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A STUDY ON INSULIN RESISTANCE AND ITS ASSOCIATION WITH OBESITY IN POLYCYSTIC OVARY SYNDROME

Biochemistry

Ankur Purohit* Ph D Scholar, Department of Biochemistry, Sardar Patel Medical College, Bikaner Rajasthan. *Corresponding Author

Dr. Yogita Soni Senior Professor and Head, Department of Biochemistry, Sardar Patel Medical College, Bikaner Rajasthan.

ABSTRACT

Objective: - The aim of this study was to compare the level of Insulin Resistance in PCOS women with healthy women and analyze its association with obesity. **Methodology:-**The study was conducted on 150 PCOS women and 150 age-matched healthy controls. BMI was calculated from height (m) and weight (kg) in all the subjects. Serum fasting glucose and insulin were estimated by photometric and immunoassay methods. Insulin Resistance was calculated using HOMA index. Difference in all the parameters between PCOS women and healthy women were analyzed by t-test and correlation between two parameters were accessed with Pearson's correlation test. **Results:-** PCOS women had significantly high ($p < 0.0001$) levels of BMI (27.12 ± 3.51 v/s 23.34 ± 2.12 kg/m^2), fasting glucose (91.28 ± 11.88 v/s 84.81 ± 10.68 mg/dl), fasting insulin (23.11 ± 6.25 v/s 10.98 ± 5.11 µIU/ml) and HOMA-IR (5.32 ± 1.93 v/s 2.39 ± 1.40) compared to healthy controls. A significant positive correlation ($r = 0.784$; $p < 0.0001$) was observed between HOMA-IR values and BMI in PCOS. **Conclusion: -** Increased level of Insulin Resistance indicates its role in disease progression. Further, the positive correlation of HOMA-IR with BMI explains the development of the disease to be related with obesity.

KEYWORDS

PCOS, Insulin Resistance, BMI.

INTRODUCTION

Polycystic ovary syndrome (PCOS) with a prevalence of about 5-10% in different communities is the most common endocrine disease in reproductive age women.[1] The condition was first described in 1935 by the American gynecologists Irving F Stein and Michael L Leventhal and termed as Stein-Leventhal syndrome.[2] PCOS is characterized by polycystic ovarian morphology, hyperandrogenism, and ovulatory impairment.[3] The etiology of PCOS is still unclear. However, evidence suggests a multi-factorial origin, with expression being seen in women with a genetic disposition.[4] PCOS has metabolic characteristics that include prominent defects in insulin action and β-cell function, defects that confer a substantially increased risk for glucose intolerance and type 2 diabetes.[5] Insulin also stimulates the theca cells of the ovary to produce excessive testosterone, which is responsible for the clinical symptoms of hyperandrogenism (acne, hirsutism, alopecia).[6] This hyperandrogenemia stops follicular development and therefore causes anovulation and menstrual disturbance.[7]

Pathophysiological mechanisms related to obesity influencing PCOS expression are poorly understood. Androgens have been shown to induce abdominal adipose accumulation[8] including increased lipid accumulation and insulin resistance.[9] Abdominal obesity and insulin resistance synergistically stimulate androgen synthesis in the ovaries and adrenal glands[10] and subsequently further increase abdominal obesity and inflammation, thus creating a cycle.

Obesity is present in more than half of patients with PCOS.[11] Together with the presence of insulin resistance, obesity contributes to the approximately 33% to 47% prevalence of the metabolic syndrome in PCOS patients.[12] Hence pathogenic determinants of PCOS include insulin resistance and obesity.

The purpose of the present study was to evaluate the BMI and Insulin Resistance in PCOS women and compare these values with healthy women. Also, the aim was to analyze the relationship of Insulin Resistance with obesity in women with PCOS in population.

MATERIAL AND METHODS

Subjects

The present study was done on 150 patients suffering from Polycystic Ovary Syndrome that were attending the Gynaecology OPD at PBM Hospital, Bikaner. The diagnosis of PCOS was done on the basis of Rotterdam's criteria[13] in which patients fulfilling at least 2 of the 3 criteria—that is, (1) oligo- or anovulation, (2) clinical and/or biochemical hyperandrogenism, and (3) polycystic ovaries on ultrasound measurement—were recruited into the PCOS group. These were taken as Case Group. 150 similar age-matched healthy women were selected as Control Group.

Patients with other hormonal disorders, having similar clinical features like adult-onset congenital adrenal hyperplasia, hyperprolactinemia, Cushing's syndrome, liver and renal disorders, DM, and on medications containing sex steroids, lipid-lowering agents or insulin sensitizing agents etc. were excluded from the study.

Measurements

Blood samples were drawn from patients and controls during their early follicular phase, after an overnight fast of at least 12 hours. 5 ml blood was collected in plain vial and clear non-haemolysed serum was separated. BMI was calculated by the formula using the values of height in meter and weight in kilograms.[14] Estimation of serum fasting glucose was done by photometric method.[15] Estimation of serum fasting insulin was done by immunoassay method.[16] Insulin resistance was measured by the homeostasis model assessment (HOMA-IR) method: [fasting insulin (µIU/ml) × fasting glucose (mg/dl)]/405.[17]

Data analysis

The results were presented as Mean ± SD for all quantitative parameters. Differences between means of various parameters were compared by independent t-test. Correlations between variables were tested using the Pearson's correlation test. Statistical analysis was considered to be statistically significant at $p < 0.05$.

RESULTS

The clinical and endocrine characteristics of the women studied and their statistical significance are summarized in Table 1.

Table No. 1. Clinical and Endocrine parameters of Cases and Controls.

Parameter	Controls (n = 150)	Cases (n = 150)	p-value*
Height (m)	1.62 ± 0.11	1.65 ± 0.10	< 0.05
Weight (Kg)	61.53 ± 9.31	73.64 ± 11.15	< 0.0001
BMI (kg/m^2)	23.34 ± 2.12	27.12 ± 3.51	< 0.0001
F. Glucose (mg/dl)	84.81 ± 10.68	91.28 ± 11.88	< 0.0001
F. Insulin (µIU/ml)	10.98 ± 5.11	23.11 ± 6.25	< 0.0001
HOMA-IR	2.39 ± 1.40	5.32 ± 1.93	< 0.0001

*p<0.05 was considered as statistically significant.

BMI of the PCOS patients were significantly ($p < 0.0001$) high compared to controls (27.12 ± 3.51 v/s 23.34 ± 2.12 kg/m2). PCOS patients had high level of serum fasting glucose (91.28 ± 11.88 mg/dl) and insulin levels (23.11 ± 6.25 µIU/ml) compared to serum fasting glucose (84.81 ± 10.68 mg/dl) and insulin (10.98 ± 5.11 µIU/ml) level of healthy women [Table 1, Figure 1]. This increase of glucose and insulin in PCOS was statistically significant ($p < 0.0001$).

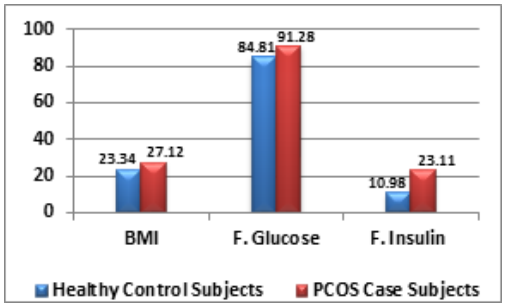

Figure 1. Mean BMI and Serum Fasting Glucose and Insulin Levels in Healthy women and PCOS women

The HOMA-IR value in PCOS patients (5.32 ± 1.93) was found significantly high compared to healthy women (2.39 ± 1.40) [Table 1, Figure 2].

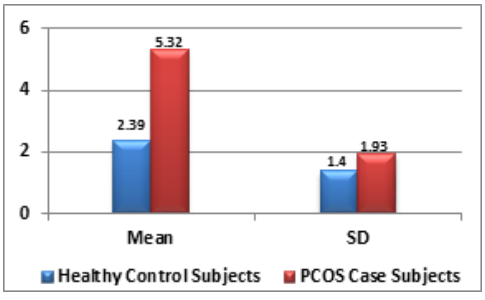

Figure 2. Mean HOMA-IR values in Healthy women and PCOS women

Table 2. Correlation of Insulin Resistance with various parameters in PCOS women.

Parameters	r-value	p-value	Significance*
Fasting Glucose	0.824	<0.001	HS
Fasting Insulin	0.954	<0.001	HS
BMI	0.784	<0.001	HS

*HS=Highly Significant

As it is shown in table 2 (Figure 3), a positive correlation was observed between Insulin Resistance and BMI (r = 0.784). This association was also statistically significant (p < 0.001).

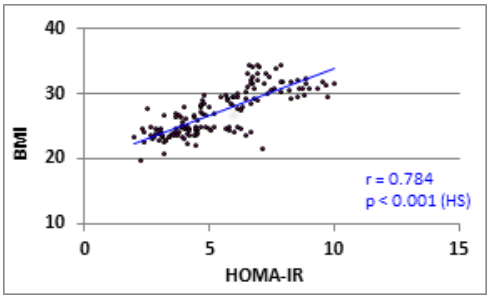

Figure 3. Correlation of Insulin Resistance with BMI in PCOS women

DISCUSSION

Over the past 30 years, it has been clearly documented that insulin resistance plays an important role in the pathogenesis of the reproductive and metabolic abnormalities of PCOS.[18] As a consequence of the perturbed insulin action, a higher amount of insulin is required to attain its metabolic effects, which results in increased production and release of insulin from pancreatic β-cells. This is why IR is frequently associated with compensatory hyperinsulinemia.[19]

Insulin resistance is a metabolic disorder caused by the impairment of insulin function in inducing glucose uptake and utilization.[20] Seow et al. demonstrated that IR in PCOS involves both receptor and post receptor defects, including defects in phosphatidylinositol 3-kinase and the GLUT-4 glucose transporter.[21] Insulin enhances the stimulating effects of LH on androgen production in ovarian theca cells by activating P450c17 expression and activity.[22] Further, insulin excess may contribute to increasing androgen levels is by inhibition of sex hormone-binding globulin (SHBG) release from the liver.[23] This attenuation of SHBG levels increases the bioavailability of free testosterone in the blood, thus promoting increased androgenic activity.

Obesity increases the risks of insulin resistance and cardiovascular disease and impairs reproductive functions.[24] Obesity-induced chronic inflammation and oxidative stress also play roles in damaging oocyte maturation. Adiponectin, IL-6, C reactive protein and TNF-α are strongly correlated with FFAs in follicular fluid.[25]

Levels of the sex hormone-binding protein (SHBG) tend to linearly decrease with increasing body fat, and this may lead to an increased fraction of free androgens delivered to target sensitive tissues.[11] The net balance of this regulation, with the dominant role of insulin, which inhibits SHBG synthesis in the liver, may be responsible for the decrease of SHBG concentrations observed in obesity.

Hyperestrogenemia is a paramount alteration, stemming from extra ovarian estrogen production in visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT), due to expression of aromatase in these adipocytes.[26] Excess estrogens may exert a positive feed-back regulation on gonadotrophin release, triggering in turn a rise in ovarian androgen production which not only cause the typical manifestations of PCOS, but also serve as substrates for extra ovarian aromatization, reinforcing this cycle of hyperestrogenemia-hyperandrogenemia in obese women with this pathology.[27]

It can therefore be speculated that insulin resistance and hyperinsulinaemia, which develop together with the obese state, may play a dominant role in favouring hyperandrogenism in women susceptible to the development of PCOS.

In the present study BMI and insulin resistance was found to be significantly (p < 0.001) elevated in Polycystic Ovary Syndrome cases. Further, the HOMA-IR values were positively correlated with BMI values in PCOS group which explained insulin resistance to be positively linked with obesity in Polycystic Ovary Syndrome.

Finding of the present study were found similar with many previous studies where insulin resistance and BMI levels were significantly high in PCOS women[28] and insulin resistance had positive association with obesity[29] while present results were contradictory with the results obtained by Mahmoudi et al.[30]

This study shows that obese PCOS have a higher risk of IR. But, this study fails to clarify if this increased risk of IR is entirely due to obesity or obesity is an independent contributor in the development of PCOS.

CONCLUSION

These results suggested the importance of insulin resistance in PCOS in terms of its clinical manifestations as well as its pathogenesis. Understanding the mechanism may help to elucidate the pathophysiology of the syndrome. It will be important to identify effective diagnostic and treatment methods in order to better identify the causes of PCOS. One possible implication of this study is that fit seems like that insulin resistant subjects with PCOS may derived increased benefit from pharmacological agents that improve insulin sensitivity and/or the drugs that reduces obesity.

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