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Comparative study of serum fasting blood glucose level, insulin resistance, serum thyroid stimulating hormone level, serum ferritin level and serum gama amino butyric acid level in diagnosed polycystic ovarian syndrome patients

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***Abstract*---**Aim and Objective: To evaluate to evaluate the levels of Serum Fasting blood glucose, IR, Serum TSH, Serum Ferritin and Serum GABA in diagnosed PCOS patients and normal controls. Methods: The study was conducted on 160 subjects aged between 18 to 45 years comprising of 80 healthy control and 80 patients with clinically diagnosed cases of PCOS, acted as study group. The blood samples of controls as well as study groups were withdrawn and Clinical evaluation included anthropometry, Height, Weight, Body Mass Index (BMI) and waist-to-hip ratio (WHR) were calculated. Circulating levels of fasting glucose, insulin resistance, Serum Thyroid stimulating hormone level, Serum Ferritin level and Serum Gama amino butyric acid level were determined by Chemiluminescence based immunoassay (CLIA) on fully automated Biochemistry analyzer

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MAGLUMI 1000. Results: Total 160 subjects with both control and study group PCOS patients were included in the study. The age of these control group was ranged from 18 to 45 years, with a mean of 26.23±5.58 years and PCOS study were found 27.76 ±6.54 years. The findings of anthropometric measurements of the subjects of both PCOS syndrome (n=80) and non-PCOS (n=80). As expected, mean levels of BMI, Weight, Height showed marked difference and were statistically significantly increased (P<0.0001) in both the groups. The serum levels of serum Fasting blood glucose level, insulin resistance, Serum TSH level, and Serum Ferritin were significantly increased (P<0.0001) and Serum GABA level levels were significantly reduced (P<0.0001) in subjects with PCOS and without PCOS compared to controls. Conclusion: Our study suggested a strong association of PCOS with insulin resistance, Ferritin, TSH along with GABA in this part of the country.

***Keywords*---**Polycystic ovarian syndrome, Insulin resistance, HOMA-IR, Ferritin, TSH

Introduction

Polycystic ovarian syndrome (PCOS) is most common form of chronic anovulation associated with androgen excess.[1] It occurs in 5-10 % of women of reproductive age group.[2] Stein and Leventhal[3] described association of bilateral polycystic ovaries with signs of amenorrhea, oligomenorrhea, hirsutism and obesity and it was referred to as polycystic ovarian disease, later on to be known as PCOS to reflect the heterogeneity of this disorder. It can be defined as association of hyperandrogenism with chronic anovulation without specific underlying disease of the adrenal or the pituitary glands.4 According to European Society for Human Reproduction and embryology (ESHRE) and American Society for Reproductive Medicine (ASRM)[5] presence of any two of the following three criteria can be used for diagnosis: (a) polycystic ovaries on ultrasound scan; (b) oligo and/or anovulation; and (c) clinical or biochemical evidence of hyperandrogenism, provided other etiologies (congenital adrenal hyperplasia, androgen-secreting tumors, Cushing syndrome) have been excluded. Also the presence of 12 or more follicles in each ovary, measuring 2-9 mm in diameter, and or increase ovarian volume (>10ml) is considered as morphological diagnostic criteria based on ultrasonography.[1, 6]

One of the most significant disorder was the demonstration of unique form of insulin resistance (IR) and associated hyperinsulinemia.[2,7] IR is characterized by impaired glucose response to specific amount of insulin1. It can be clinically defined as inability of known quality of exogenous or endogenous insulin to increase glucose uptake and use in an affected individual as much as it does in normal person. It is a major factor in pathogenesis of non-insulin dependent diabetes mellitus. IR is frequently observed in lean and obese women with PCOS.

This association of IR and anovulatory hyperandrogenism is commonly found throughout the world and among different ethnic groups.[8]

Long term health implications of PCOS includes metabolic disorders (hyperinsulinemia and IR, impaired pancreatic beta cell function and increased risk of type 2 diabetes, obesity, hyperlipidemia) and increased risk of cardiovascular disease.[5,9-13]

Factors contributing to potential iron overload in women with PCOS include the iron-sparing effect of chronic anovulation and oligo or amenorrhea, insulin resistance, and a decrease in hepcidin, which leads to increased iron absorption.

Iron is essential for cell metabolism and is a constituent of hemoproteins, such as hemoglobin, myoglobin, and cytochrome P450, and total body iron levels are precisely regulated under normal physiologic conditions.4 Ferritin is a ubiquitous intracellular protein that stores iron in cells and its circulating levels serve as a marker for body iron stores. Ferritin is essential for the regulation of iron homeostasis, it is found in proportion to the size of cellular iron stores in absence of other confounding factors. Iron is a strong pro-oxidant, and high body iron levels are associated with an increased level of oxidative stress, which causing inhibition of insulin internalization and actions, results in hyperinsulinemia and insulin resistance. In the progression of diabetes excess iron induced free radicals can cause both β cell failure and insulin resistance.[6,15] The first and clearest evidence for a relation between iron and human diabetes was observed in individuals with pathologic iron overload like hereditary hemochromatosis (HH), and later on also with transfusional iron overload.[16,17-20]

The aim of the current study was comparing the levels of Serum Fasting blood glucose level, insulin resistance, Serum Thyroid stimulating hormone level, Serum Ferritin level and Serum Gama amino butyric acid level in diagnosed polycystic ovarian syndrome patients and normal controls and also to analyze the Pearson Correlation Coefficient between Variables of Ferritin, HOMA IR with TSH, and GABA in women with Polycystic Ovarian Syndrome Subjects.

Methods

The present study was conducted in urban tertiary hospital based a Case-control analytic cross-sectional study in Departments of Biochemistry and Gynecology & Obstetrics of Faculty of Medicine and Health Sciences, SGT University, Budhera, Gurugram, India on 160 subjects aged between 18 to 45 years comprising of 80 healthy control and 80 patients with clinically diagnosed cases of PCOS, acted as study group. The blood samples of controls as well as study groups were withdrawn and Clinical evaluation included anthropometry, Hight, Weight, Body Mass Index (BMI) and waist-to-hip ratio (WHR) were calculated. Circulating levels of fasting glucose, insulin resistance, Serum Thyroid stimulating hormone level, Serum Ferritin level and Serum Gama amino butyric acid level were determined by Chemiluminescence based immunoassay (CLIA) on fully automated Biochemistry analyzer MAGLUMI 1000.

Inclusion criteria

Known cases of PCOS having at least two of the three following features as per Rotterdam's criteria[33]

1. Radiologically confirmed multiple small cysts in ovary
2. Irregular menses
3. Hirsutism (acne)

Exclusion criteria

1. Patients on drugs having androgen excess
2. Patients with Androgen secretion tumour
3. Patients with Other endocrinal disorder
4. Patients on Vitamin D drugs
5. Chronic illness (Hypertension, Chronic Kidney Disease, Coronary artery disease)

Eighty BMI and age matched healthy volunteers from general population were taken as control. After explaining the purpose details of the study to all the subjects of both the groups, a written and informed consent was taken. Ethical clearance was taken from the Institutional Ethical Committee before the start of collecting the samples.

Statistical Analysis

Detailed data of all subjects of case and control group were collected. After complete evaluation all findings were expressed in terms of Mean ± SD. Comparison between case group and control group was done using paired "t" test. All statistical analysis was done using SPSS software version 20.

Results

The clinical and biochemical parameters of the groups studied are presented in Table. 1 and Total 160 subjects with both control and study group PCOS patients were included in the study. The age of these control group was ranged from 18 to 45 years, with a mean of 26.23±5.58 years and PCOS study were found 27.76 ±6.54 years. The findings of anthropometric measurements of the subjects of both PCOS syndrome (n=80) and non-PCOS (n=80). As expected, mean levels of BMI, Weight, Height showed marked difference and were statistically significantly increased ($P<0.0001$) in both the groups. The serum levels of serum Fasting blood glucose level, insulin resistance, Serum TSH level, and Serum Ferritin were significantly increased ($P<0.0001$) and Serum GABA level levels were significantly reduced ($P<0.0001$) in subjects with PCOS and without PCOS compared to controls. (Table no. 1 & 2). Table-3 depicts the correlation coefficient analysis between variables of HOMA IR and Fasting blood sugar, Ferritin, TSH, GABA, BMI as well as weight in subjects with PCOS group. In the whole group, HOMA IR was correlated positively with Ferritin, TSH, BMI as well as weight except GAMA.

HOMA IR was significantly correlated with Fasting blood sugar (r=0.679;r=0.001), Ferritin (r=0.521;r=0.02), Thyroid Stimulating Hormone (r=0.270;r=0.029), Gamma Amino Butyric Acid (r=-0.063r=0.032), BMI (r=0.368;r=0.001), and WC (r=0.657;r=0.001) all correlation were found to be statistically significant at the 0.01 level(2-tailed). In our study, significant correlation was found between serum ferritin levels and serum insulin levels or serum glucose levels and insulin resistance in women with PCOS. Ko et al. found significant positive correlations between serum ferritin levels and serum insulin levels in addition to serum glucose levels and insulin resistance in obese women with PCOS.

Observation Tables

Table:1
The clinical, hormonal and metabolic parameters in patients with PCOS and control women

Sr.No	Parameters	Healthy control subjects (n= 80)	Polycystic Ovarian Syndrome Subjects (n= 80)	*p*-value
1.	Age (Years)	26.23±5.58	27.76 ±6.54	0.45
2.	Body Weight (Kg)	56.87±10.75	60.59±12.36	0.0001
3.	BMI (kg/m^2)	22.87±2.87	26.98±5.38	0.0001

Table: 2
The clinical, hormonal and metabolic parameters in patients with PCOS and control women

Sr.No	Parameters	Healthy control subjects (n= 80)	Polycystic Ovarian Syndrome Subjects (n= 80)	Statistical Significance (p)
1.	**Fasting blood sugar (mg/dl)**	83.12 ± 6.98	90.29 ± 8.33	0.0001
2.	**Serum Insulin (µU/L)**	18.76 ± 13.72	24.99 ± 6.93	0.0001
3.	**Serum Insulin resistance HOMA IR**	2.38 ± 1.01	5.56 ± 1.64	0.0001
4.	**Serum Ferritin level (ng/mL)**	42.67 ± 9.87	77.45 ± 19.39	0.0001
5.	**Serum Thyroid Stimulating Hormone level (ng/mL)**	2.46 ± 2.76	4.14 ± 4.34	0.0001
6.	**Serum Gamma Amino Butyric Acid level (µmol/L)**	5.67 ± 1.43	2.02 ± 0.43	0.0001

Table No. 3
Pearson Correlation Coefficient between Variables of HOMA IR with clinical, hormonal, biochemical and Anthropometric Parameters in women with Polycystic Ovarian Syndrome Subjects

S. No.	Pearson Correlated with	HOMA IR	
		r-value	Statistical Significance (p)
1.	Fasting blood sugar	0.679**	0.0001
2.	Ferritin	0.521**	0.002
3.	Thyroid Stimulating Hormone	0.270*	0.029
4.	Gamma Amino Butyric Acid	-0.063*	0.032
5.	BMI	0.368**	0.0001
6.	WC	0.657**	0.0001

** Correlation is significant at the 0.01 level (2-tailed)

* Correlation is significant at the 0.05 level (2-tailed)

HS* - Highly Significant

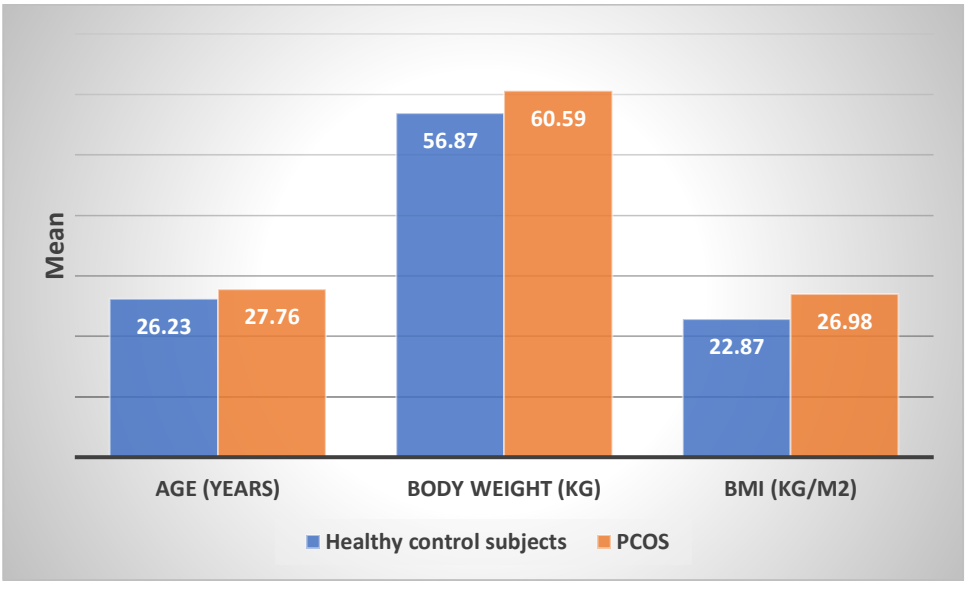

Figure: 1 Comparison of Mean±SD of Anthropometric Parameters of the Polycystic Ovarian Syndrome Subjects and without PCOS Control Subjects

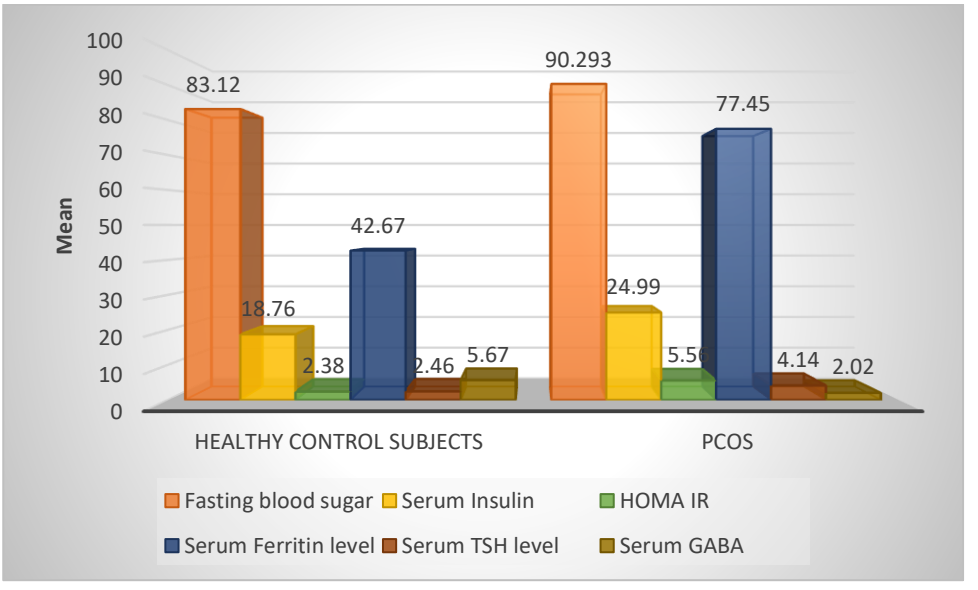

Figure: 2 Comparison of Mean±SD of Biochemical Parameters of the Polycystic Ovarian Syndrome Subjects and without PCOS Control Subjects

Discussion

This study aimed to determine the association between serum ferritin level and insulin resistance in women with PCOS. In the present study serum ferritin level is found to be associated with insulin resistance in women with PCOS. Previous findings suggest there is a relationship between iron overload and the development of insulin resistance. The central role of iron in biology can be understood by the fact that iron is the fourth most abundant element in Earth's crust as well as the transition element, most abundant in all living organisms including human being.5 Iron induced cell oxidative stress can explain some extent of its association with abnormal insulin sensitivity.[12-20]

On the other hand, it is well established that there is increased NIDDM among women with PCOS that has been ascribed to the insulin resistance characteristic of PCOS.11,17,22,33 Serum ferritin levels are also found to be increased in PCOS, suggesting mild iron overload.1,2,3,26 Therefore there is a possibility that increased iron status of PCOS patients is an associated feature with insulin resistance syndrome. A total of 99 previously diagnosed PCOS patients were included in this study maintaining selection criteria. Patients aged 20-40 years diagnosed as PCOS according to the 2003 Rotterdam revised consensus meeting were included.31 PCOS patients with known hormonal disorder or medical disorder, with recent H/O blood transfusion or intake of iron, anemic (Hb<11 g/dl), with history of heavy menstrual bleeding and history of taking drugs in previous 6 months like OCP, glucocorticoids, thiazide diuretics, anti-androgens, anti-diabetic drugs, anti-obesity drugs or other hormonal drugs were excluded from the study.

Our study suggested a strong association of PCOS with insulin resistance in this part of the world. The cause of hyperinsulinemia among women with PCOS remains unknown. This can be due to increase phosphorylation of insulin receptor proteins, which decreases its protein tyrosine kinase activity leading to abnormal insulin secretion.[20]

There are significant differences in insulin sensitivity between ovulatory and anovulatory women with PCOS. Anovulatory women with PCOS display insulin resistance whereas those with regular menstrual cycle (but who present with symptoms of hyperandrogenism) do not demonstrate insulin resistance.145 These observations suggest that there is a strong association between menstrual irregularity and insulin resistance among women with PCOS.146 Several studies have assessed glucose tolerance among PCOS women and overall risk of developing type-2 diabetes was found to be increased 3 to 7 times.[21]

The risk of glucose intolerance in PCOS women appears to be equally increased in mixed ethnicities of US population and Asian PCOS groups.[21-25] However in young Mediterranean population, prevalence of glucose was lower.[26]

The onset of glucose intolerance in PCOS occurs at an early age typically in 3rd - 4th decade of life. 156-159Also hyperinsulinemia was found to be common among female and male 1st degree relatives of women with PCOS. [27]

In our study, insulin resistance (HOMA-IR) was found to be higher in women with PCOS than in control group. However, a statistically significant result was found only in the overweight group ($p < 0.001$). Similar to our study, Durmuş et al. it was shown that women with PCOS have higher HOMA-IR.161 To achieve insulin action in a healthy metabolism, it must bind to its specific receptor in the cell membrane and phosphorylation of tyrosine. Interestingly, however, serine phosphorylation of the insulin receptor occurs in women with PCOS, resulting in post-receptor abnormalities in insulin action. [28]

In the current study, we show evidence to confirm PCOS women with relatively higher TSH level is associated with increased risk of HA phenotype from a large population. The elevated HA risk is evident after statistical correction for differences in age, BMI, thyroid autoimmunity, and increased across TSH level divided by 2.5 mU/L, suggesting the important role of TSH level and HA in PCOS women.

To the best of our knowledge, this is the first study to investigate the association between TSH levels and HA risk in a large PCOS population with normal thyroid function in a single center.

There was also no significant difference in the prevalence of subclinical hypothyroidism between women with PCOS and controls after adjusting for potential confounders. Several assumptions may explain the association between thyroid hormones and PCOS; this syndrome is associated with impaired pulsatile LH secretion and decreased SHBG through increased TRH secretion and a subsequent increase in prolactin secretion, resulting in an increase in testosterone levels.[29] On the other hand, glucose production and consumption are reduced by hypothyroidism, leading to insulin resistance. [30]

Deficiency in thyroid hormones can also be associated with weight gain and excess body mass, dyslipidemia, decreased sex hormone-binding globulin (SHBG) levels, and increased conversion of androstenedione to testosterone; these disturbances are also observed in women with PCOS.[31]

Serum GABA level was significantly decreased in PCOS subjects compared to healthy controls. However, Kawwass et al. observed significant high levels of GABA in the serum of PCOS women compared to healthy controls. Additionally, patients who take valproate antiepileptic drugs to induce GABAergic tone in the brain, usually show PCOS like symptoms.[32]

Conclusion

In conclusion, this study indicates a positive relationship between PCOS women with infertility was studied regarding insulin resistance and serum ferritin level.

Most of the PCOS patients were in 3rd decade, either overweight or obese having central obesity. Significantly increased fasting insulin level, HOMA-IR, and insulin resistant cases were reported in PCOS patients with high ferritin level.

Significantly increased serum ferritin was found in insulin resistance cases.

Statistically significant strong positive correlation was observed between serum ferritin and fasting insulin as well as between serum ferritin and HOMA IR. These results demonstrated that elevated level of serum ferritin was associated with insulin resistance in PCOS women.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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