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Comparison of clinical, metabolic, and hormonal parameters in lean vs. obese women with polycystic ovary syndrome: a single-center study from Bangladesh

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Abstract

A bi-directional relationship exists between obesity and polycystic ovary syndrome (PCOS). Although most of the patients with PCOS are obese, patients with normal body mass index (BMI) still account for a certain proportion of women with PCOS; such non-obese patients with PCOS have lesser degrees of insulin resistance and fewer metabolic risk factors. This study was conducted to compare the clinical, metabolic, and endocrine parameters of the two categories of women with PCOS: lean- and obese PCOS. We evaluated 523 women with PCOS attending the Endocrinology outpatient department of a tertiary hospital in Bangladesh. The women with PCOS having BMI <23 kg/m^2 were categorized as lean PCOS and BMI ≥23 kg/m^2 as obese PCOS. Out of 523 women with PCOS studied, the frequencies of lean and obese PCOS were 23.3% and 76.7%, respectively. Age, systolic blood pressure (BP), diastolic BP, fasting plasma glucose, plasma glucose 2-hours after oral glucose tolerance test, serum triglyceride, total cholesterol, low-density lipoprotein cholesterol, total testosterone, and thyroid-stimulating hormone were higher in the obese PCOS group. Serum prolactin was higher in the lean PCOS group. Modified Ferriman-Gallwey score and high-density lipoprotein cholesterol were similar in the two groups. Acanthosis nigricans (89.3% vs. 45.9%), prediabetes (24.4% vs. 13.1%), diabetes (6.7% vs. 1.6%), pre-hypertension (22.2% vs. 9.8%), hypertension (8.7% vs. 0.8%), metabolic syndrome (61.3% vs. 14.8%), and biochemical hyperandrogenism (27.7% vs. 11.5%) were more frequent in the obese group than the lean group. The obese PCOS group had an 8.35-fold higher risk of having metabolic syndrome than the lean group. The two groups had similar frequencies of menstrual irregularity, hirsutism, a family member with type 2 diabetes, and dyslipidemia. Though metabolic abnormalities are more frequently observed when obesity is associated with PCOS, lean women with PCOS also have adverse metabolic consequences. Screening for metabolic abnormalities should be considered in all patients with PCOS irrespective of BMI category.

Keywords: PCOS, lean PCOS, obese PCOS, metabolic syndrome, hyperandrogenism

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Introduction

Polycystic ovary syndrome (PCOS) is the commonest endocrine disorder in women of reproductive age. The prevalence of PCOS varies from country to country, which is as low as 6-10% in the western world and as high as 22.5% in the Indian subcontinent[1,2]. This heterogeneous androgen-excess disorder presents with different degrees of reproductive and metabolic dysfunctions. PCOS is associated with insulin resistance (IR) and metabolic syndrome [1]. There is a bi-directional relationship between obesity and PCOS; both exacerbate each other in a never-ending cyclical manner [3]. Although 50-80% of patients with PCOS are obese, normal-weight patients still account for a significant proportion of the PCOS population[4,5]. In clinical practice, patients with PCOS are classified into two broad categories based on their body mass index (BMI), obese PCOS with BMI ≥23 kg/m^2, and lean PCOS with BMI <23 kg/m^2 [6,7]. Lean patients with PCOS have lesser degrees of insulin resistance and fewer metabolic risk factors, which suggests that the pathogenesis of this group may be different from that of obese PCOS patients[4,5]. In addition to the metabolic features, differences in the reproductive and endocrine parameters between the two groups are also observed[6-11].

Data highlighting the reproductive, endocrine, and metabolic characteristics of lean and obese Bangladeshi women with PCOS are scarce. This study was conducted to compare the features of the two categories of women with PCOS in our setting.

Subjects and methods

This cross-sectional study was conducted among newly diagnosed patients with PCOS attending the Endocrinology outpatient department of Mymensingh Medical College Hospital, Mymensingh, Bangladesh, from January 2017 to December 2019. The study protocol was approved by the institutional review board of Mymensingh Medical College. In adults, the diagnosis of PCOS was made by using the year 2003, revised Rotterdam criteria [12]. The diagnosis of PCOS in adolescent girls was made based on the presence of clinical and/or biochemical evidence of hyperandrogenism (after exclusion of other pathologies) in the presence of persistent menstrual irregularities[13]. Those receiving drug treatment for diabetes, hypertension (HTN), dyslipidemia, and obesity, on hormonal contraceptives, pregnant and lactating women, those having the pelvic inflammatory disease, malignancy, and patients with abnormal serum thyroid-stimulating hormone (TSH) or very high serum prolactin (i.e., ≥2000 μIU/mL) were excluded. A semi-structured questionnaire-based interview was conducted on a one-to-one basis to collect detailed information on clinical presentation and family history. Height (to ±0.1 cm) was measured in all the individuals using wall-mounted stadiometers, and body weight (to ±0.1 Kg) measured using electronic calibrated scales; BMI was calculated from height and weight using the formula: height / weight^2. These women with PCOS were divided into two groups: overweight or obese ones with BMI ≥23 kg/m^2 (based on the BMI categories applicable to the Asian Indians)[14] were included in the obese PCOS group and those with BMI <23 kg/m^2 (normal and underweight women) were included in the lean PCOS group[6-7]. Waist circumference (WC) was measured (to ±0.5 cm) at the end of a gentle expiration midway between the lower rib margins and the iliac crests. Blood

pressure(BP) was measured twice in each study subject by the auscultatory method, using a standard validated aneroid sphygmomanometer, after at least five minutes of rest; two separate readings were taken at an interval of minimum three minutes, and the average of the two readings was used. Hypertension (HTN) and pre-hypertension (pre-HTN) were defined according to the Joint National Committee VII criteria[15]. Hirsutism was assessed by the modified Ferriman-Gallwey (F-G) score; a score ≥8 was the cut-point for diagnosis of hirsutism[16]. Oral glucose tolerance test (OGTT) with a 75-gram glucose load was done in all after overnight fasting for at least 8 hours; fasting plasma glucose (FPG) and plasma glucose 2-hour after OGTT (PG 2H-OGTT) were measured by glucose oxidase method using fully automatic biochemistry analyzer (MINDRAY BS-380). Prediabetes and diabetes mellitus (DM) were diagnosed according to criteria described by the American Diabetes Association[17]. The lipid profile was measured in fasting states using the above analyzer. Dyslipidemia was defined according to cutoffs described in the Adult Treatment Panel (ATP) III guideline[18]. Metabolic syndrome was diagnosed using the modified National Cholesterol Education Program (NCEP) ATP III diagnostic criteria [19]. In adults, WC ≥80 cm was considered as the cutoff for abdominal obesity[19]. In the adolescents aged 10-16 years, WC ≥90th percentile (or adult cutoff if lower) for Indians was used to define abdominal obesity[20]. Transvaginal ultrasonography (USG) was preferred in the married patients, whereas transabdominal pelvic USG was done in unmarried ones. Serum thyroid-stimulating hormone (TSH), total testosterone (TT), and prolactin were measured using radioimmunoassay (RIA) by automated hormone analyzer LB 2111 Multi Crystal Gamma Counter. A total of 523 cases were included in the final analysis.

Statistical analysis: Statistical analysis was done using Statistical Product and Service Solutions (SPSS) for Windows, version 23.0 software (SPSS Inc; Chicago, IL, USA). The categorical variables were presented as number (%), measurable variables with normal distribution were presented as mean±standard deviation (SD), and those not following normal distribution were presented as median (interquartile range, IQR). Student's *t*-test, Chi-square test, and Mann-Whitney U tests were performed as applicable for comparing the variables between different groups. *p*-value ≤0.05 was considered as statistically significant.

Results

Out of 523 women with PCOS studied, the frequencies of lean- and obese PCOS were 23.3% (18.7% normal weight, 4.6% underweight) and 76.7% (35.8% overweight, 40.9% obese), respectively.

The comparison of clinical, metabolic, and hormonal parameters between lean and obese PCOS groups is given in Tables 1 and 2. Age, BMI, WC, systolic BP, diastolic BP, FPG, PG 2H-OGTT, serum triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), TT, and TSH were higher in obese PCOS group; serum prolactin was higher in the lean PCOS group; modified F-G score and high-density lipoprotein cholesterol (HDL-C) levels were similar in the two groups. The frequencies of acanthosis nigricans, prediabetes, diabetes, pre-HTN, HTN, metabolic syndrome, and biochemical hyperandrogenism were higher in the obese group. The two groups had statistically similar frequencies of menstrual irregularity, hirsutism, type 2 diabetes in the first-degree family members, and dyslipidemia.

Though polycystic ovarian morphology (enlarged ovary and polycystic appearance) was higher in the obese group, the difference was not statistically significant.

Table 1: Comparison of the quantitative (clinical, metabolic, and hormonal) parameters between the lean and obese PCOS groups

Parameters	All PCOS (N=523) Mean±SD or Median (IQR)	Lean PCOS (n=122) Mean±SD or Median (IQR)	Obese PCOS (n=401) Mean±SD or Median (IQR)	*p*
Age (years)	21.9±5.9	20.0±3.9	22.6±5.7	<0.001
Modified F-G score	12±6	12±5	12±6	0.959
BMI (kg/m^2)	26.8±5.2	20.3±1.9	28.8±4.2	<0.001
WC (cm)	88.0±12.0	74.0±6.5	93.0±11.0	<0.001
Systolic BP (mmHg)	115±12	108±10	117±12	<0.001
Diastolic BP (mmHg)	75±8	70±7	77±8	<0.001
FPG (mmol/mL)	5.1±1.1	4.8±0.7	5.2±1.2	0.001
PG 2H-OGTT	6.8±2.2	6.1±1.3	7.1±2.4	<0.001
S. TG (mg/dL)	144±51	126±43	150±53	<0.001
S. TC (mg/dL)	174±33	161±32	177±33	<0.001
S. LDL-C (mg/dL)	105±27	96±26	107±27	<0.001
S. HDL-C (mg/dL)	38±7	37±8	39±7	0.077
S. TT (ng/mL)	0.76 (0.47-1.19)	0.57 (0.40-0.94)	0.84 (0.50-1.28)	<0.001
S. TSH (µIU/mL)	1.28 (0.79-2.08)	1.03 (0.72-1.59)	1.37 (0.84-2.19)	0.001
S. Prolactin (µIU/mL)	252.5 (181.4-416.0)	276.1 (201.4-483.0)	241.2 (173.6-384.4)	0.016

p-value by Student's *t*-test or Mann-Whitney U test as applicable

F-G score= Ferriman-Gallwey score; BMI= Body mass index; WC= Waist circumference; BP= Blood pressure; FPG= Fasting plasma glucose; PG 2H-OGTT= Plasma glucose 2-hour after oral glucose tolerance test; S. TC= Serum total cholesterol; S. TG= Serum triglyceride; S. LDL-C= Serum low-density lipoprotein cholesterol; S. HDL-C= Serum high-density lipoprotein cholesterol; S. TT= Serum total testosterone; S. TSH= Serum thyroid-stimulating hormone.

Table 2: Comparison of the qualitative (clinical, metabolic, and hormonal) parameters between the lean and obese PCOS groups

Parameters	Categories	All PCOS (N=523) n (%)	Lean PCOS (n=122) n (%)	Obese PCOS (n=401) n (%)	*p*
Menstrual irregularity	Present	477 (91.2)	114 (93.4)	363 (90.5)	0.366
	Absent	46 (8.8)	8 (6.6)	38 (9.5)	
Hirsutism	Present	422 (80.7)	99 (81.1)	323 (80.5)	1.000
	Absent	101 (19.3)	23 (18.9)	78 (19.5)	
Type 2 DM in Family	Present	141 (27.0)	33 (27.0)	108 (26.9)	1.000
	Absent	382 (73.0)	89 (73.0)	293 (73.1)	
Acanthosis nigricans	Present	414 (79.2)	56 (45.9)	358 (89.3)	<0.001
	Absent	109 (20.8)	66 (54.1)	43 (10.7)	
BP category	Normal	386 (73.8)	109 (89.3)	277 (69.1)	<0.001
	Pre-HTN	101 (19.3)	12 (9.8)	89 (22.2)	
	HTN	36 (6.9)	1 (0.8)	35 (8.7)	
Glycemic status	Normal	380 (72.2)	104 (85.2)	276 (68.8)	0.001
	Prediabetes	114 (21.8)	16 (13.1)	98 (24.4)	
	Diabetes	29 (5.5)	2 (1.6)	27 (6.7)	
Dyslipidemia	Present	473 (90.4)	110 (90.2)	363 (90.5)	0.862
	Absent	50 (9.6)	12 (9.8)	38 (9.5)	
Metabolic syndrome	Present	264 (50.5)	18 (14.8)	246 (61.3)	<0.001
	Absent	259 (49.5)	104 (85.2)	155 (38.7)	
Biochemical hyperandrogenism	Present	125 (23.9)	14 (11.5)	111 (27.7)	<0.001
	Absent	398 (76.1)	108 (88.5)	290 (72.3)	
Ovarian morphology in USG	Normal	84 (16.1)	15 (12.3)	69 (17.2)	0.053
	Enlarged ovary	213 (40.7)	61 (50.0)	152 (37.9)	
	Polycystic	226 (43.2)	46 (37.7)	180 (44.9)	

p-value by Chi-square test. HTN= Hypertension; USG= Ultrasonography

The comparison of the frequencies of metabolic syndrome, BP status, glycemic status, dyslipidemia, and biochemical hyperandrogenism between PCOS patients aged <25 years and ≥25 years of both lean and obese groups are given in Table 3.

Table 3: Comparison of metabolic and androgen status between age groups <25 years and ≥25 years

Parameters	Categories	Lean PCOS (n=122)			Obese PCOS (n=401)		
		<25 years (n=103)	≥25 years (n=19)	*p*	<25 years (n=265)	≥25 years (n=136)	*p*
Metabolic syndrome	Present	11.7%	31.6%	0.036	58.5%	66.9%	0.106
	Absent	88.3%	68.4%		41.5%	33.1%	
BP category	Normal	91.3%	78.9%	0.189	72.8%	61.8%	0.029
	Pre-HTN	7.8%	21.1%		20.8%	25.0%	
	HTN	1.0%	0%		6.4%	13.2%	
Glycemic status	Normal	89.3%	63.2%	0.001	72.5%	61.8%	0.020
	Prediabetes	10.7%	26.3%		23.0%	27.2%	
	Diabetes	0%	10.5%		4.5%	11.0%	
Dyslipidemia	Present	89.3%	94.7%	0.689	90.6%	90.4%	1.000
	Absent	10.7%	5.3%		9.4%	9.6%	
Biochemical hyperandrogenism	Present	12.6%	5.3%	0.694	30.2%	22.8%	0.127
	Absent	87.4%	94.7%		69.8%	77.2%	

p-value by Chi-square test. BP= Blood pressure; HTN= Hypertension

Table 4: Binary logistic regression for the predictors of metabolic syndrome in the study subjects

Variables	Subgroups	Odds Ratio (95% Confidence Interval)	*p*
PCOS category	Lean PCOS	Reference	
	Obese PCOS	8.35 (4.82-14.45)	<0.001
Age group	<25 years	Reference	
	≥25 years	1.60 (1.06-2.43)	0.026
Biochemical hyperandrogenism	Absent	Reference	
	Present	1.04 (0.68-1.61)	0.848
Hyperprolactinemia	Absent	Reference	
	Present	0.59 (0.32-1.09)	0.093

Metabolic syndrome and dysglycemia were more common among the lean PCOS subjects aged ≥25 years than those aged <25 years in the group. Elevated BP (HTN and pre-HTN) and dysglycemia were more common among the obese PCOS subjects aged ≥25 years than those aged <25 years.

In binary logistic regression analysis, study subjects in the obese PCOS group and age group ≥25 years had significantly higher metabolic syndrome risks than their counterparts [Table 4].

Discussion

In this study, the frequencies of lean- and obese PCOS were 23.3% and 76.7%, respectively. The obese PCOS subjects had higher metabolic risk factors and a higher degree of biochemical hyperandrogenism.

Insulin resistance (IR) is generally agreed to be the underlying cause of PCOS[1,12]. Obesity and higher BMI further add to the risk of IR and metabolic syndrome[6]. Though the prevalence of IR is reported to be 6-22% in lean PCOS, there is disagreement whether these thin women with PCOS suffer from IR to the same degree as their obese counterparts[21]. A study done by Yildirim et al. has demonstrated the presence of a higher proportion of preperitoneal and visceral adiposity among lean PCOS patients compared to weight-matched controls [22]. They concluded that lean patients with PCOS have intrinsic IR, whereas obese patients with PCOS have intrinsic resistance as a part of the disease and extrinsic resistance due to obesity[22]. Another study done by Bozkirli et al. has demonstrated both lean and obese PCOS phenotypes have insulin resistance compared to controls, indicating that factors other than obesity may be involved in IR seen in PCOS[23]. Faloia et al., in a study conducted to evaluate metabolic characters in lean and obese patients with PCOS, did not find significant metabolic alterations in lean women with PCOS[24]. The observation of Faloia et al. indicates that obesity underpins the metabolic alterations exhibited by overweight or obese patients[24].

A study done by Sachdeva et al. in India observed that lean- and obese PCOS prevalence were 24.39% and 75.61%, respectively[6]. However, the prevalence of lean PCOS was found higher in other Indian studies done by Majumdar et al. (33.3% lean and 66.7% obese) and Akshaya et al. (44% lean and 56% obese)[7,9]. Nahar et al., in their study, found 52% of Bangladeshi women diagnosed with PCOS to have BMI ≥25 kg/m^2; the rest (44%) of them had BMI <25 kg/m^2[25]. In the current study, the frequencies of lean and obese PCOS were 23.3% and 76.7%, respectively, which are almost similar to the observation of Sachdeva et al.[6]. The higher frequency of obese PCOS in this study than another study conducted by Nahar et al. in Bangladesh is probably due to lower BMI cutoffs used to define obese and overweight women in this study[25].

In a meta-analysis done by Chowdhury et al., the weighted pooled prevalence of metabolic syndrome in Bangladeshi women using any criteria was 32%, with a higher prevalence in older age[26]. A study done by Jesmin et al. to assess the prevalence of metabolic syndrome in 1485 rural women of Bangladesh using NCEP ATP III modified criteria demonstrated that the prevalence of metabolic syndrome was 31.25%, and the prevalence increased with age; 6.40% in <25 years, 20.07% in 25-34 years, 31.98% in 35-44 years, and 46.02% in the age group 55-64 years[27]. In this study, 50.5% of the women with PCOS had metabolic syndrome; the frequency was 14.8% in lean PCOS and

61.3% in obese PCOS; the obese group had more than 8-fold higher risk of metabolic syndrome compared to the lean group. Among the lean PCOS subjects, we found metabolic syndrome in 11.7% in the age group <25 years and 31.6% in those aged ≥25 years; in the obese PCOS, the frequencies were 58.5% and 66.9% in the age groups, respectively. So, it may be said that even lean PCOS women have a higher prevalence of metabolic syndrome than their non-PCOS otherwise healthy counterparts of the same age in our setting. Sachdeva et al. observed a lower prevalence of metabolic syndrome (24.39%) among Indian women with PCOS; though, like our study, the prevalence was higher in the obese PCOS compared to the lean PCOS (29.03% vs. 10%) in their study[6].

In Indian women with PCOS, HTN was more common in the obese group as compared to lean PCOS in the studies done by Sachdeva et al. (4.03% vs. 2.5%, p=0.547) and Majumdar et al. (16% vs. 6%, p=0.261), and though the differences were not statistically significant[6,7]. Pre-HTN was more common in lean PCOS than obese PCOS, according to Majumdar et al.'s observation (29.2% vs. 23.0%, p=0.261) [7]. Saxena et al. observed higher (statistically insignificant) systolic and diastolic BP in the obese PCOS [28]. We observed higher frequencies of HTN (8.7% vs. 0.8%) and pre-HTN (22.2% vs. 9.8%) in the obese PCOS subjects compared to the lean ones (p<0.001). Both the systolic and the diastolic BP levels were higher in the obese group. The frequency of hypertension was higher in the higher age group.

In India, Majumdar et al. observed a higher prevalence of both prediabetes (25% vs. 10%, p=0.000) and diabetes (11.7% vs. 6%, p=0.000) in obese compared to the lean POCS patients[7]. On the contrary, Sachdeva et al. and Saxena et al. observed no differences in FPG and PG 2H-OGTT between lean and obese groups[6,28]. Indian obese PCOS women had a higher frequency of family history of T2DM than their lean counterparts[9,28]. Though the frequency of type 2 DM in the first degree relatives was identical in the lean- and obese PCOS women in our study (27.0% vs. 26.9%), prediabetes (13.1% vs. 24.4%) and diabetes (1.6% vs. 6.7%) were less common in the lean group compared to the obese group (p=0.001); moreover, FPG (4.8±0.7 vs. 5.2±1.2 mmol/L, p=0.001) and PG 2H-OGTT (6.1±1.3 vs. 7.1±2.4 mmol/L, p<0.001) were also lower in the lean group.

In this study, the prevalence of dyslipidemia was similar among lean- and obese groups (90.2% vs. 90.5%). However, TG, TC, LDL-C, and HDL-C were higher (the differences are significant for all except for HDL-C) in the obese PCOS subjects compared to lean PCOS subjects. Sachdeva et al. and Saxena et al. had similar observations, though Thathapudi et al. observed no differences in the lipid parameters between lean- and obese Indian women with PCOS[6,10,28].The menstrual irregularity is more common in the obese PCOS group as compared to lean PCOS according to Sachdeva et al. (86.29% vs. 70%) and Majumdar et al. (79.2% vs. 44%), though the frequencies were similar according to Akshaya et al. (96.4% vs. 90.9%) and Saxena et al. (96.6% vs. 92.8%)[6,7,9,28]. We observed no differences in the lean and obese groups regarding menstrual irregularity (93.4% vs. 90.5%, p=0.366).

The frequency of hirsutism was similar in both lean and obese PCOS groups in the studies done by Akshaya et al. and common

in the obese PCOS women according to Sachdeva et al.and Majumder et al.[6,7,9,28]. Sachdeva et al. also observed higher F-G scores in obese patients [6]. The mean F-G score and frequency of hirsutism in our study were similar in the two groups (81.1% vs. 80.5%, p=1.000), though biochemical hyperandrogenism was more common in the obese subjects (27.7% vs. 11.5%, p<0.001) compared to the lean ones. The obese ones also had a higher serum testosterone level (0.84 vs. 0.57 ng/mL, p<0.001). Contrary to our finding, Sachdeva et al. and Saxena et al. observed similar testosterone levels in both groups [6,28].

Akshaya et al. (14.3% vs. 9.1%) and Saxena et al. (12.06% vs. 9.5%) demonstrated higher frequencies of acanthosis nigricans in obese PCOS though the differences were not statistically significant[9,28]. However, acanthosis nigricans was more common in the obese subjects than the lean ones (89.3% vs. 45.9%, p<0.001) in this study.

Both lean and obese groups had similar TSH in the studies done by Thathapudi et al. and Saxena et al[10,28]. However, we observed significantly higher TSH (1.37 vs. 1.03 μIU/mL, p=0.001) in the obese PCOS than lean PCOS. Serum prolactin was higher in the lean PCOS (276.1 vs. 241.2 μIU/mL, p=0.016) in our study. Saxena et al. also had similar observations (13.6±8.2 vs. 11.9±4.6 ng/mL), though the difference observed by them was not statistically significant[28].

This study has some limitations. It was a single-center study; the sample may not represent the whole country. No healthy control group was included limiting the comparison with the lean and obese PCOS. hirsutism was more Nevertheless, this one is the first study in Bangladesh comparing the clinical, metabolic, and hormonal parameters in lean and obese PCOS and may serve as the basis for further large-scale, multi-center study in this subject.

Conclusion

Lean and obese women have similar menstrual irregularities and hirsutism, but biochemical hyperandrogenism is more prevalent in the obese PCOS. Both lean and obese women with PCOS have adverse metabolic consequences; metabolic abnormalities are more frequently observed when obesity is associated with PCOS. All patients with PCOS should be considered for screening for metabolic abnormalities irrespective of BMI category.

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Conflict of interest

None

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