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Are insulin resistance and serum resistin levels increased in women with idiopathic hirsutism?

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Abstract. – OBJECTIVE: To investigate the insulin resistance and serum resistin levels in women with idiopathic hirsutism compared to controls and women with polycystic ovary syndrome (PCOS).

PATIENTS AND METHODS: Three groups of women including 23 women with idiopathic hirsutism, 28 women with PCOS and 28 non-hirsute women serving as controls were included into the study. The Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), serum fasting insulin and resistin levels were compared between the groups.

RESULTS: There were no statistically significant differences regarding the age, BMI and waist circumferences between the groups. Mean and median fasting blood glucose, fasting insulin, HOMA-IR, serum resistin levels were statistically similar between the groups ($p = 0.966$, $p = 0.378$, $p = 0.409$ and $p = 0.784$, respectively). There were no correlations between the resistin, HOMA-IR, fasting insulin levels and BMI in any of the three groups.

CONCLUSIONS: Insulin resistance and serum resistin levels do not appear to be increased in women with idiopathic hirsutism compared to controls at similar BMI's and waist circumferences.

Key Words:
Insulin resistance, Idiopathic hirsutism, Resistin, PCOS.

Introduction

Hirsutism is the excessive growth of terminal hair in androgen sensitive regions of skin in a male-like pattern. Hirsutism is due to either pathologies resulting in increased circulating androgens or it may be due to an increased sensitivity of the pilosebaceous unit (PSU) to androgens or a combination of these factors[1,2]. Polycystic ovary syndrome (PCOS), the most common cause of hirsutism, is characterized by ovarian and/or adrenal hyperandrogenism, oligo-anovulation, obesity and metabolic disturbances including insulin resistance[3,4]. Idiopathic hirsutism is the second most common cause of hirsutism and it is considered to be associated with increased peripheral 5-α reductase activity and/or androgen receptor gene polymorphysm with resultant increased activity in PSU[5,6]. Its diagnosis is based on documentation of normal ovulatory function and normal serum androgen levels with exclusion of other etiologies.

Insulin resistance is well documented in pathologies with increased ovarian and/or adrenal androgen excess[7]. Insulin resistance and resultant hyperinsulinemia may not only result in long-term metabolic and cardiovascular hazards, but it may also directly or indirectly stimulate hyperandrogenism, hair growth and contribute to the hirsutism[8-10]. Resistin is a novel adipocyte-derived polypeptide considered to induce insulin resistance and impaired glucose tolerance, and it is thought to play a role in obesity and type 2 diabetes[11-13]. Numerous studies have reported on the association between the PCOS, obesity, insulin resistance, hirsutism[14-20] and serum resistin level was also proposed to be increased and play a role in pathogenesis of PCOS through inducing insulin resistance, although controversial[16,20-23]. However, the presence of insulin resistance in idiopathic hirsutism is reported in only few studies with controversial results, and none reported on the serum resistin levels in idiopathic hirsutism so far[9,24-25].

The aim of our study is to investigate the insulin resistance and serum resistin levels in women with idiopathic hirsutism and PCOS.

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Patients and Methods

This case-control study was carried out in the Departments Obstetrics and Gynecology and Endocrinology outpatient clinics of Duzce University School of Medicine. The study was approved by the Duzce University Non-Invasive Human Research Ethics Committee. Informed consent was obtained from all women.

Population

Three groups of women within their reproductive ages including 23 women with idiopathic hirsutism, 28 women with PCOS and 28 non-hirsute women serving as controls, 79 in total, were sequentially recruited. Hirsutism was diagnosed with a Feriman Gallway Score of ≥ 8. Women with a history of diabetes (fasting blood glucose ≥ 126 mg/dl), thyroid dysfunction, hyperprolactinemia, hyperandrogenemia, cardiovascular system diseases, kidney or liver dysfunction, malignancy, Cushing syndrome, adrenal or ovarian tumour, autoimmune disease such as asthma and psoriasis and tobacco or any drug use that may have interfered with the resistin level were excluded from the study. Women who have been using hormonal preparations such as oral contraceptive pills in the last 3 months were also excluded.

Idiopathic hirsutism group consisted of hirsute women who were normoovulatory determined by serum progesterone level of 10 ng/ml or higher on the 21st-22nd days of the menstrual cycle and who were normoandrogenic confirmed with normal serum total and free testosteron, androstenedion, 17 hydroxyprogesterone and dihydroepiandrosterone sulphate levels on 2nd or 3rd day of menstural cycle with exclusion of other causes of hirsutism. The diagnosis of PCOS was based on the revised 2003 Rotterdam diagnostic criteria with the presence of at least two of the three of the following criteria: oligo- or anovulation; clinical and/or biochemichal findings of hyperandrogenism; polycystic ovaries, in addition to exclusion of other related disorders[26]. Blood samples of women with PCOS were drawn on 2nd or 3rd day of natural or progesterone induced menstrual cycle. Control group consisted of regularly menstruating women who complained of symptoms unrelated to hirsutism or any other endocrinopathy including hyperandrogenemia and ovarian dysfunction confirmed with normal serum Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH), Estradiol (E_2), Total and free Testosterone, Androstenedione or DHEAS and 17 - hydroxyprogesterone levels.

Laboratory

Venous blood samples were drawn from women after 12-hour-night fasting in morning, at 08:00 h-08:30 h in 2nd or 3rd days of the menstrual cycle. Serum specimens were separated from whole blood samples by centrifugation at 5000 rpm for 10 minutes and stored at –20 C in a deep-freeze until assayed. Hemolytic and lipemic serum samples were excluded from the study.

Serum FSH, LH, E_2, progesterone, insulin, total testosterone and dehydroepiandrosterone sulphate (DHEAS) levels were analysed by chemiluminescent immunoassay method (IMMULITE 2000, Siemens Healtcare Diagnostics Inc., Flanders, NJ, USA). Serum glucose was measured using the hexokinase method and the lipid panel including total cholesterol, LDL-cholesterol, HDL-cholesterol and triglyceride (TG) levels were measured using the enzymatic colorimetric method (Cobas 6000 C501 Roche Diagnostics GmbH, Mannheim, Germany); Serum LDL-cholesterol level was calculated using the Friedewald formula for those with a TG ≤ 400 mg/dL. The HOMA-IR (Homeostasis Model Assessment of Insulin Resistance) was used for assessing the insulin resistance using the following formula: [Fasting plasma glucose (mg/dl) x Fasting plasma insulin (μIU/ml)]/405[27,28].

Serum resistin levels were measured using the commercial ELISA kit (BioVendor, Laboratorni Medicina A.S., Brno, Czech Republic) according to manufacturers instructions. The intra-assay and inter-assay coefficients of variation were 5.2% and 7.0%, respectively with a sensitivity of 0.012 ng/mL.

Statistical Analysis

The PASW program (PASW Inc, Chicago, IL, USA, vers. 18.0 for Windows) was used for the statistical analyses. The normal range of the numeric data was analyzed using the Shapiro Wilk test and the slope histogram. Normally ranged numerical data were expressed as mean ± standard deviation (SD). The Independent Samples *t* test was used for the comparison of the two groups and the One Way ANOVA test was used for groups of more than two. Aberrantly distributed numerical data were expressed as median (minimum-maximum) and for these, the Mann Whitney U test was used for the comparison of the two groups, and the Kruskal Wallis test was used for the comparison of groups of more than two. The Spearman correlation test was used to investigate the linear correlation between the two numerical

Table I. Comparison of demographic and hormonal characteristics of groups.

	Control (n = 28)	IH (n = 23)	PCOS (n = 28)	p
Age (years)	22 (18-33)	23 (18-41)	24 (18-34)	0.770
BMI (kg/m^2)	23.6 (20.6-39.6)	22.8 (17.9-38.3)	23.4 (17.5-37.2)	0.624
WC (cm)	80.7 ± 13.1	81.8 ± 12.8	83.6 ± 13.4	0.711
FGS	3 (0-6)	11 (8-20)	6 (0-30)	**0.001**
LH (mIU/ml)	5.35 (1.80-13.50)	5.50 (2.72-31.60)	7.67 (1.4-34.0)	0.056
LH/FSH	0.93 (0.24-5.64)	1.05 (0.40-4.39)	1.38 (0.24-5.15)	0.089
E_2 (pg/ml)	30.95 (20-243)	47.2 (21.8-250.0)	57.4 (19.0-390.0)	**0.006**
Testosterone (ng/dl)	38.2 (20.0-103.0)	45.00 (19.0-176.0)	44.95 (0.55-141.0)	0.097
E_2/testosterone	0.96 (0.19-4.91)	1.26 (0.18-8.33)	1.14 (0.16-709)	0.412
DHEAS (μg/dl)	228.21±81.01	249.91±124.28	226.58±112.93	0.695
FSH (mIU/ml)	5.88 ± 2.32	5.66 ± 1.88	5.82 ± 1.65	0.918

IH: Idiopathic hirsutism; BMI: Body mass index; WC: Waist circumference; FGS: Ferriman Gallway score.

data. The qualitative categorical data were analyzed using the χ^2 test, and the results were often expressed as frequency and percentage (%). A *p* value of lower than 0.05 was accepted significant.

Statistical software Minitab V.15® was used for calculating sample size. Resistin is accepted as reference value. Mahde et al[29] reported that mean and standard deviation of resistin was 7.66±0.66 in 30 controls. We assumed the percent of larger difference of means among three groups was 10%. When power was 80% and α was 0.05, the effect size f was 0.42 and the required sample size for each group was calculated as 19.

Results

The demographic characteristics and the serum hormone levels of the PCOS, idiopathic hirsutism and control groups are presented in Table I. There were no statistically significant differences regarding the age, BMI and waist circumferences between the groups. Corresponding mean and median fasting blood glucose, fasting insulin, insulin resistance, serum resistin levels and the lipid profiles did not differ statistically between the groups (Table II).

Additionally, the median fasting insulin level [11.4 (7.2-25.6)] of 11 women with PCOS who had BMIs of > 25 kg/m^2 was found to be higher than 21 women in the slim control group [4.7 (2-6.6)] and 16 women in the slim PCOS [4.4 (2-8.4)] group. No differences were observed between the latter two groups ($P_{overall}$ = 0.003, Figure 1). The median HOMA-IR [2.6 (1.5-5.9)] of the women with PCOS who had BMI >25 kg/m^2 was found to be higher than that of the women in the slim control group [1 (0.4-1.6)] and the slim PCOS [0.9 (0.4-1.8)] groups. No differences were observed between the latter two groups ($P_{overall}$ = 0.004, Figure 1). The median resistin level [8.1 (6.9-9.7)] of the women with PCOS that had BMI>25 kg/m^2 was found to be similar to women

Table II. Comparison of metabolic parameters between the groups.

	Control (n = 28)	IH (n = 23)	PCOS (n = 28)	p
FBG (mg/dl)	88.3 ± 11.7	87.6 ± 12.1	88.5 ± 12.0	0.966
Fasting insulin (μIU/ml)	4.93 (2.00-41.00)	4.50 (1.00-18.10)	7.21 (1.0-124.0)	0.378
HOMA-IR	1.11 (0.39-12.35)	0.94 (0.20-3.93)	1.53 (0.21-23.58)	0.409
Resistin (ng/ml)	9.1 (4.4-24.3)	9.4 (3.6-37.4)	8.6 (5.3-21.3)	0.784
TG (mg/dl)	83 (33-230)	108 (41-275)	79 (44-264)	0.461
HDL (mg/dl)	52 ± 13	55 ± 11	52 ± 13	0.593
LDL (mg/dl)	98 ± 31	94 ± 19	99 ± 37	0.884

IH: Idiopathic hirsutism; FBG: Fasting blood glucose.

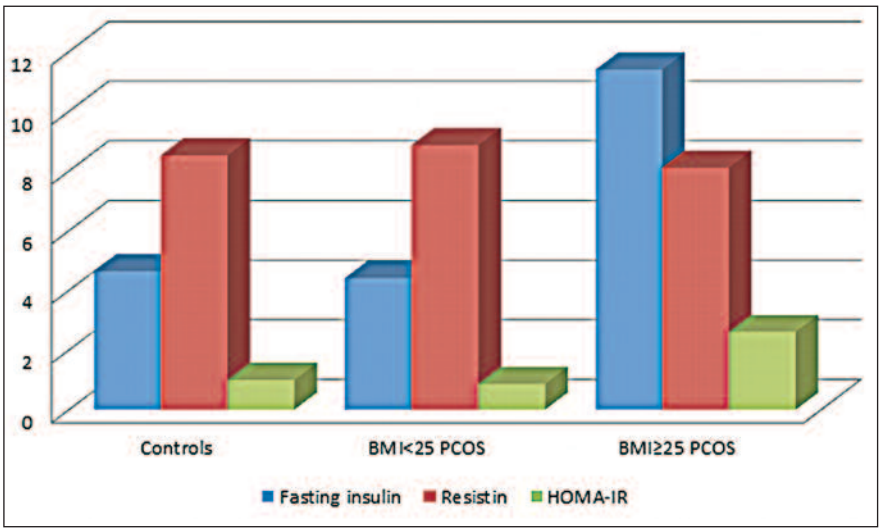

Figure I. Comparison of fasting insulin, resistin and HOMA-IR between overweight and lean PCOS groups and control group. (P_1 = Controls vs Lean PCOS; P_2 = Lean PCOS vs Obese PCOS; P_3 = Controls vs Obese PCOS; For Fasting Insulin: $P_{overall}$ = 0.003, P_1 = 0.988, P_2 = 0.001, P_3 = 0.003; For Resistin: $P_{overall}$ = 0.743, P_1 = 0.844, P_2 = 0.639, P_3 = 0.422; For HOMA-IR: $P_{overall}$ = 0.004, P_1 = 0.964, P_2 = 0.02, P_3 = 0.003).

in slim control [8.5 (7.2-11.2)] and slim PCOS [8.9 (7.6-11.2)] groups. No differences were observed between the latter two groups ($P_{overall}$ = 0.743, Figure 1).

No correlation was observed between the resistin and HOMA-IR, the fasting insulin and the BMI in groups (Table III).

When all the groups were considered, insulin resistance was observed to be positively correlated with BMI, waist circumference, DHEAS and TG, and negatively correlated with HDL. According to the results of the regression analysis, the BMI (beta = 0.478, p = 0.023) and TG (beta = 0.279, p = 0.014) were found to be independent predictors for HOMA-IR. There were no correlations between the serum resistin levels and BMI, waist circumference or any other parameters except LDL (r = 0.305, p = 0.006).

Discussion

In this study, we found that the serum resistin, fasting insulin, insulin resistance, fasting blood glucose and lipid profile did not display statistically significant differences among the groups. Additionally, we did not find any correlations between the resistin, HOMA-IR, fasting insulin levels and BMI in any of the three groups. As far as we know, our study is first to report serum resistin levels in women with idiopathic hirsutism in the literature.

Hyperinsulinemia secondary to insulin resistance may play a role and act in concert with circulating androgens in promoting hair growth with hirsutism. Insulin may directly or indirectly stimulate ovarian granulosa or theca cell steroid synthesis resulting in hyperandrogenemia and hirsutism[8]. Since the steroid-secreting cells are present in human pilosebaceous unit; insulin may stimulate local androgen production[30-32]. It may also directly increase the sensitivity of hair follicules to androgens[9]. Additionally, it has been shown that insulin and insulin-like growth factor-1 can stimulate hair follicule growth *in-vitro*[10]. Therefore, elucidation of the presence of insulin resistance in women with idiopathic hirsutism is important for both the possible long term cardiovascular risks and also for the therapeutic utility of interventions directed toward insulin resistance such as insulin sensitizers similar to their use in hirsute women with PCOS.

However, there are only few studies with conflicting results concerning insulin resistance in idiopathic hirsutism[9,24,25]. Ünlühızarcı et al[9] compared the insulin resistance of 26 women with idiopathic hirsutism and 17 controls, and they found high HOMA-IR and fasting insulin levels in idiopathic hirsutism group compared to the controls. In contrast, Kuo et al[25] detected insulin resistance in obese women with idiopathic hirsutism and PCOS. However, they determined that the insulin resistance was actually a manifestation of high BMI in idiopathic hirsutism group such that there was no evidence of insulin resistence when BMI's were one to one matched. In another recent study[24], increased insulin resistance was observed in BMI-matched non-obese woman with idiopathic hirsutism and PCOS compared to the control groups. However, when they compared the insulin resistance according to the pattern of obesity, all women with insulin resistance were the women with android obesity

Table III. Correlation analysis within the groups.

	Controls		IH		PCOS	
	r	p	r	p	r	p
Resistin vs. HOMA-IR	0.325	0.098	-0.059	0.793	-0.224	0.261
Resistin vs. Fasting insulin	0.200	0.316	-0.165	0.464	-0.187	0.349
Resistin vs. BMI	0.222	0.265	-0.177	0.431	-0.162	0.420

and they concluded that insulin resistance in idiopathic hirsutism appears to be related to android obesity. Our results were in agreement with that of Kuo et al[25] such that the insulin resistance and serum resistin levels did not differ among the idiopathic hirsutism and control groups. Additionally, there were no correlations between resistin and insulin resistance parameters in the idiopathic hirsutism group. We cannot explain the discrepancy between our results and the other studies. However, idiopathic hirsutism may be a heterogenous syndrome involving different subgroups of women like PCOS since the proposed underlying pathophysiological mechanisms in idiopathic hirsutism differ.

Women with PCOS are affected by a wide range of metabolic risk factors for cardiovascular disease, including metabolic syndrome, obesity, prediabetic states due to insulin resistance including fasting hyperglycemia, impaired glucose tolerance and type-2 diabetes[32]. Insulin resistance with secondary hyperinsulinemia is present in 50-80% of woman with PCOS and it may play important role in pathogenesis of PCOS[32]. Resistin as a novel protein secreted from the adipocytes, the primary target of insulin action, have been reported to induce insulin resistance and impaired glucose tolerance[35], and thus serve as a potential link between the obesity and insulin resistance[36]. However, the evidence for the role of resistin in insulin resistance and pathogenesis of PCOS is much less convincing[20,21,37,38]. Chu et al[16] reported that the plasma resistin levels in women with PCOS correlated positively with insulin resistance, and that the resistin protein and its mRNA expression were increased. They concluded that resistin may play a role in the pathogenesis of insulin resistance in patients with PCOS. Similarly, Yılmaz et al[19] found increased serum resistin levels in both obese and non-obese women with PCOS compared to obese and non-obese controls, respectively. However, they found no correlations with insulin resistance and BMI. In contrast, most of the studies concerning resistin in PCOS reported no significant increase in serum resistin levels and/or incerase only in obese subjects[14,19,21,23]. Seow et al[14] demonstrated 2-fold higher expression of resistin mRNA in omental fatty tissue of PCOS cases despite similar plasma resistin levels compared to controls and they suggested that resistin gene over-expression can be a local determinant in the pathogenesis of PCOS. Baba et al[17] demonstrated that the resistin gene (RETN-420G/G) homozygous protein variant was approximately 2-fold higher than that of the control group, and cases carrying this gene had high BMIs and increased insulin resistances. They also reported that the resistin gene is not a major predisposing factor for PCOS, but that it may be related to the fat deposition pattern in patients with PCOS. Our findings are in line with those studies that reported similar resistin levels in PCOS compared to controls.

Previously, it has been reported that resistin and LDL correlate strongly in women with type 2 diabetes[39]. Although our study did not include any women with type 2 diabetes, a weak correlation was observed between resistin and LDL and TG. This may show that resistin is related to dyslipidemia to some extent although it is not directly related to idiopathic hirsutism or PCOS. Our findings also show that insulin resistance (i.e. HOMA-IR) is affected by high BMI. However, there was no correlation between the resistin and high BMI or having PCOS. Additionally, although the insulin resistance was higher, the plasma resistin levels in the PCOS patients with BMI > 25 were similar to those with BMI < 25 and the slim controls. This demonstrates that insulin resistance in PCOS patients is related to a high BMI, independent from the serum resistin levels. Our data agree with the previous reports concluding that resistin levels are related to metabolic parameters such as the fat mass, triglycerides and LDL cholesterol rather than insulin resistance in obese women or women with metabolic syndrome[40-42].

Although we can conclude that serum resistin levels do not appear to be related to insulin resistance in PCOS, we cannot exclude the local role of resistin in inducing insulin resistance as Seow et al.[14] have proposed. Similarly, we cannot exclude the contribution of the local effect of resistin in idiopathic hirsutism despite the similar serum resistin levels in idiopathic hirsutism compared to controls and the absence of any correlation between the plasma resistin and HOMA-IR or BMI in any of the groups. This should especially be considered in the context of the data demonstrating that insulin and insulin-like growth factor-1 can stimulate hair follicule growth *in-vitro*[10] and insulin stimulates local androgen production since the steroid-secreting cells are present in human pilosebaceous unit[30-32]. Additionally, it is observed that increased resistin levels responds to insulin sensitizers such as thiazolidinones[36,43]. In addition, our findings should be discussed with caution because the small sample restricted us in further grouping of women based on their BMI's since that obesity is a major for insulin resistance and resistin level. However, BMI's were comparable among the groups. We did not exclude the women with impaired glucose tolerance despite excluding the women with diabetes at recruitment. Nevertheless, groups did not differ significantly among the groups for parameters of interest: fasting blood glucose, HOMA-IR.

Conclusions

Our results imply that insulin resistance do not appear to be increased in women with idiopathic hirsutism compared to controls at similar BMI's and waist circumferences. Serum resistin does not seem to be a involved in the pathogenesis of idiopathic hirsutism and PCOS regarding insulin resistance. However, wider scale studies including molecular basis are needed to conclude on this issue.

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Conflict of interest

The Authors declare that they have no conflict of interests.

References

1) Ferriman D, Gallwey JD. Clinical assessment of body hair growth in women. J Clin Endocrinol Metab 1961; 21: 1440-1447.
2) Azziz R, Carmina E, Sawaya ME. Idiopathic hirsutism. Endocr Rev 2000; 21: 347-362
3) Lobo RA, Carmina E. The importance of diagnosing the polycystic ovary syndrome. Ann Intern Med 2000; 132: 989-893.
4) Zawadzki JK, Dunaif A. Diagnostic criteria for polycystic ovary syndrome: towards a rational aproach. In: Dunaif A, Givens JR, Hasltine F, et al. eds. Polycystic Ovary Syndrome. Cambridge, MA: Blackwell Scientific, 1992; pp. 377-384.
5) Serafini P, Lobo RA. Increased 5a-reductase activity in idiopathic hirsutism. Fertil Steril 1985; 43: 74-78.
6) Legro RS, Shahbahrami B, Lobo RA, Kovacs BW. Size polymorphisms of the androgen receptor among female Hispanics and correlations with androgenic characteristics. Obstet Gynecol 1994; 83: 701-706.
7) Escobar-Morreale HF, Serrano-Gotarredona J, García-Robles R, Varela C, Sancho JM. Abnormalities in the serum insulin-like growth factor-1 axis in women with hyperandrogenism. Fertil Steril 1998; 70: 1090-1100.
8) Kopera D, Wehr E, Obermayer-Pietsch B. Endocrinology of hirsutism. Int J Trichology 2010; 2: 30-35.
9) Unlühizarci K, Karababa Y, Bayram F, Kelestimur F. The investigation of insulin resistance in patients with idiopathic hirsutism. J Clin Endocrinol Metab 2004; 89: 2741-2744.
10) Itami S, Kurata S, Takayasu S. Androgen induction of follicular epithelial cell growth is mediated via insulin-like growth factor-I from dermal papilla cells. Biochem Biophys Res Commun 1995; 212: 988-994.
11) Wang H, Chu WS, Hemphill C, Elbein SC. Human resistin gene: molecular scanning and evaluation of association with insulin sensitivity and type 2 diabetes in Caucasians. J Clin Endocrinol Metab 2002; 87: 2520-2524.
12) McTernan PG, Fisher FM, Valsamakis G, Chetty R, Harte A, McTernan CL, Clark PM, Smith SA, Barnett AH, Kumar S. Resistin and type 2 diabetes: regulation of resistin expression by insulin and rosiglitazone and the effects of recombinant resistin on lipid and glucose metabolism in human differentiated adipocytes. J Clin Endocrinol Metab 2003; 88: 6098-6106.
13) Pagano C, Marin O, Calcagno A, Schiappelli P, Pilon C, Milan G, Bertelli M, Fanin E, Andrighetto G, Federspil G, Vettor R. Increased serum resistin in adults with Prader-Willi syndrome is related to obesity and not to insulin resistance. J Clin Endocrinol Metab 2005; 90: 4335-4340.
14) Seow KM, Juan CC, Wu LY, Hsu YP, Yang WM, Tsai YL, Hwang JL, Ho LT. Serum and adipocyte resistin in polycystic ovary syndrome with insulin resistance. Hum Reprod 2004; 19: 48-53.
15) Wang Y, Sun Y, Qiu H. Expression of resistin mRNA in adipose tissue of rat model with polycystic ovarian syndrome and its implication. J Huazhong Univ Sci Technolog Med Sci 2004; 24: 621-624.

16) Chu Y, Cui Q, Feng G, Song Z, Jiang X. The expression of resistin in adipose tissues of patients with polycystic ovary syndrome and insulin resistance. J Huazhong Univ Sci Technolog Med Sci 2009; 29: 642-645.
17) Baba T, Endo T, Sata F, Nagasawa K, Honnma H, Kitajima Y, Hayashi T, Manase K, Kanaya M, Moriwaka O, Kamiya H, Yamada H, Minakami H, Kishi R, Saito T. The contributions of resistin and adiponectin gene single nucleotide polymorphisms to the genetic risk for polycystic ovary syndrome in a Japanese population. Gynecol Endocrinol 2009; 25: 498-503.
18) Yilmaz M, Bukan N, Demirci H, Oztürk C, Kan E, Ayvaz G, Arslan M. Serum resistin and adiponectin levels in women with polycystic ovary syndrome. Gynecol Endocrinol 2009; 25: 246-252.
19) Panidis D, Koliakos G, Kourtis A, Farmakiotis D, Mouslech T, Rousso D. Serum resistin levels in women with polycystic ovary syndrome. Fertil Steril 2004; 81: 361-366.
20) Arikan S, Bahceci M, Tuzcu A, Kale E, Gökalp D. Serum resistin and adiponectin levels in young non-obese women with polycystic ovary syndrome. Gynecol Endocrinol 2010; 26: 161-166.
21) Lu XE, Huang HF, Li MG, Zhu YM, Qiang YL, Dong MY. Resistin levels of serum andfollicular fluid in non-obese patients with polycystic ovary syndrome during IVF cycles. J Zhejiang Univ Sci B 2005; 6: 897-902.
22) Escobar-Morreale HF, Villuendas G, Botella-Carretero JI, Alvarez-Blasco F, Sanchón R, Luque-Ramírez M, San Millán JL. Adiponectin and resistin in PCOS: a clinical, biochemical and molecular genetic study. Hum Reprod 2006; 21: 2257-2265.
23) Carmina E, Orio F, Palomba S, Longo RA, Cascella T, Colao A, Lombardi G, Rini GB, Lobo RA. Endothelial dysfunction in PCOS: role of obesity and adipose hormones. Am J Med 2006; 119: 1-6.
24) Abdel Fattah NS, Darwish YW. Is there a role for insulin resistance in nonobese patients with idiopathic hirsutism? Br J Dermatol 2009; 160: 1011-1015.
25) Kuo J, Kumar A, Decherney AH, Azziz R. Are patients with idiopathic hirsutism (IH) insulin resistant? Comparing women with IH to body mass index-matched patients with polycystic ovary syndrome (PCOS) and controls. Fertil Steril 2004; 82: S301-302.
26) The Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Human Reprod 2004; 19: 41-47.
27) Borai A, Livingstone C, Kaddam I, Ferns G. Selection of the appropriate method for the assessment of insulin resistance. BMC Med Res Methodol 2011; 11: 158.
28) Borai A, Livingstone C, Ferns G. The biochemical assessment of insulin resistance. Ann Clin Biochem 2007; 44: 324-342.
29) Mahde A, Shaker M, Al-Mashhadani Z. study of omentin1 and other adipokines and hormones in PCOS patients. Oman Med J 2009; 24: 108-118.
30) Pham-Huu-Trung M, Villette J, Bogyo A. Effects of insulin-like growth factor 1 (IGF-1) on enzymatic activity in human adreno-cortical cells: interactions with ACTH. J Steroid Biochem Mol Biol 1991; 39: 903-909.
31) Chen W, Thiboutot D, Zouboulis C. Cutaneous androgen metabolism: basic research and clinical perspectives. J Invest Dermatol 2002; 119: 992-1007.
32) Mark C, David M, Diane T. Correlation between serum levels of insulin-like growth factor-1, dehydroepiandrosterone sulfate, and dihydrotestosterone and acne lesion counts in adult women. Arch Dermatol 2005; 141: 333-338.
33) Huang G, Coviello A. Clinical update on screening, diagnosis and management of metabolic disorders and cardiovascular risk factors associated with polycystic ovary syndrome. Curr Opin Endocrinol Diabetes Obes 2012; 19: 512-519.
34) Alvarez-Blasco F, Botella-Carretero JI, San Millán JL, Escobar-Morreale HF. Prevalence and characteristics of the polycystic ovary syndrome in overweight and obese women. Arch Intern Med 2006; 166: 2081-2086.
35) Kim KH, Lee K, Moon YS, Sul HS. A cysteine-rich adipose tissue-specific secretory factor inhibits adipocyte differentiation. J Biol Chem 2001; 276: 11252-11256.
36) Steppan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, Wright CM, Patel HR, Ahima RS, Lazar MA. The hormone resistin links obesity to diabetes. Nature 2001; 409: 307-312.
37) Carmina E, Orio F, Palomba S, Cascella T, Longo RA, Colao AM, Lombardi G, Lobo RA. Evidence for altered adipocyte function in polycystic ovary syndrome. Eur J Endocrinol 2005; 152: 389-394.
38) Olszanecka-Glinianowicz M, Kuglin D, D bkowska-Hu A, Skałba P. Serum adiponectin and resistin in relation to insulin resistance and markers of hyperandrogenism in lean and obese women with polycystic ovary syndrome. Eur J Obstet Gynecol Reprod Biol 2011; 154: 51-56.
39) Al-Daghri N, Chetty R, McTernan PG, Al-Rubean K, Al-Attas O, Jones AF, Kumar S. Serum resistin is associated with C-reactive protein & LDL cholesterol in type 2 diabetes and coronary artery disease in a Saudi population. Cardiovasc Diabetol 2005; 4: 10.
40) de Luis DA, Gonzalez Sagrado M, Conde R, Aller R, Izaola O, Perez Castrillon JL, Dueñas A. Relation of resistin levels with cardiovascular risk factors and insulin resistance in non-diabetes obese patients.Diabetes Res Clin Pract 2009; 84: 174-178.
41) De Luis DA, González Sagrado M, Conde R, Aller R, Izaola O. Resistin levels and inflammatory markers in patients with morbid obesity. Nutr Hosp 2010; 25: 630-634.
42) de Luis DA, Gonzalez Sagrado M, Conde R, Aller R, Izaola O, Primo D. Lack of association of serum resistin levels with metabolic syndrome criteria in obese female patients. Clin Biochem 2011; 44: 1280-1283.
43) Rangwala SM, Rich AS, Rhoades B, Shapiro JS, Obici S, Rossetti L, Lazar MA. Abnormal glucose homeostasis due to chronic hyperresistinemia. Diabetes 2004; 53: 1937-1941.