation coefficients in the different pubertal stages. —— prepuberty; - - - - - - early puberty; – – – late puberty.

between leptin and insulin sensitivity, both independently of BMI SDS. These observations are intriguing since they were observed only in PCOS daughters and the real meaning of these associations is uncertain. Thus, it is possible to speculate that the negative association between adiponectin and testosterone concentrations could reflect the direct effect of adiponectin on ovarian steroidogenesis. Both isoforms of adiponectin receptors are present in granulosa and theca cells [26]. Moreover, an in vitro study indicated that adiponectin may have an inhibitory effect on steroidogenesis in bovine theca cells. In turn, in this same model adiponectin decreased the mRNA expression of luteinizing hormone receptor [27]. Therefore, in PCOS daughters the lower adiponectin levels observed during prepubertal age may affect the sensitivity of ovarian cells to the physiological increase of LH secretion during early puberty, contributing to the development of hyperandrogenism during the later stages of puberty. On the other hand, the negative relationship between leptin and insulin sensitivity could be explained by possible pro-inflammatory factors secreted by the adipose tissue that modify insulin sensitivity [1]. Therefore, it is possible that during early puberty, subtle relationships are established between the distribution and/or function of adipose tissue and the mechanisms that control insulin sensitivity and ovarian steroidogenesis.

In the present study we observed that in PCOS daughters the leptin–adiponectin ratio was positively correlated with insulin sensitivity in all Tanner stages. This suggests a possible dysfunction of adipose tissue in the establishment of insulin resistance in PCOS daughters. In this regard, it has been shown that, in PCOS women, an increased adipocyte size with lower adiponectin levels, rather than elevated androgens levels, are strongly correlated with

insulin resistance, suggesting an important role of adipose cell in the pathogenesis of impaired insulin sensitivity in PCOS [28].

In summary, we observed that adiponectin serum concentrations were lower in PCOS daughters during the prepubertal period. Therefore, we suggest that during the prepubertal period PCOS daughters present an abnormal adiponectin secretion, which is not related to the body mass index. Adiponectin and leptin may be related to metabolic and reproductive abnormalities observed in PCOSd during early stages of sexual development.

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