ORIGINAL RESEARCH PAPER

Endocrinology

A STUDY OF INSULIN RESISTANCE IN LEAN PATIENTS WITH POLYCYSTIC OVARY SYNDROME

KEY WORDS: Lean PCOS, insulin resistance, BMI

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ABSTRACT

Introduction: Polycystic ovary syndrome (PCOS) affects 6– 15% of females in their reproductive age. [1] Hyperandrogenaemia and insulin resistance (IR) underly the important hormonal defects affecting the patients. These results have been majorly derived from patients with PCOS with an elevated BMI. There is hardly any data on IR in lean PCOS. But this knowledge may help bring out protective pathways to lessen the rise of DM in these subjects. [3]. Here, an attempt was made to assess the relevance of IR in lean patients affected by PCOS as these parameters represent a risk for atherosclerotic cardiovascular disease. **Materials And Methods:** 100 patients of lean PCOS with BMI <23kg/m2 were enrolled and thorough history and examination was conducted. HOMA IR was calculated and correlated with the BMI and clinical parameters. **Results:** Our results demonstrated that 46% women had insulin resistance. The mean Fasting serum insulin was 15.21 ± 15.89 μU/mL. The Fasting Plasma Glucose (FPG) was 88.25 mg/dL ± 9.38 mg/dL. HOMA-IR had an average of 3.43 ± 3.78. **Conclusions:** Insulin resistance is prevalent among patients with lean PCOS, as evidenced by elevated HOMA-IR readings. Fasting serum insulin demonstrates exceptional predictive ability for distinguishing between patients with lean PCOS and controls while fasting plasma glucose level and BMI show moderate to good predictive abilities.

INTRODUCTION:

Polycystic ovary syndrome (PCOS) affects 6– 15% of females in their reproductive age. [1] Hyperandrogenaemia and insulin resistance (IR) underly the important hormonal defects affecting these patients. The results have been majorly derived from patients with obese PCOS. >50% of affected females exhibit IR. [2] This insulin resistance predisposes them to a 5–8 times increased likelihood of arising of type 2 Diabetes Mellitus (DM) vis-a-vis to age-matched and weight-matched controls. There is hardly any data on IR in lean PCOS. Nevertheless, this is important to know, as this knowledge may help bring out protective pathways to lessen the rise of DM in these subjects. [3] Understanding the distinct body composition profile and metabolic profiles in these groups is essential for developing effective dietary interventions. Here, an attempt was made to assess the relevance of IR in lean patients affected by PCOS as these parameters represent a risk for atherosclerotic cardiovascular disease.

MATERIALS AND METHODS:

Source Of Data: Patients attending the Endocrinology and Gynaecology Department at Index Medical College, Indore.

Study Design: Cross sectional study

Study Duration: October 2022 to March 2024 (18 months).

Method Of Data Collection: 100 eligible patients were enrolled in accordance to the eligibility and exemption criteria given below by purposive sampling. A detailed history for Lean Polycystic Ovarian Syndrome was taken and IR assessed.

Diagnostic Criteria for PCOS: In accordance with the Rotterdam criteria (2003), PCOS is established if minimum two of three stipulated requirements are present after excluding other endocrine diseases: 1. The clinical features viz. oligo-anovulatory cycles, 2. Phenotypic and/or laboratory features of excess androgen 3. Polycystic ovarian anatomy on ultrasonological evaluation

The Rotterdam criteria for considering a given ovary as polycystic: 12 follicles minimum every possessing a diameter of between 2 and 9 mm with or without an expanded ovarian volume greater than 10 mm3 [4].

Criteria for Lean PCOS: Body mass index (BMI) was calculated using Quetelet index. Indian population has a genetic propensity toward intraabdominal obesity and the associated lifestyle disease risks such as heart disease and diabetes and hence, guidelines quote BMI above 23kg/m2 for overweight and obesity for India [5] and lean as those with BMI <23 kg/m2. Evaluation of insulin resistance: The plasma glucose was determined by the means of hexokinase technique. Commercial kits and an electro-chemiluminescence based method (Dia Sorin Liaison) were

used to estimate serum insulin levels. Calculation for Insulin resistance (IR) used the HOMA model: fasting plasma glucose (mg/dL) × fasting plasma insulin (U/mL)/405. A value more than 2.5 was taken for considering insulin resistance. [6].

Inclusion Criteria:

 All lean female patients with PCOS with the Rotterdam 2003 criteria as the diagnosing criteria [4] Patients who are at least 18 years old. Patients giving valid, informed and written consent

Exclusion Criteria:

 Subjects already diagnosed to have medical impairments including dysglycemia, or active thyroid dysfunction. Subjects on pharmacotherapy including metformin, pioglitazone, corticosteroids, oral contraceptive pills and drugs which could affect the endocrine and metabolic evaluations being undertaken. Subjects affected with diseases like hyperprolactinemia, 21-hydroxylase-deficient nonclassic adrenal hyperplasia, iatrogenic hyperandrogenism, neoplastic androgen secretion, insulin resistance syndromes, glucocorticoid resistance and Cushing's syndrome.

Sample Size:

With the aid of Cochran's formula, a sample size was determined as follows: The formula used Cochran's formula Sample size= Z2 PQ/E2 Z= 1.96 (95% confidence interval) P= Disease prevalence (6-15%) Q= 1-P E= Allowable error 5%

Data were entered into MS Excel sheet and analysed using SPSS v26 and Open Epi online software.

Statistical Analysis:

The gathered information was displayed as mean ± standard deviation or as a number (%). Next, the parametric variables were investigated utilizing independent student's t-test as far as categorical groups are concerned. The non-parametric variables were subjected to chi-squared test, Mann Whitney-U test. Pearson's correlation coefficient was derived to investigate the degree to which HOMA-IR and the other parametric measurements correlate. Finally, ROC analysis was done to calculate cut-off points of parameters utilizing the Area under curve (AUC >0.5 was statistically significant). p <0.05 was considered statistically significant.

RESULTS:

This study was undertaken among 100 diagnosed subjects of lean PCOS.

Table 1: Age distribution

Age groups	N/%
18-25	72
26-30	20
31-35	4
36-40	0
>40	4
Total	**100**
Mean ± S.D. Age (in years)	23.5 ± 5.5
Mean ± S.D. Age at menarche (in years)	13.71 ± 1.3

Table 1 presents data regarding the distribution of age groups and corresponding percentages, along with the mean as well as standard deviation (S.D.) for both age as well as age when menarche was noticed in PCOS population who were lean. The majority of individuals lie between of 18 and 25 years, making up 72% of the population followed by groups aged 26 to 30 years with 20%, 4% each in the 31 to 35 years >40 years and no individuals in the 36 to 40 years category. The population averages 23.5 ± 5.5 years. Mean age at menarche was 13.71 years of age ± 1.3 years.

Table 2: Clinical Profile for Lean PCOS

Clinical profile	Present, N/%	Absent, N/%
Irregular menses	73	27
Hirsutism/acne	65	35
Acanthosis nigricans	47	53
Dysmenorrhea	24	76
Infertility	15	85
mFGS (Mean ± S.D.)	7.18 ± 7.3	

Table 2 represents the clinical profile of lean individuals with PCOS. It represents: 73% patients presented with irregular menses, 65% with Hirsuitism/ acne, 47% patients had Acanthosis nigricans, 24% patients had dysmenorrhea and 15% patients presented with infertility. Mean mFGS (Modified Ferriman Gallwey Score) was 7.18+ 7.3. Overall, the table provides insight into the diverse clinical presentations of PCOS, emphasizing the range of features and their prevalence within the studied population.

Table 3: Anthropometric Measurements of patients with Lean PCOS

Anthropometric Measurements	N	Minimum	Maximum	Mean	SD
Height (in cm)	100	146	175	156.99	6.19
Weight (in kg)	100	30	67	49.91	8.10
BMI (kg/m2)	100	13.3	22.9	20.16	2.42

The table 3 presents anthropometric measurements studied-height, weight, and Quetelet index (BMI), for 100 study participants. Height (in cm): Measured height of the individuals ranges from 146 cm to 175 cm, having a mean height of approximately 156.99 ± 6.19 cm. Weight (in kg): The weight of the individuals varies between 30 kg and 67 kg, an average weight of approximately 49.91 ±8.10 kg. BMI (kg/m2): The BMI values stretch from 13.3 to 22.9 kg/m2, averaging 20.16 ± 2.42 kg/m2.

Table 4: Insulin Resistance In Lean PCOS

Insulin Resistance	N	Minimum	Maximum	Mean	SD
Fasting Sr Insulin	100	1.15	84.85	15.21	15.89
FPG	100	58.3	128	88.25	9.38
HOMA- IR	100	0.2	20.7	3.43	3.78

Table 4 represents results related to insulin resistance among patients with lean PCOS: 46% patients in our study presented with IR. Fasting serum insulin: Readings among the patients stretch from 1.15 μU/mL to 84.85 μU/mL, with an average of 15.21 ± 15.89 μU/mL. Fasting Plasma Glucose (FPG): Readings stretch from 58.3 mg/dL to 128 mg/dL, averaging around 88.25 mg/dL ± 9.38 mg/dL. These values fall within the normal fasting plasma glucose range, indicating that the patients, on average, do not have impaired fasting glucose levels. HOMA-IR: Readings stretch from 0.2 to 20.7, with an average of 3.43 ± 3.78. HOMA-IR values obtained suggest that, while some patients exhibit low levels of insulin resistance, others show higher levels, contributing to the overall variability observed in this population.

Table 5: Correlation Of HOMA IR With PCOS Profile

Lean PCOS parameters	HOMA- IR	
Age	Pearson Correlation	.261**
	Sig. (2-tailed)	0.009
BMI	Pearson Correlation	0.046
	Sig. (2-tailed)	0.648
Age at Menarche	Pearson Correlation	-0.097
	Sig. (2-tailed)	0.335
mFGS	Pearson Correlation	0.071
	Sig. (2-tailed)	0.484
Acanthosis nigricans	Pearson Correlation	.538**

The table presents correlations between various parameters and HOMA-IR among lean subjects having PCOS: Age: Age and HOMA-IR correlate affirmatively (r = 0.261, p = 0.009), pointing out that older patients tend to have higher insulin resistance levels. BMI (Body Mass Index): The correlation shared by BMI and HOMA-IR is not mathematically noteworthy (r = 0.046, p = 0.648), indicating that BMI may not strongly influence insulin resistance in PCOS patients within

the lean BMI range. Age at Menarche: No significant correlation is found between age at menarche and HOMA-IR (r = -0.097, p = 0.335). mFGS (modified Ferriman-Gallwey Score): The correlation between mFGS and HOMA-IR is not noteworthy in statistical terms (r = 0.071, p = 0.484). Acanthosis Nigricans: There is an important positive coherence between an established acanthosis nigricans and HOMA-IR calculated (r = 0.538, p < 0.001), indicating that patients vis-a-vis acanthosis nigricans tend to have higher insulin resistance levels. In summary, among subjects with lean PCOS, age and the presence of acanthosis nigricans reveal mathematically important correlations with IR as measured by HOMA-IR, suggesting potential clinical clues for assessing insulin resistance in this population.

The area under the curve (AUC) readings with regards to IR among patients with lean PCOS, along with their respective cut-off points are as folows: BMI (Body Mass Index):The AUC value is 0.586, indicating a moderate predictive ability for distinguishing between patients with lean PCOS and controls. The optimal cut-off limit for BMI is 17.0 kg/m2. 91 F-PLASMA GLUCOSE: The AUC value is 0.715, suggesting a good predictive ability for distinguishing between patients with lean PCOS and controls. The optimal cut-off level for fasting plasma glucose is 75.5 mg/dL. Fasting sr insulin (Fasting Serum Insulin): The AUC value is exceptionally high at 0.998, indicating an excellent predictive ability for distinguishing between patients with lean PCOS and controls. The optimal cut-off reading for fasting serum insulin is 18.19 µIU/mL. In summary, fasting serum insulin demonstrates exceptional predictive ability for distinguishing between patients with lean PCOS and controls while fasting plasma glucose level and BMI show moderate to good predictive abilities.

DISCUSSION:

The intent of the current investigation was to gauge insulin resistance in lean subjects with PCOS. In this section, we interpret and analyze the results obtained from our study, focusing on their implications for better deciphering the pathophysiology of PCOS in lean subjects.

Clinical profile of lean PCOS: The majority of lean PCOS subjects in the investigation spanned between 18 to 25 years, with anovulation being the hallmark feature. 73% individuals have irregularity in menses. 65% of the individuals exhibit acne or hirsutism, defining manifestations of hyperandrogenism commonly observed in PCOS. Acanthosis nigricans was present in 47% of the individuals. Dysmenorrhea was reported in 24% of the individuals. 15% of the individuals experienced infertility. The mean mFGS was 7.18 ± 7.3. A systematic review Sehar Toosy et al (2018), [7] examines the relationship between Polycystic Ovary Syndrome (PCOS) and insulin resistance (IR) based on their body mass index (BMI). It notes that around 80% of PCOS subjects have higher BMI and exhibit classical manifestations like polycystic ovarian morphology, hyperandrogenism and insulin resistance. However, a lesser percentage of PCOS subjects have a low to normal BMI. This study finds that clinical features in both overweight and lean subjects having PCOS may be similar. Both groups exhibit similar prevalence of features such as acanthosis nigricans, anovulation, hirsutism and endometrial hyperplasia. Jayashree S et al (2018) [n=60] conducted a prospective study whereby the age range of 16-20 years constituted 40% study individuals and had a mean age of 22.5 years. In obese subjects with PCOS, 46.7% were aged 21-25 years and an average age of 24 years. Acanthosis nigricans, a marker of IR was observed in 3.3% of lean PCOS subjects and around 10% of obese PCOS subjects. These findings did not differ statistically between both the groups. [8]. This was the knowledge gap addressed by our study, to find the clinical manifestations particularly with regards to lean PCOS, and better aid in early diagnosis and intervention. Insulin resistance in lean PCOS: Our results demonstrated that 46% women had insulin resistance with the HOMA-IR values from 0.2 to 20.7, averaging 3.43 ± 3.78. This suggests that even among lean individuals, PCOS may be associated with disruptions in insulin metabolism, contributing to metabolic dysfunction. Sehar Toosy et al (2018), stated in their study that both groups (lean and obese) were insulin resistant, with prevalence rates ranging from 44% to 70%. [7] Jayashree S et al (2018) [n=60] in their study showed a prevalence of 33.3 % in lean PCOS cohort of impaired glucose tolerance. They highlighted a significant positive correlation of fasting insulin levels and HOMA-IR with BMI. [8]

Correlations: The Pearson correlation analysis was used in this study. Weight and BMI demonstrate negative correlations with statistically significant p values, indicating that higher weights and BMIs are associated with lower correlations with other variables. This finding suggests that weight and BMI may not be strongly linked to other clinical parameters and biomarkers in lean PCOS patients, which is consistent with the characteristic absence of obesity in this phenotype.

CONCLUSIONS:

Patients with lean PCOS exhibit features such as younger age, lower BMI, and a high prevalence of anovulation, hirsutism, acne as well as acanthosis nigricans. Insulin resistance is prevalent among patients with lean PCOS, as evidenced by elevated HOMA-IR readings. Fasting serum insulin demonstrates exceptional predictive ability for distinguishing between patients with lean PCOS and controls while fasting plasma glucose level and BMI show moderate to good predictive abilities. Overall, these results provide valuable insights into the metabolic characteristics of lean PCOS patients and their associations with insulin resistance. Further extensive look is required to corroborate these results and explore potential implications for the management and treatment of lean PCOS.

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