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Original Research Article

A comparative study of insulin levels in lean versus obese polycystic ovarian syndrome patients

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ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women of reproductive age group. PCOS has been frequently associated with insulin resistance and obesity. Although most of the cases with PCOS are obese or overweight, a significant proportion of patients have normal body mass index (BMI≤25 kg/m^2) that makes diagnostic work up and therapeutic approach more difficult. These cases are referred to as "lean PCOS."
Methods: This hospital based prospective, comparative cross-sectional study was conducted to estimate the insulin levels and insulin resistance in lean versus over-weight or obese PCOS patients and to evaluate the correlation of BMI with clinical parameters, serum insulin levels, and hormone profile in these patients. Patients were grouped according to their BMI: Lean group-(n=46) BMI<25 kg/m^2 and obese group-(n=40) BMI≥25 kg/m^2.
Results: Serum insulin levels in obese PCOS patients were significantly higher than in lean PCOS patients (p<0.001). Overweight or obese PCOS women achieved significantly higher HOMA-IR than lean PCOS patients (p<0.001). The difference in fasting blood sugar levels in lean versus obese PCOS patients were not significantly different. Comparisons of the two groups showed no statistical differences in gonadotrophins (LH and FSH) values and LH/FSH ratio. The serum testosterone level was significantly higher in the obese group compared with the lean group (p=0.043).
Conclusions: We conclude that the overweight/obese PCOS patients had higher tendency to develop insulin resistance and elevated fasting insulin levels as compared to their lean counterparts. Thus, weight reduction and metformin therapy hold great potential in managing a patient with insulin resistance in PCOS but will not have much effect on hormonal profile of a patient with PCOS but will not have much effect on hormonal profile of a patient with PCOS.

Keywords: PCOD, Lean PCOS, Obese PCOS, Insulin resistance

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women of reproductive age group.[1,2] Polycystic ovaries were first described in 1935 by Stein and Leventhal. It is characterized by a combination of hyperandrogenism (either clinical or biochemical), chronic anovulation and ultrasound documented polycystic ovaries. It is prevalent in about 5-10% of women worldwide however it has been predicted that it might affect up to 25% of women in their reproductive age. PCOS has been regarded as the commonest cause of anovulatory infertility, about 90-95%, and menstrual irregularities during the reproductive age.[3] Other risks associated with PCOS are of cardiovascular diseases, diabetes, metabolic complications, increased risk of pregnancy complications such as pregnancy-induced hypertension, pre-eclampsia, gestational diabetes and premature delivery.

The pathogenesis of PCOS is complex and is thought to be a result of interactions between genetics, epigenetics,

ovarian dysfunction, endocrine, neuroendocrine and metabolic alterations. However, ovarian pathology has been attributed as the major causative element of the PCOS.[4]

Different diagnostic criteria have been formed for diagnosis of PCOS. In 1990, the U.S. national institute of health (NIH) suggested diagnostic criteria for PCOS (referred to as "classical PCOS").[5] It included clinical or biochemical hyperandrogenism together with chronic anovulation. In 2003, representatives from the European society for human reproduction and embryology (ESHRE) and the American society for reproductive medicine (ASRM), modified these criteria and included transvaginal ultrasound evaluation of the ovaries. The revised ESHRE/ASRM criteria (also referred to as the Rotterdam criteria) are the ones primarily used nowadays.[6] In 2006, the androgen excess and PCOS society (AE-PCOS), suggested a new diagnostic criterion emphasizing the hyper androgenic features of the syndrome.[7]

PCOS has been frequently associated with insulin resistance and obesity. Although most of the cases with PCOS are obese or overweight, a significant proportion of patients have normal body mass index (BMI≤25 kg/m^2) that makes diagnostic work up and therapeutic approach more difficult. These cases are referred to as "lean PCOS".

There are some studies suggesting that clinical manifestations in lean and overweight women with PCOS are comparable.[8-10] However, greater prevalence of metabolic abnormalities is seen in the presence of obesity alongside PCOS phenotype.[11,12]

Aim

Aim of the study was to estimate the insulin levels and insulin resistance in lean versus over-weight or obese PCOS patients and to evaluate the correlation of BMI with clinical parameters, serum insulin levels, and hormone profile in these patients.

METHODS

This is a hospital based prospective, comparative cross-sectional study conducted on PCOS patients attending gynaecological OPD in Acharya Shri Chander College of Medical Sciences and Hospital, Jammu and Kashmir from January 2022 to December 2022. A total of 86 patients were enrolled who were diagnosed with PCOS based on Rotterdam ESHRE/ ASRM criteria. Patients were enrolled according to inclusion criteria. Patients were grouped according to their BMI: Lean group-(n=46) BMI<25 kg/m^2 and obese group-(n=40) BMI≥25 kg/m^2. The study has been approved by the institutional ethical committee.

Inclusion criteria

Patients diagnosed with PCOS based on modified Rotterdam ESHRE/ASRM criteria, age 15-40 years and patient giving valid consent were included in the study.

Exclusion criteria

Patients on treatment for PCOS within last 3 months, patients having other conditions associated with hyperandrogenism, patients having associated medical disorders like diabetes, hypertension, thyroid disorder, etc, patients on anti-obesity treatment or treatment for dyslipidaemia and pregnant patients were excluded.

Ultrasound criteria were used to detect polycystic ovaries, defined as the presence of at least 12 follicles of 2 to 9 mm diameter, and/or increased ovarian volume (>10 ml). Clinical criteria included amenorrhea or infrequent cycles (a cycle length >38 days). Hyper androgenic features of PCOS including hirsutism assessed using modified Ferriman and Gallway score system (≥8), acne and alopecia were also assessed.

Complete history of each case was taken, including type and duration of infertility, menstrual history, previous investigations, and previously offered treatment; Routine general, abdominal, and local gynaecological examination was performed; BMI was calculated; and patients were examined for clinical signs of hyperandrogenism. All cases underwent ultrasonography scan to measure ovarian volume and to evaluate the sonographic criteria for polycystic ovaries. Blood samples were collected from all cases and sent to the laboratory. Hormonal and biochemical analysis (serum fasting glucose, serum fasting insulin, S. FSH, S. LH, S. TSH and total testosterone) was done. IR was measured according to the homeostatic model assessment insulin resistance (HOMA-IR) equation:

HOMA-IR=fasting blood glucose (mg/dl) × fasting insulin (μIU=ml)/405

Statistical analysis

We have used descriptive statistics to describe characteristics of the groups. Data were represented as mean (±SD) and percentage for continuous and categorical variables respectively. The parameters of the two groups were compared by the student t-test or the Mann-Whitney test for normally and non-normally distributed continuous variables, respectively. The comparison between the two groups in terms of categorical variables was done by the chi-square test. A $p<0.05$ was considered as statistically significant. All analyses were conducted by the Epi Info version 4.0 and SPSS version 23.

RESULTS

This study was conducted in a tertiary care centre on 86 patients who were diagnosed with PCOS based on Rotterdam ESHRE/ASRM criteria. Patients were grouped according to their BMI: lean group-(n=46) BMI<25 kg/m^2 and obese group-(n=40) BMI≥25 kg/m^2. The mean age of

lean and obese PCOS patients was 24.78±5.31 and 25.56±7.36 years. Baseline characteristics show significantly lower BMI in lean group as compared to obese group (p<0.0001).

Most patients, about 91% presented with complaint of infrequent cycles. 55.7% of lean patients and 79.6% of obese patients had clinical hyperandrogenism, which was not statistically significant (p=0.43). USG criteria for PCO was met in 70.8% of lean patients and 73.2% of obese patient, with no significant difference (p=0.58). Comparisons of the two groups showed no statistical differences in gonadotrophins (LH and FSH) values and LH/FSH ratio. The serum testosterone level was significantly higher in the obese group compared with the lean group (p=0.043). The difference in fasting blood sugar levels in lean versus obese PCOS patients were not significantly different. However, it was quite evident that BMI had a significant positive correlation with fasting serum insulin and HOMA-IR. Serum insulin levels in obese PCOS patients were significantly higher than in lean PCOS patients (p<0.001). Overweight or obese PCOS women achieved significantly higher HOMA-IR than lean PCOS patients (p<0.001). There was no significant difference between the two phenotypes regarding the serum TSH values (Table 1).

Table 1: Characteristics of the study population.

Variables	Lean group, (n=46)	Obese group, (n=40)	P value
Age (years)	24.78±5.31	25.56±7.36	0.63
Height (cm)	159.4±5.5	159.7±6.2	0.92
Weight (kg)	58.9±11.5	78.3±14.6	<0.0001*
BMI (kg/m^2)	21.7±1.9	30.6±4.1	<0.0001*
Clinical hyper-androgenism	55.7%	79.6%	0.43
USG criteria for PCO	70.8%	73.2%	0.58
Fasting blood glucose (mg/dl)	81.78±5.57	86.93±5.23	0.299
S. Insulin (µU/ml)	6.12±2.17	12.93±2.46	<0.001*
HOMA-IR	1.3±0.38	4.8±1.64	<0.001*
LH (IU/litre)	11.05±4.96	10.9±4.36	0.49
FSH (IU/litre)	5.2±2.8	4.4±2.5	0.57
LH/FSH ratio	2.82±1.68	2.66±1.42	0.46
Testosterone (ng/ml)	0.41±0.03	0.65±0.14	0.043*
TSH (mIU/l)	2.89±1.86	2.68±1.5	0.96

Data are presented as mean ± SD or n (%); †Mann-Whitney test or t test for continuous variables and chi-square test for categorical variables; * statistically significant.

As shown in Table 2, in our study 91.3% of obese/ overweight PCOS patients were insulin resistant as compared to only 7.6% of lean patients. It was also seen that 83.6% of the obese PCOS patients had higher levels of fasting insulin levels whereas only 13.7% of lean patients had elevated fasting insulin levels. There was not much difference in the percentage of obese and lean patients who had elevated levels of fasting glucose (21.4% and 18.2%, respectively) (Table 2 and Figure 1).

Table 2: Insulin and insulin resistance parameters in study population.

Elevated levels of	Lean	Overweight	P value
Fasting glucose (mg/dl)	18.2%	21.4%	>0.5
Fasting insulin (µU/ml)	13.7%	83.6%	<0.001*
HOMA-IR	7.6%	91.3%	<0.001*

Data are presented as n (%); rates were compared with chi-square test; * statistically significant.

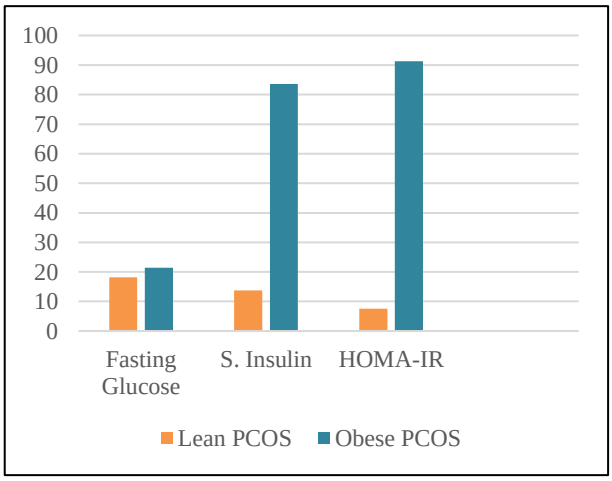

Figure 1: Comparison of fasting glucose, S. insulin and HOMA-IR in lean and obese PCOS patients.

DISCUSSION

Insulin resistance is implicated in various pathologies including the PCOS.[13] Obesity, is a well-recognized risk of insulin resistance and abnormal glucose tolerance. Therefore, obese PCOS patients would theoretically have a greater risk of developing insulin resistance and abnormal glucose tolerance than lean PCOS patients.

Insulin levels are often used as an indirect evaluation of insulin resistance. However, they are considered inadequate as: (a) levels of insulin in peripheral blood depend on the secreting capacity of the pancreas as well as on liver insulin extraction; (b) conventional assay methods are found to interfere with pro-insulin, which also increase during other conditions associated with insulin resistance (e.g. NIDDM); (c) insulin secretion decreases during OGTT as soon as Fasting blood glucose levels exceeds 6.7 mmol/l.[14-17] We preferred to choose HOMA (IR)

(homeostatic assessment of IR tool) and fasting insulin in the assessment of IR for their simplicity and identical diagnostic accuracy.[18,19]

In our study, we found that 91.3% of the overweight/obese PCOS patients showed high IR as compared to 7.6% of lean PCOS patients. Also, 85% of the overweight/obese PCOS participants demonstrated elevated fasting insulin concentration as compared to 13.7% lean PCOS patients.

Morciano and co-workers in their study classified 72% of Italian overweight/ obese PCOS women as insulin resistant as compared to 26.3% of the lean PCOS women and the difference was statistically significant.[20] Morciano's findings are in accordance with those of our study; however, the discrepancy in the rates could be attributed to the method of IR calculation (as they evaluated IR through hyperinsulinemic- euglycemic clamp) and ethnic variation. Our findings are consistent to the study by Stepto et al in Australia who showed that 95% of overweight/ obese PCOS and 75% of lean PCOS women are in the risk of IR.[21] Behboudi-Gandevani et al in their study concluded that the mean of HOMA IR in Iranian obese PCOS group was 4.38 which are significantly higher than their non- obese counterparts.[22]

Another important finding was that 83.6% of overweight/ obese PCOS patients had elevated fasting insulin concentration as compared to 13.7% of lean PCOS patients. This difference was significant. Gholinezhad-Chari et al in their study concluded that over 85% of overweight/obese PCOS patients revealed fasting insulin≥13 as compared to 10.3% in the normal PCOS control.[23]

Our study did not find any significant difference between fasting glucose concentration in lean as opposed to overweight/obese PCOS patients. A study by Gagnon et al concluded that the mean result of fasting plasma glucose testing remained below the cutoff limit of 5.6 mmol/l in the group with abnormal glucose tolerance, even though their mean 2-hour glucose levels were much above 7.8 mmol/l.[24]

The limitation of our study was the small sample size. Therefore, larger studies including leaner PCOS patients are needed to confirm our findings.

CONCLUSIONS

We conclude that the overweight/obese PCOS patients had higher tendency to develop insulin resistance and elevated fasting insulin levels as compared to their lean counterparts. PCOS women are more prone to adiposity and excess body mass index was associated with IR. Also, overweight and obese PCOS patients demonstrated elevated levels of serum testosterone as compared to lean PCOS patients. However, there was no significant difference in LH/FSH ratio between the two groups. Thus, weight reduction and metformin therapy hold great potential in managing a patient with insulin resistance in PCOS but will not have much effect on hormonal profile of a patient with PCOS.

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