MEDICAL CHANNEL

Original Article

SERUM STATUS OF RESISTIN AND INSULIN IN POLYCYSTIC OVARY SYNDROME

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ABSTRACT

Background: Resistin is secreted from the adipose tissue. It causes impairment in glucose utilization. Polycystic ovary syndrome (PCOS) is associated with amenorrhea or oligomenorrhea, chronic anovulation and polycystic ovaries.
Objective: To estimate serum level of resistin and insulin and their relation in patients with PCOS.
Study Design: Case control study.
Material and Methods: Fifty one diagnosed patients of PCOS age ranging between 18-35 years were selected from gaenocology and Obstetric department, JPMC and 25 age-matched control were included from the general population as control group with regular monthly cycle. Age, weight, height and body mass index measured. Hormones were estimated using kits in serum such as resistin, Follicle stimulating hormone, lutinizing hormone, Insulin and HOMA-IR in addition to fasting blood glucose,.
Result: Total 51 patients included in this study. They have got significantly high level of serum resistin and insulin in PCOS group as compared to control. But resistin has no correlation with the parameters such as BMI, fasting blood glucose and HOMA-IR.
Conclusion: Serum resistin is significantly higher in patients with PCOS while it has no correlation with fasting blood glucose, BMI and HOMA-IR

Key words: Resistin, insulin, HOMA-IR, PCOS.

INTRODUCTION

Adipose tissues in addition to storing energy, secretes numerous hormones involved in modulating insulin sensitivity and energy balance, such as leptin, adiponectin and resistin. The hormone resistin is a 12.5 KDa cysteine rich protein also known as 'Adipokine', produced during adipocyte differentiation in mice. Its levels decreased by insulin sensitizing agent and are increased in diet induced and genetic forms of obesity.[1] Administration of anti-resistin antibody improves blood sugar and insulin action in mice with diet induced obesity. Heilbronn et al., (2004)[2] observations demonstrates that there are multiple cellular sources of resistin in humans. Munir et al., (2005)[3] showed a positive association between resistin levels and insulin resistance but some failed to demonstrate this relationship.[4] Resistin levels observed to be higher in women than compared with men. A significant association exists between obesity and polycystic ovary syndrome (PCOS), and it observed that women with PCOS have higher resistin levels[5], so it was assumed that resistin is involved directly or indirectly in promoting the severity of symptoms in PCOS.

Polycystic ovary syndrome previously called Stein-Leventhal syndrome, defined as chronic oligmenorrhea or amenorrhea, elevated levels of circulating androgens or hyperandrogenism and presence of polycystic ovaries on ultrasonography.[6] This is also associated with insulin resistance, hyperinsulinemia, chronic anovulation and obesity.[7] No single etiological factor is fully responsible for abnormalities in PCOS, in response to stimulation by luteinizing hormone (LH) the stromal cells of the ovaries synthesizes

increased levels of androdgens (testosterone)[8]. There is increased secretion of luteinizing hormone as compared to follicle stimulating hormone (FSH) in PCOS.[9]

Insulin acts synergistically with LH to enhance the androgen production from theca cells. Increased insulin level inhibits hepatic synthesis of sex hormone binding globulin, the key circulating protein that binds to testosterone and thus increases the proportion of testosterone that circulates in the unbound form.[10] Insulin is vital for transportation of glucose at the cellular levels, it regulates blood glucose level and has role in carbohydrate and lipid metabolism. Insulin resistance causes increased insulin secretion may be one of the contributors in the development of PCOS.[11] In present study, emphasis has been given to estimate the level of serum resistin and insulin in patients with PCOS and to find any correlation among these parametes.

MATERIALS AND METHODS

This study was carried out in the Department of Biochemistry, Basic Medical Sciences Institute in collaboration with Gynaecology & Obstetrics, Jinnah Postgraduate Medical Centre, Karachi. A total 76 subjects included in the study after informed consent as 51 diagnosed patients with polycystic ovary syndrome (PCOS) age range18-35 years and 25 age matched healthy females from general population as control group, with regular monthly cycle for comparison.

Inclusion criteria: Inclusion criteria of PCOS was based on ESHRE/ASRM (2004)[6], also called Rotterdam Criteria for PCOS followed by amenorrhea or oligomenorrhea, elevated levels of circulating androgens and/or clinical manifestation of androgen excess or presence of polycystic ovaries on ultransonography.

Exclusion criteria: Patients having diabetes mellitus, hormonal diseases related to adrenals, thyroid or pituitary diseases excluded from the study.

Following biophysical Parameters: Age (years), weight (Kg), height (m) and body mass index (Kg/m^2) were measured. The height and weight of all subjects measured in feet and kilogram respectively, weight by using weighing scale machine (China made) and height in feet (converted into meters). Body mass index (BMI) and HOMA-IR were calculated by formula: BMI= weight (Kg)/height(m^2) and HOMA-IR= Fasting blood glucose (mg/dl) X Fasting serum insulin (mIU/ml)/405 . About 8ml of blood was taken after an over night fast, serum was separated and biochemical parameters were analyzed: Fasting blood glucose by glucose oxidase method (Randox, UK), serum insulin, resistin, testosterone, LH and FSH by ELISA, using Kit Monobind Inc, USA,.

Sample Collection Blood sample were collected on the day second of menses after 12 hours of fasting from each subject. About 8 ml of blood was taken, 2 ml was put in separate tube for blood glucose testing and 6 ml was transferred into centrifuge tube, then after 45 minutes, it was centrifuged and supernatant was preserved for analysis at -20ºC. Before analysis, serum was allowed to attain room temperature.

Statistical analysis :Statistical analysis was done on SPSS(statistical package for social sciences) version 11. A descriptive statistical analysis of continuous variables was performed. Data on continuous variables include age, weight, height, BMI, FBG, serum insulin, resistin, FSH, LH and testosterone and HOMA-IR was presente as Mean± SEM. Statistical comparison between diseased group and normal control group was done by student t-test. Pearson coefficient of correlation was used to find the relationship between the PCOS and normal control groups.

RESULTS

Table 1 showed the comparison of biophysical parameters between PCOS and age matched control group. The mean age and height of PCOS and control group were non-significant, while weight and BMI were significantly higher in PCOS group as compared to control.

Biochemical parameter compared between PCOS and age matched control groups, the levels of fasting serum insulin, resistin, LH and testosterone hormones and HOMA-IR were statistically significantly high ($p<0.05$) while serum FSH was low in PCOS as compared to control. Fasting blood glucose was not significant when compared to controls as shown in table 2.

Table 3 showed the correlation coefficient of age BMI and blood glucose versus parameters. Age show significant positive correlation with BMI (r=0.37), fasting blood glucose (r=0.54) and HOMA-IR (r=0.34), while serum insulin, resistin, FSH, LH and testosterone showed weak correlation with age. BMI showed significant positive correlation with blood glucose (r=0.41), serum insulin (r=0.40) and HOMA-IR (r=0.29), whereas serum FSH, serum LH, serum resistin and serum testosterone showed positive but weak association with BMI. Blood glucose showed weak association with serum insulin, resistin, LH and FSH, while serum testosterone showed weak negative correlation, but HOMA-IR showed significant positive correlation (r=0.38) with blood glucose.

Table 4 showed the correlation coefficient of serum insulin and serum resistin versus parameters in PCOS group. Serum insulin showed non-significant positive correlation with age, fasting blood glucose, serum resistin and testosterone hormones. Serum insulin showed weak association with serum FSH and LH, whereas it showed significant positive association ($r=0.40$, $p<0.05$) with BMI and HOMA-IR ($r=0.74$, $p<0.05$). Serum resistin showed non-significant correlation with all parameters.

DISCUSSION

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder of reproductive-aged women with an estimated prevalence of 4-8%.[12] Obesity is very common clinical feature in women affected by PCOS. Approximately fifty percent women are overweight or obese and history of weight gain frequently precedes the onset of oligomenorrhea and hyperandrogenism. Insulin resistance or hyperinsulinemia present in women with PCOS, is considered the key factor responsible for hyperandrogenism.[13] Elevated insulin level causes increased secretion of luteinizing hormone (LH) over follicle stimulating hormone (FSH), increased LH secretion stimulates ovaries to synthesize more androgens.[14] Utzschneider et al., (2005)[15] states that there was no difference in resistin level with high or low BMI and high or low insulin sensitivity. Resistin was initially shown to be released in large amount from mouse adipocytes, its release was increased in obese mice and accompanied by insulin resistance.[1]

Yildiz et al. (2007)[16] studied the prevalence rate of PCOS with obesity and obesity was present in more than 50% of women in their PCOS group. For the BMI, they also gave the prevalence rate and states that the prevalence rate of PCOS increased with

TABLE 1
BIOPHYSICAL PARAMETERS OF PCOS AND CONTROL GROUP

(Values are expressed as Mean ± SEM)

Biophysical parameters	PCOS (n=51)	Control (n=25)
Age (Years)	25.6±0.67	26.7±0.88
Weight (Kg)	77.7±1.64*	55.6±1.68
Height (m)	1.6±0.01	1.6±0.01
BMI (Kg/m^2)	29.8±0.67*	21.6±0.62

* Significantly higher as compared to control ($p<0.05$).

TABLE 2
BIOCHEMICAL PARAMETERS OF PCOS AND CONTROL GROUP

(Values are expressed as Mean ± SEM)

Biochemical parameters	PCOS (n=51)	Control (n=25)
FBG (mg/dl)	98.1±1.66	93±2.13
Serum insulin (µIU/ml)	16.1±0.75*	9.1±0.93
Serum resistin (ng/ml)	21.1±2.03*	9.6±0.53
Serum FSH (µIU/ml)	5.8±0.23º	6.7±0.37
Serum LH (µIU/ml)	14.8±0.65*	3.0±0.41
Serum testosterone (ng/ml)	0.94±0.04*	0.38±0.03
HOMA-IR	3.9±1.88*	2.1±0.21

* Significantly high as compared to control ($p<0.05$). ºSignificantly low as compared to control ($p<0.05$).

FBG = Fasting blood glucose, FSH = Follicle stimulating hormone, LH = Lutinizing hormone, HOMA-IR = Homeostasis Model Assessment for Insulin Resistance.

TABLE 3
CORRELATION COEFFICIENT OF AGE, BMI AND FASTING BLOOD GLUCOSE WITH PARAMETER IN PATIENTS WITH PCOS

Parameters	Age (Years)	BMI (Kg/m^2)	Fasting blood glucose (mg/dl)
Age (Years)	-	0.37*	0.54*
BMI (Kg/m^2)	0.37*		0.41*
Fasting blood glucose	0.54*	0.41*	
Serum insulin (IU/ml)	0.20	0.40*	0.19
Serum resistin (ng/ml)	0.19	0.07	0.00
Serum FSH (mIUml)	0.20	0.19	0.15
Serum LH (mIU/ml)	-0.009	0.19	0.09
Serum testosterone (ng/ml)	0.005	0.04	-0.07
HOMA-IR	0.34*	0.29*	0.38*

*Significant correlation $p<0.05$.

TABLE 4
CORRELATION COEFFICIENT (r) OF SERUM INSULIN AND RESISTIN IN PATIENTS WITH PCOS

Parameters	Serum insulin (mlU/ml)	Serum resistin (ng/ml)
Age (Years)	0.20	0.19
BMI (Kg/m^2)	0.40*	0.07
Fasting blood glucose	0.19	0.00
Serum insulin (IU/ml)	-	0.15
Serum resistin (ng/ml)	0.15	-
Serum FSH (mIUml)	0.03	-0.02
Serum LH (mIU/ml)	-0.05	0.01
Serum testosterone (ng/ml)	0.15	0.21
HOMA-IR	0.74*	0.07

*Significant correlation $p<0.05$.

increase in BMI and may reach upto 12.4% and 11.5% in women with BMI 35-40 kg/m^2. Our study is consistent with Yildiz *et al.,*(2007)[16] study, because there was high BMI in our PCOS group as compared to normal control. This indicates that prevalent obesity may increase the risk of PCOS in a population but this effect is relatively modest because stress is the fact that PCOS is likely due to intrinsic or inherited factors,

PCOS is one of the most common endocrine disorders in women of childbearing age and often connected to insulin resistance and its consequences. All studies have shown that there is impaired insulin metabolism in a large number of women with PCOS.[17] In our study we found elevated fasting insulin levels in PCOS group as compared to normal control. These findings are in agreement with the study of Carmina *et al.,* (2005)[18] and Ducluzeau *et al.,* (2003)[19] they found high levels of insulin in PCOS subjects. Glintborg *et al.*, (2006)[14] and Ilhan *et al.*, (2005)[20], also found elevated fasting serum insulin levels in the subjects with PCOS group than normal control. Our results are in agreements with these studies as shown in table 2.

We also evaluated fasting blood glucose levels in study and normal control group. It was similar and within normal limits in both groups. Ilhan *et al.*, (2005)[20] studied that fasting insulin levels were higher in PCOS group but there were no significant differences in fasting blood glucose levels. Our results are in agreement with above study.

One of the most important parameter is HOMA-IR[21]. our study is in justification with the study of Carmina and Lobo, (2009)[22], but our results contradict with Arikan *et al.*, (2010)[23] who states

that mean HOMA-IR values were similar in PCOS group and in normal control.

Serum resistin is an important peptide hormone and is an adipokine secreted from human adipose tissues. Escobar-Morreale *et al*., (2006)[24] found high levels of serum resistin in obese PCOS group. Panidis *et al*., (2004)[25] recovered that resistin levels were elevated in obese women with PCOS as compared to lean weight PCOS and lean normal control, whereas Heilbronn *et al*., (2004)[2] studied that resistin levels were not related with BMI, and also states that resistin is unlikely to be a major link between obesity and insulin resistance in humans, our results are consistent with these studies. However, Carmina *et al*., (2006)[26] found same serum levels of resistin in PCOS and control group while our results contradict with their study.

Yongli *et al*.,(2002)[27] studied that hyperandrogenemia is a significant feature when associated with menstrual disturbance and male type hair growth in women having PCOS. Further states that serum testosterone levels were significantly higher in these subjects. Our results are in agreement with the study of Yongli *et al*., (2002)[27] as shown in table 2. Our study showed raised levels of LH in PCOS group as compared to normal control and justified with study of Kumar *et al*., (2007)[28].

Glucose tolerance deteriorates with aging; prevalence of type 2 diabetes has been estimated to increase linearly with age in both men and women. In our results age has significant positive correlation with fasting blood glucose and HOMA-IR like the results of *Iozzo et al*., (1999). [29]

Lu *et al*., (2005)[30] and Yilmaz *et al*., (2009)[31] in their study stated that serum resistin levels were higher in normal weight (lean) PCOS group and also age matched normal control group. But the serum resistin level did not correlated with BMI, LH and insulin level and HOMA-IR in PCOS group and they concluded that serum resistin did not have any correlation with hormonal and metabolic parameters and suggested that resistin is unlikely a factor to take part in severity of symptoms of PCOS. Our results are consistent with this study because resistin levels was higher in our PCOS group and resistin had no correlation with BMI, insulin, testosterone, LH and HOMA-IR as shown in table 4.

We found significantly high levels of serum resistin in PCOS groups while fasting blood glucose was normal in PCOS. It is suggested that fasting serum insulin and glucose may be included as a routine investigation along other diagnostic tools in PCOS.

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