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Original Research Article

A Study on Assessment of Testosterone, Insulin Resistance and HbA1c in Women with Polycystic Ovarian Syndrome

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ABSTRACT

Background: Polycystic ovarian syndrome (PCOS), the most common cause of infertility, is a disorder characterized by chronic anovulation, hyperandrogenism, hyperinsulinemia, and often presence of obesity. The purpose of this study was to assess serum Testosterone, Insulin resistance and glycated hemoglobin (HbA1c) in women with PCOS and to compare with healthy women as controls.
Methodology: A comparative study including 30 women diagnosed as PCOS and 30 age and BMI matched healthy women as controls was conducted. The age group for the study was 18 to 35 years. Fasting blood samples were drawn to measure serum testosterone, serum insulin, fasting blood sugar (FBS) and glycated hemoglobin (HbA1c). Insulin resistance (IR) was calculated by homeostasis model assessment (HOMA). Body Mass Index (BMI) was also calculated.
Results: A significant increase in fasting serum insulin ($p<0.001$) was found in women with PCOS in comparison with controls. Similarly, a significant increase HOMA-IR was observed in PCOS women compared to controls ($p<0.001$). Mean BMI, FBS, HbA1c and testosterone were found elevated in the PCOS population compared to controls but they were not statistically significant. No significant correlation was found between testosterone and fasting insulin.
Conclusions: The current study provides further evidence that significantly higher fasting insulin and HOMA in PCOS group indicates presence of IR. IR and high HbA1c in PCOS group may have a potential role in the prediction of dysglycemic disease in women with PCOS.

Key words: PCOS, Testosterone, Insulin resistance, HbA1c.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrine disease and metabolic disorder in adolescence and reproductive women, which is the first reason for female infertility, with the incidence of 5-10% in reproductive women. [1] According to ESHRE/ASRM consensus workshop at Rotterdam in 2003, the diagnosis of PCOS is based on the presence of any two of (1) chronic anovulation, (2) clinical/ biochemical parameters for hyperandrogenism, and (3) polycystic ovaries on ultrasonography. [2] Obesity, insulin resistance (IR) and dyslipidemia which may predispose patients to metabolic syndrome are common in PCOS. [3] Obesity modifies insulin sensitivity and gonadotropin dynamics and is associated with disorders of ovulation. [4] Compared to eumenorrheic women in the early

follicular phase of the menstrual cycle, PCOS affected women have elevated serum luteinizing hormone (LH) and low or low normal follicle stimulating hormone (FSH) levels, with an increased ratio of LH to FSH. The increased LH secretion stimulates the cal cells in the ovary to produce excess androgen and the androgen in turn, stimulates LH secretion, while the vicious cycle goes on. The androgen also inhibits production of sex hormone binding globulin (SHBG) resulting in excess free androgen responsible for hirsutism. Altered insulin action precedes the increase in androgens in PCOS. The hyperinsulinemia may cause hyperandrogenism by inhibiting hepatic synthesis of SHBG and by binding insulin like growth factor -1 (IGF -1) receptors in the ovary leading to increased androgen production by the cal cells. [5] The purpose of this study was to assess serum Testosterone, Insulin resistance and glycated hemoglobin (HbA1c) in women with PCOS and to compare with healthy women as controls.

MATERIALS AND METHODS

The study was carried out on 30 PCOS subjects in the age group of 18 to 35 years and 30 voluntary age and BMI matched healthy women with normal menstrual cycle as controls. The study was conducted at Kempegowda Institute of Medical Sciences & Hospital. The diagnosis of PCOS was fulfilled as per Rotterdam criteria. Presence of at least two criteria from clinical, hormonal and abdominal USG category was considered diagnostic of PCOS. Patients with diabetes mellitus, hypertension, renal and liver failure and other endocrine disorders and patients receiving hormonal / non-hormonal treatment for PCOS were excluded from the study. The institutional ethical committee approved the study protocol. Informed consent was obtained from all the participants.

A pre-structured and pre-tested proforma was used to collect the data. Baseline data including age, BMI, detailed medical history, clinical examinations and relevant investigations were included as part of the methodology. Serum testosterone, serum insulin, blood sugar and glycated hemoglobin (HbA1c) were measured in all participants from blood samples collected after 12 hours of fasting. Serum testosterone and serum insulin were measured by electrochemiluminescence immunoassay (Elecsys 2010 analyzer, Roche Diagnostics). HbA1c was measured by boronate affinity method (NycoCard HbA1c Glycated Hemoglobin Assay k993131). Fasting blood sugar was measured by GOD/POD method. IR was estimated via the homeostasis model assessment insulin resistance index (HOMA-IR), as follows: HOMA-IR = fasting insulin (mU/L) × fasting glucose (mmol/L)/22.5. Body mass index (BMI) was calculated as the ratio of weight (Kg) to height squared (m^2).

Statistics analysis: SPSS software version 13.0 was used for statistical analysis. Comparisons between groups were performed using the Mann-Whitney test. Correlation analysis between BMI, serum insulin and serum testosterone were done using Spearman's rank order correlation coefficients. A P value < 0.05 was considered statistically significant.

RESULTS

Results on continuous measurements are presented as Mean ± SD. The basic characteristics of the cases and controls are depicted in Table 1. There was no significant difference in age between two groups. Slightly higher mean BMI was recorded in cases than in controls but the difference in mean BMI between the two groups was not statistically significant (P>0.05). Higher mean Fasting Serum Insulin and higher mean HOMA-IR were recorded in cases compared to controls and the difference between them

were found to be statistically significant (P<0.001). Higher mean HbA1c, serum testosterone and FBS were recorded in cases compared to controls but the difference between the two groups were not statistically significant (P≥0.05). Mean distribution of biochemical parameters in PCOS cases and controls are given in Figure 1. Correlation of BMI, serum testosterone and fasting serum insulin is depicted in Table 2. No significant correlations were found between BMI, serum testosterone and fasting serum insulin in cases. Though correlation between testosterone and insulin, testosterone and HOMA-IR, and BMI and testosterone showed change in control groups (p = 0.001. p = 0.010, p = 0.012 respectively), there were no significant correlations could be found between them in cases (p = 0.251, p = 088, p = 0.652 respectively).

Table 1: Mean distribution of biochemical parameters in PCOS cases and controls. Values are expressed as means ±SD.

Parameters	Cases with PCOS (n=30)	Controls (n = 30)	P value
Age (years)	23.37 ± 4.09	23.73 ± 3.81	0.744
BMI ((kg/m2)	24.00 ± 4.41	22.51 ± 2.31	0.126
Serum Testosterone	51.02 ± 24.34	46.44 ± 21.00	0.564
Serum Insulin	12.01 ± 6.74	6.80 ± 3.10	<0.001*
HOMA-IR	2.35 ± 1.40	1.27 ± 0.58	<0.001*
HbA1c	5.91 ± 0.97	5.63 ± 0.36	0.432
FBS	80.33 ± 10.53	74.67 ± 9.59	0.050

*denotes significant difference

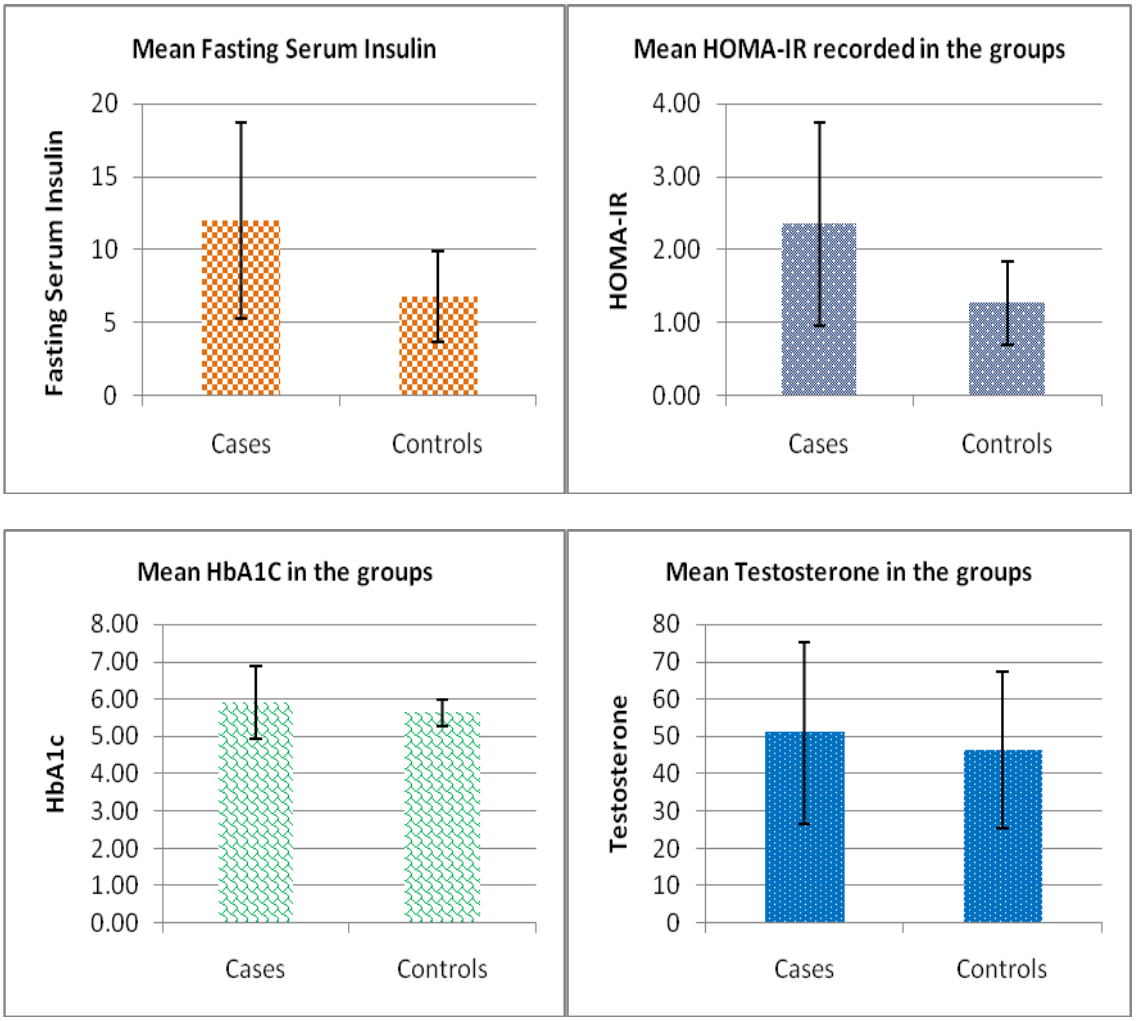

Fig 1: Mean distribution of biochemical parameters in PCOS cases and controls.

Table 2: Correlation between various parameters.

Parameters	Cases		Controls	
	ρ value	P value	ρ value	P value
Testosterone and Insulin	-0.216	0.251	-0.556	0.001*
Testosterone and HOMA-IR	-0.317	0.088	-0.462	0.010*
BMI and Insulin	0.283	0.130	-0.163	0.388
BMI and Testosterone	-0.086	0.652	0.455	0.012*

*denotes significant difference

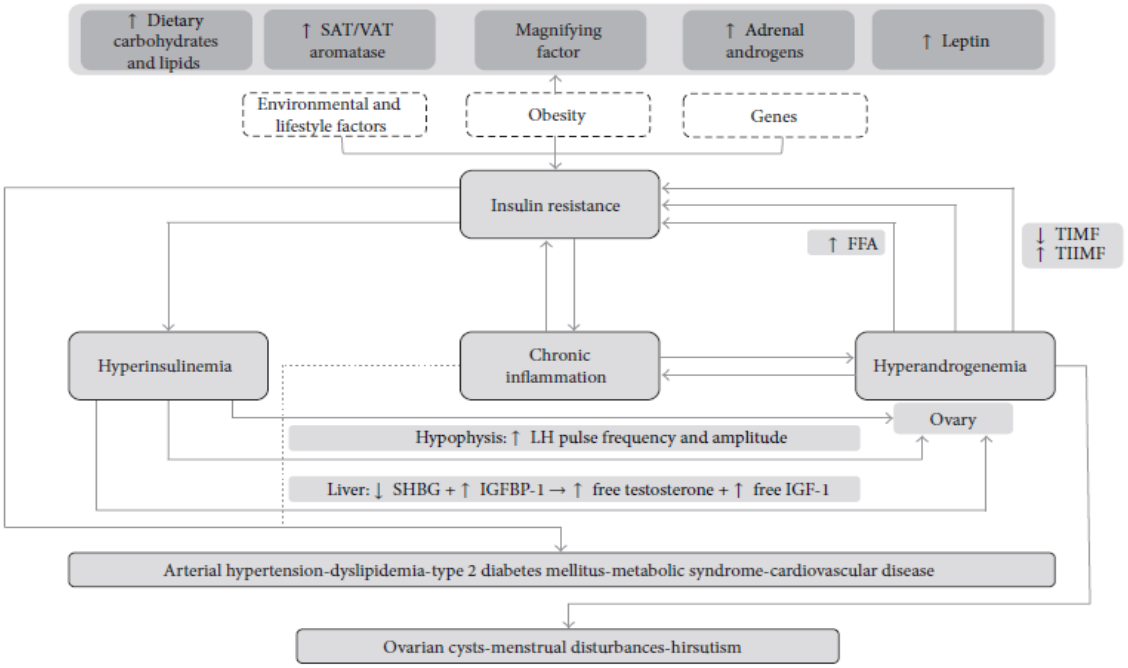

Fig.2: Interactions among insulin resistance, hyperinsulinemia, and hyperandrogenemia in the etiopathogenesis and progression of polycystic ovary syndrome and related comorbidities. [11]
SAT = subcutaneous adipose tissue; VAT = visceral adipose tissue LH = luteinizing hormone; SHBG = sex hormone binding globulin; IGFBP-1 = insulin-like growth factor binding protein-1; IGF-1 = insulin-like growth factor- 1; FFA = free fatty acids; TIMF = type I muscle fibers; TIIMF = type II muscle fibers.

DISCUSSION

The polycystic ovary syndrome (PCOS) affects between 5% and 10% of women of reproductive age. [6] The major endocrine symptom of PCOS, hyperandrogenism, is associated with a preferred fat accumulation at the upper body which is associated with hyperinsulinemia, impaired glucose tolerance, diabetes mellitus, increased androgen production rates, decrease in SHBG levels and increased levels of free testosterone and estradiol. [7] The current study compared serum testosterone, fasting insulin and HbA1c levels in PCOS cases and healthy controls.

In our study significantly higher mean Fasting Serum Insulin and higher mean HOMA-IR were recorded in cases with PCOS compared to healthy controls. Higher mean HbA1c, serum testosterone, FBS and BMI were recorded in PCOS cases compared to controls but the differences between the two groups were not statistically significant ($P \geq 0.05$). Though insulin resistance and hyperandrogenism are characteristics of PCOS, we couldn't find any significant correlations between serum testosterone and serum insulin. This finding is similar to the report by Dunaif A et al. [8]

Identification of insulin receptors throughout the ovary and the ability of insulin to stimulate biosynthesis of androgens, estrogen and progesterone in ovarian cell culture suggest that ovary is one of the target organs of insulin action. These findings clearly indicate that insulin

may play a role in normal follicular development and hence in a variety of insulin resistant states, ovarian dysfunctions are manifested. [9] Insulin resistance in PCOS has been characterized in skeletal muscle where the pathogenesis involves both intrinsic, presumably genetic, post-receptor defects in insulin metabolic signaling, as well as acquired defects due to in vivo environmental factors. Adipocytes from women with PCOS also have post-insulin receptor binding resistance to insulin effects on glucose uptake. The most common cause of androgen excess in women is PCOS, due to both intrinsic upregulation of steroid genesis and augmentation of androgen production by high circulating insulin levels. [10] In the context of PCOS, IR and hyperandrogenemia may assemble a vicious cycle, continuously stimulating each other in a reciprocal fashion. Moreover, this conjunction of endocrine-metabolic alterations sets the stage for the progressive development of additional comorbidities, both metabolic and cardiovascular, further complicating the management of these patients. [11] Interactions among insulin resistance, hyperinsulinemia, and hyperandrogenemia in the etiopathogenesis and progression of polycystic ovary syndrome and related comorbidities is given in Figure 2.

Saxena P et al advocated that hyperinsulinemia probably acts at the level of hypothalamic–pituitary axis and stimulates LH secretion which leads to anovulation with irregular cycles. In the liver, it decreases production of sex hormone-binding protein and IGF-1-binding protein which results in an increase in free androgen in the blood and an increase in free IGF-1 in the ovary. Within the ovary, it promotes formation of androstenedione and testosterone which is seen clinically as hirsutism and acne. Increased androgens are converted to estrones and are responsible for causing endometrial hyperplasia and potentiate LH secretion. Insulin resistance and hyperinsulinemia are presently considered risk factors in the development of atherosclerosis and cardiovascular disease. [2] Our finding were consistent with study done by P. Supriya et al. who found a significant increase in fasting serum insulin, serum testosterone levels and HOMA-IR in PCOS cases in comparison with controls. [12] Burghen GA et al also demonstrated a striking positive correlation between hyperandrogenism and hyperinsulinism in PCOS with relatively mild glucose intolerance. [13] Puder JJ et al showed in their study that patients with PCOS were more insulin resistant compared to a group of age and BMI matched controls. [14] Thus the metabolic disorders associated with PCOS along with their long-term sequelae have to be closely evaluated in PCOS patients.

CONCLUSION

We conclude that insulin resistance is inherent to PCOS, irrespective of whether the subject is lean or obese. Higher testosterone in PCOS cases is probably because of hyperinsulinemia. It is suggested that all PCOS subjects should be considered at risk of metabolic syndrome and its manifestations in view of the insulin resistant state; periodic monitoring of serum insulin, lipids, and HbA1c for obese PCOS patients should be performed. We could not demonstrate a direct relationship between BMI, serum insulin, HbA1c and serum testosterone. This could probably be due to the small sample size.

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