ORIGINAL ARTICLE

Clinicobiochemical Analysis of Polycystic Ovary Syndrome and Metabolic Syndrome: Do They Go "Hand in Glove"?

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Abstract

Aims and objectives: To study the clinical and biochemical markers for metabolic syndrome in women diagnosed with polycystic ovary syndrome (PCOS).

Materials and methods: This is an observational (cross-sectional) study involving 105 patients of PCOS, carried out over 2 years (2018–2020) in a tertiary care hospital of Berhampur, Odisha. Weight, height, waist circumference, hip circumference, and blood pressure were measured. The W to H ratio (WHR) and body mass index (BMI) was calculated. Venous blood samples were collected after an overnight fast for glucose, serum triglycerides, and high-density lipoprotein- cholesterol. A 2-hour 75 g glucose tolerance test was done, along with fasting insulin. Homeostatic model assessment-insulin resistance (HOMA-IR) was calculated. Statistical analysis was performed by the SPSS program for Windows (v 25.0). Tests of significance were carried out.

Results: The patients fell into the age range of 16–30 years. The average body mass index (BMI) was 27 $\pm$ 5.3 kg/m^2, with central obesity in 40% cases. Thirty-seven patients (35.2%) fulfilled three or more criteria of metabolic syndrome, maximum cases (49%) in the age group of 20–24 years. Central obesity (Waist circumference $\geq$80 cm) is the most deranged parameter among 32/37 (86.5%) followed by dyslipidemia—serum HDL-C $\leq$50 mg/dL in 27/37 (73%). Fasting plasma glucose levels are least deranged in 43.2% of cases (16/37). Women with PCOS had a significant association with all parameters of metabolic syndrome ($p \leq 0.05$).

Conclusion: Several studies have proved a consistent association between PCOS and metabolic dysfunction. It is, thus, imperative to screen every case of PCOS, with appropriate follow-up, to catch derangements at the earliest. Encouraging healthy lifestyle practices is important to improve ovulatory and menstrual symptoms as well as prevent future morbid metabolic ailments.

Keywords: Insulin resistance, Metabolic syndrome, Obesity, PCOS.

Journal of South Asian Federation of Obstetrics and Gynaecology (2022): 10.5005/jp-journals-10006-2000

Introduction

Polycystic ovary syndrome (PCOS) is, worldwide, one of the most prevalent disorders among women of child-bearing age. However, global variations in prevalence exist due to a lack of unanimity in diagnostic criteria for different age groups.[1] Most studies in India report a prevalence of 9.13–36%.[2] The 2003 Rotterdam definition formed the basis of the 2011 evidence-based guidelines for the diagnosis and treatment of PCOS, which requires the presence of at least two of the following features: oligoanovulation, hyperandrogenism, and polycystic ovaries on ultrasound.[3]

Common comorbidities of PCOS are classified under three categories:—(1) reproductive; (2) metabolic; and (3) psychological. The metabolic comorbidities such as insulin resistance, hyperinsulinemia, impaired glucose tolerance, type 2 diabetes mellitus, dyslipidemia, hypertension, cardiovascular risk factors, and obstructive sleep apnea are of particular interest, as the burden of "metabolic syndrome" is on the rise, even among the young adult females.

"Metabolic syndrome" (syndrome X, insulin resistance syndrome) consists of interconnected risk factors, metabolic in origin, with insulin resistance being the chief pathogenesis. Consequently, the patients develop atherosclerotic cardiovascular disease. The major features of metabolic syndrome include central obesity, hyperglycemia, hypertension, hypertriglyceridemia, and low levels of high-density lipoprotein (HDL) cholesterol.

One of the diagnostic criteria of metabolic syndrome is the AHA/ NHLBI ATP III criteria (2005). The diagnosis is made when $\geq$3 of the following is present: (1) waist circumference (WC) $\geq$80 cm, (2) serum triglycerides $\geq$150 mg/mL, (3) serum HDL-C <50 mg/mL, (4) blood pressure $\geq$130/85 mm Hg, and (5) fasting plasma glucose $\geq$100 mg/mL. A Greek study comparing the different diagnostic criteria of a metabolic syndrome found the AHA/NHLBI definition a better predictor of risk for cardiovascular events.[4]

In women of the reproductive age group, one of the major risk factors for the development of metabolic syndrome is PCOS with a prevalence of 40–50%.[5] According to literature, insulin resistance is found among 25–70% of women with PCOS.[6] Around 75% of lean PCOS women and 95% obese PCOS women will be insulin resistant.[7] Thus, it is the common link in women with obesity, PCOS, and metabolic syndrome. Vitamin D deficiency is an upcoming area of interest in the possible explanation of this relationship between insulin resistance and PCOS. A review by Garg et al.[8] showed an inverse relationship between serum 25

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How to cite this article: Mishra N, Mishra R. Clinicobiochemical Analysis of Polycystic Ovary Syndrome and Metabolic Syndrome: Do They Go "Hand in Glove"? J South Asian Feder Obst Gynae 2022;14(1): 29–34.

Source of support: Nil

Conflict of interest: None

(OH) D levels and HOMA-IR in PCOS and control groups. Metabolic features such as glucose intolerance, hypertension, dyslipidemia, and visceral fat deposits are more commonly observed in PCOS women.[9] The relative contribution of clinical, demographic, or biochemical factors to metabolic syndrome in lean PCOS women is unknown.

The aim of this study was to study the prevalence and patterns of individual components of metabolic syndrome in women already diagnosed with polycystic ovary syndrome.

Materials and Methods

This was a prospective observational study conducted over 2 years in a tertiary hospital in Odisha.

Selection of Cases

Patients attending the gynecology outpatient department (OPD) with complaints of fewer than eight cycles per year and/or clinical evidence of hyperandrogenism were recruited. Women over 40 years, known cases of hypo/hyperthyroidism, or hyperprolactinemia or those currently on medications that affect reproductive hormones (hormonal contraceptives) were excluded.

The calculation for the sample size proportions was carried out based on the prevalence of metabolic syndrome in PCOS of 36%, sourced from several Indian studies. The sample size was estimated using a modification of the Cochran formula.

Written informed consent was obtained from all participants and/or their parent or legal guardian, where necessary, before participating in the study.

Data Collection

Weight, height, waist circumference, and hip circumference were measured in the study participants. The waist to hip ratio (WHR) was calculated by dividing waist circumference by hip circumference. Waist-to-hip ratio ≥0.85 was taken as abnormal; <0.85 as normal.[10] Body mass index (BMI) (kg/m^2) was calculated by dividing weight (in kg) by height (in m) squared, as a rough measure of obesity. Systolic and diastolic blood pressure was measured manually with a sphygmomanometer in the right arm, after 5 minutes of rest. Venous blood samples were collected after an overnight fast for glucose, serum triglycerides, and HDL-C. A 2-hour 75 g glucose tolerance test was done, along with fasting insulin. Homeostatic model assessment-insulin resistance (HOMA-IR) was calculated as [fasting insulin (U/mL)*fasting glucose (mmol/L)]/22.5. Subjects with HOMA-IR value >3 were grouped as insulin resistant.[11] Transabdominal ultrasonography (TAS) was performed on day two or three of the spontaneous or progesterone-induced cycle. Transvaginal USG (TVS) is considered as the gold standard diagnosing features (unilateral or both ovaries) such as:[12]

- Increased follicle number per ovary (FNPO) ≥20, with individual follicles measuring 2–9 mm in diameter;
- Ovarian volume ≥10 mL;
- "String of pearls" appearance due to peripheral distribution of follicles;
- Central stromal brightness with or without prominence.

All the participants were screened for hyperprolactinemia (serum prolactin >20 µg/L on two occasions), thyroid dysfunction (thyroid stimulating hormone <5.5 µIU/mL), and Cushing's syndrome (history of steroid intake and clinical examination).

Statistical Analysis

The data were tabulated in the MS EXCEL spreadsheet. Statistical analysis was performed by the SPSS program for Windows, version 25.0. Continuous data (age, bodyweight, BMI, WC, WHR, systolic and diastolic BP, biochemical analysis) were expressed as mean ± SD and frequencies. Comparison of continuous data between women with metabolic syndrome (MetS) and those without was performed using the independent samples student *t*-test (mean ± SD) and proportion test in R (frequencies) to find predictive association of variables. Levene's test of equality of variance was applied to compare the mean values between groups. A "*p*" value <0.05 was considered significant, however, exact *p*-values were reported.

Results

The sample size was estimated at 105 patients ranging in age from 16 to 30 years. The majority (46.7%) cases were in the age group of 20–24 years. Chief complaints were irregular menstrual cycles (59%) followed by secondary amenorrhea (34.3%) (Fig. 1). Clinical hyperandrogenism included hirsutism (52.4%), acne (40%), or both (15.2%). Transabdominal sonograph findings included polycystic ovaries (minimum of 12 follicles in one or both ovaries) in 49.5%, increased stromal volume (≥10 mL) in 28% and both in 18.1% (Table 1). However, the recent phenotype classification shows that polycystic ovarian morphology need not be a mandatory criterion for PCOS.

The average BMI was 27 ± 5.3 kg/m^2 (mean body weight of 65.2 ± 14.6 kg) with 41% of the study population classified as obese grade I and 15.2% as overweight, according to the WHO-Asian guidelines. Insulin resistance (HOMA-IR>3) is observed in 66.7% of the cases.

The prevalence of Metabolic Syndrome in our study is 37/105 (35.2%) according to the NHLBI/AHA ATP III (2005) guidelines. Among the 37 cases having metabolic syndrome, 22 subjects (59.5%) fulfilled 3 out of 5 criteria, 11 subjects (29.7%) fulfilled 4 out of 5 criteria and 4 subjects (10.8%) fulfilled all five criteria (Fig. 2).

Age distribution of prevalence of MetS shows that the maximum cases (49%) belong to the age group of 20–24 years whereas 35% are in the age group of 25–29 years. In this, 43% of subjects with metabolic syndrome belong to obese grade I (BMI: 25–29.9 kg/m^2), followed by 38% of obese grade II

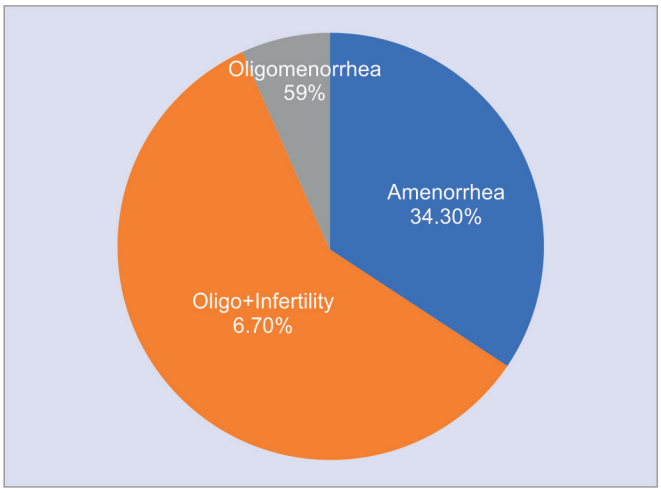

Fig. 1: Chief presenting complaints

(BMI: 30–39.9 kg/m^2). Table 2 shows that central obesity (WC ≥80 cm) is the most deranged parameter among 32/37 cases (86.5%) followed by dyslipidemia—serum HDL-C ≤50 mg/dL in 27/37 cases (73%). Fasting plasma glucose is the least deranged parameter, seen in 43.2% of cases (16/37).

On applying the independent samples *t*-test, there is a significant association of bodyweight (p = 0.008) and BMI (p = 0.000) in PCOS patients with and without metabolic syndrome. Individual components of MetS such as central obesity, systolic and diastolic BP, fasting plasma glucose, serum HDL, and serum triglyceride have a significant association with PCOS (p = 0.0001) (Table 3 and Fig. 3).

Table 1: Percentage prevalence of clinical and ultrasonographic findings in the study subjects

	No. of cases (PCOS) (n = 105)	*Percentage*
Chief complaints		
Amenorrhea	36	34.3
Irregular menstrual cycles	62	59.0
Clinical hyperandrogenism		
Hirsutism	55	52.4
Alopecia	14	13.3
Acne	42	40.0
Hyperandrogenism + acne	16	15.2
None	25	23.8
Ultrasonographic findings		
Polycystic ovaries (PCO)	52	49.5
Increased stromal volume	28	26.7
PCO with increased stromal volume	19	18.1
Normal ovaries	6	5.7

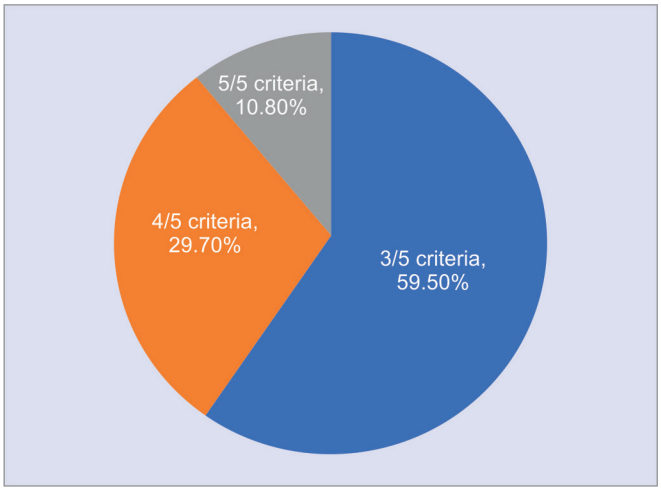

Fig. 2: No. of criteria of metabolic syndrome fulfilled

Discussion

The study included 105 known cases or newly diagnosed cases of PCOS, who had presented with different complaints to our gynecology OPD. Irregular menstrual cycles were the predominant complaint of the majority of the cases, presenting in the earlier part of their reproductive lives. This is the most common clinical feature of PCOS. Oligomenorrheic women consequently developed type 2 diabetes with a higher frequency (approximately two times more) than eumenorrheic women, regardless of their BMI or body fat composition, as reported by the nurses' health study II over an 8 year period.[13]

In our study, the most common evidence of clinical hyperandrogenism is hirsutism, found in 52.4%. It is consistent with the observations of Sobti et al.[14] (43.3%), Akgul et al.[15] (45.9%), and Bahadur et al.[16] (51%). The former misconception that the increased risk of metabolic syndrome in women with PCOS was due to obesity and metabolic derangements has been challenged by a recent study by Albu et al. (Romania). It was concluded that hyperandrogenemia [represented by free androgen index (FAI)], along with adiposity and insulin resistance, was independently associated with metabolic syndrome in PCOS patients.[17]

Central Obesity (WC ≥80 cm) was seen in 55.2%, whereas WHR ≥0.85 was found in 40% of our study population. Kar[17] also observed that a major proportion of lean women had abnormal WHR. The Asian Indian phenotype is characterized by a higher waist circumference or waist hip ratio with leaner lower limbs and high body fat composition to BMI ratio. Thus, the central distribution of body fat with BMI in the nonobese range is a characteristic feature of Asian Indians. This is a substantial risk factor for metabolic syndrome.

Insulin resistance (HOMA-IR >3), observed in 66.7% of the cases, is the uniting pathogenic factor between metabolic syndrome and PCOS. In the studies by Kar,[18] Sobti et al.,[14] and Rashid et al.,[19] the prevalence of IR in women with PCOS was 30.44, 31, and 48.1%, respectively. This is in accordance with similar studies that show Indian PCOS women as more insulin resistant than their white counterparts.[20]

The prevalence of metabolic syndrome in our study is 37/105 (35.2%) according to the NHLBI/AHA ATP III (2005) guidelines. Similar studies by Altintas et al.[21] and Tavares et al.[22] showed a prevalence of 25.7 and 33.6%, respectively. Indian studies conducted by Sobti et al.,[14] Chan et al.,[23] Tripathy et al.,[24] and Karee et al.[25] showed

Table 2: Comparison of frequency distribution of clinical and biochemical parameters

Deranged parameter	*Frequency (n = 105)*	*With MetS (n = 37)*	*Without MetS (n = 68)*	*p value*[a]
Waist circumference ≥80 cm	58 (55.2%)	32 (86.5%)	26 (38.2%)	0.001
Systolic BP ≥130 mm Hg	26 (24.8%)	20 (54.1%)	6 (8.8%)	0.001
Diastolic BP ≥85 mm Hg	32 (30.5%)	20 (54.1%)	12 (17.6%)	0.0002
FPG ≥100 mg/dL	23 (21.9%)	16 (43.2%)	7 (10.3%)	0.0002
Sr. TG ≥150 mg/dL	41 (39.0%)	26 (70.3%)	15 (22.1%)	0.001
Sr. HDL-C <50 mg/dL	36 (34.3%)	27 (73.0%)	9 (13.2%)	0.001

[a]Proportion test in R

Table 3: Comparison of the mean and standard deviation of clinical and biochemical parameters

	BMI (kg/m²)	*Waist circumference (cm)*	*Systolic BP (mm Hg)*	*Diastolic BP (mm Hg)*	*FPG (mg/dL)*	*Sr. TG (mg/dL)*	*Sr. HDL (mg/dL)*
PCOS with MetS ($n = 37$)	30.3 ± 5.3	90.5 ± 9.4	126.3 ± 7.8	83.6 ± 9.2	98.3 ± 9.7	163.4 ± 42.6	46.5 ± 9.1
PCOS without MetS ($n = 68$)	25.1 ± 4.4	78.2 ± 8.7	117.3 ± 12.3	76.7 ± 7.5	89.1 ± 9.9	123.5 ± 37.1	55.1 ± 5.8
t value	5.436	6.347	4.500	4.124	4.529	4.965	–5.848
p value[b]	0.000	0.000	0.000	0.000	0.000	0.000	0.000

[b]Independent samples *t* test

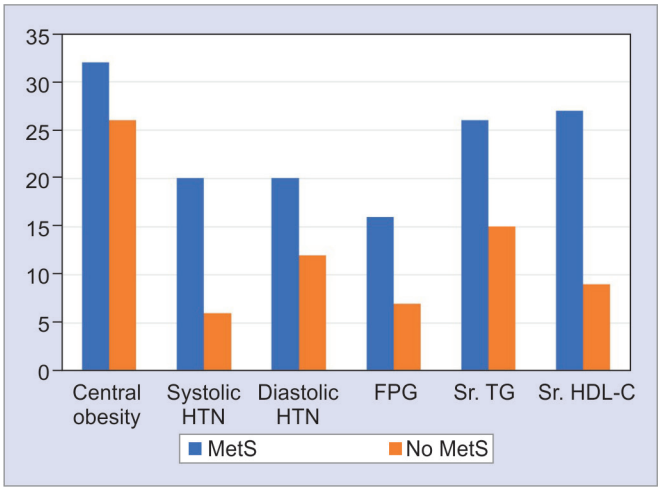

Fig. 3: Comparison of percentage prevalence of different parameters of metabolic syndrome

a prevalence of MetS as 36, 38.2, 33.6, and 38.5%, respectively, which is in agreement to our findings. In the studies by Jeengar et al.[26] and Lana et al.,[27] relatively higher percentages (58 and 44%, respectively) of the patients met the diagnostic criteria for MetS. However, Karamallah et al.[28] and Bahadur et al.[16] reported a lower overall prevalence of MetS in their respective studies as 14.6 and 11.7%. Large scale studies to determine the prevalence of metabolic syndrome in polycystic ovary women in different populations described 43% in the USA, 28.4% in Brazil, 24.9% in Hong Kong Chinese women, and only 1.6% in Czech women,[29–31] suggesting a role of hereditary factors (genetics) as well as the external milieu in the development of MetS.

The maximum prevalence of metabolic syndrome (49%) was seen in the age group of 20–24 years. A similar study by Jeengar et al.[26] reported the highest prevalence (68%) of metabolic syndrome among 15–25 years. A study by Akgul et al.[15] demonstrated MetS in 45.9% of adolescents, when diagnosed using International Diabetes Federation (IDF) criteria. According to some studies, the syndrome is predominantly observed in women below 30 years of age,[32] while others suggest an increased frequency after 25 years.[33] More than 50% of women with PCOS, mostly over 40 years of age are at higher risk of developing MetS. The trend of younger patients developing MetS might be largely lifestyle-related which makes them prone to developing obesity earlier, leading to the development of both PCOS and metabolic syndrome.

Metabolic syndrome was seen in obese grade I (43%), grade II (38%), and in both cases of super obese PCOS. A significant association of MetS with BMI is seen in our study ($p = 0.001$), with an average BMI of 30.3 ± 5.3 kg/m² while those without MetS had an average BMI of 25.1 ± 4.4 kg/m². In the study by Coviello et al.[34] and Tavares et al.,[22] the prevalence of MetS had a positive correlation with BMI (Odds ratio of 4.5 and 4.8, respectively). Dokras et al.[35] did not demonstrate any statistical significance in the prevalence of MetS between PCOS and control groups when BMI increased above 25; neither did all obese patients have MetS. Thus, the high prevalence of MetS in women with PCOS cannot be accounted for by obesity alone. In a study by Pillai et al.,[36] however, it was observed that obese PCOS patients demonstrated a more atherogenic and androgenic biochemical profile, which could act as a confounding factor while screening for metabolic syndrome.

While the average values of systolic and diastolic BP in the group with and without MetS may not seem vastly deranged in our study (126.3 ± 7.8 vs 117.3 ± 12.3 mm Hg and 83.6 ± 9.2 vs 76.7 ± 7.5 mm Hg), a significant difference was seen on applying independent samples *t*-test ($p = 0.000$).

Fasting plasma glucose (98.3 ± 9.7 vs 89.1 ± 9.9 mg/dL), serum triglyceride (163.4 ± 42.6 vs 123.5 ± 37.1 mg/dL), and serum HDL (46.5 ± 9.1 vs 55.1 ± 5.8 mg/dL) were all deranged in the group having MetS with PCOS. Even so, PCOS patients with normal blood glucose levels are at higher risk of developing impaired glucose tolerance (IGT); with figures of conversion as high as 16% per year. Talbott et al.[37] noted in a case-control study that women with PCOS aged less than 45 years had abnormal lipid profiles, while carotid artery changes were more significant in PCOS women above 45 years. This observation is crucial in helming further research on conversion of dyslipidemia at an earlier age into atherosclerosis and cardiovascular disease later in life.

Conclusion

PCOS produces an intrinsic stressful environment in the body with elevated inflammatory markers or cytokines. Metabolic syndrome results in a five-fold increase in risk for type 2 diabetes, PCOS being one of the non-modifiable risk factors.[38,39] PCOS women are likewise vulnerable to dyslipidemia, premature arteriosclerosis, and endometrial carcinoma. Our study has demonstrated a 35% prevalence of metabolic syndrome in newly diagnosed or known cases of PCOS. There is evidence of impaired metabolic parameters in our study, which highlights the importance of routine screening. However, there are some limitations of our study, which include:

- High prevalence of obesity in study subjects. The prevalence of obesity in PCOS patients is reported to be 60% in the current study. Using BMI and waist hip ratio to describe obesity may be a flaw in the institute-based studies like ours, as it does not include visceral fat which may be related to dyslipidemia. Abdominal visceral fat, rather than subcutaneous fat, would be a better marker of insulin resistance and metabolic features.
- TAS, rather than TVS findings are incorporated in our study.

- The cut-off or threshold values for HOMA-IR are not established. It is difficult to determine with no universally accepted parameter to measure IR.
- The lack of a control group.

Metabolic factors determine the quality of life and longevity. Thus, correctly diagnosing and offering pharmacotherapy where required, even in adolescent girls with PCOS is extremely important. In the early reproductive life, such metabolic abnormalities increase pregnancy complications, and in some cases, may render the woman subfertile.

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