Original Article

Comparison of metabolic and endocrinal parameters in obese and nonobese women of polycystic ovarian syndrome with normal controls

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ABSTRACT

Aim: The aim of this study is to compare the metabolic and endocrinal parameters between obese and nonobese polycystic ovarian syndrome (PCOS) women with normal controls. **Materials and Methods:** The study was a cross-sectional comparative study. One-hundred PCOS women were randomized into two groups: Group I obese (n = 50) and Group II nonobese (body mass index [BMI] cutoff <23 kg/m^2). Fifty non-PCOS normal weight women formed the control Group III. Metabolic parameters (lipid profile, blood sugar profile, and serum insulin) and endocrinal parameters (serum luteinizing hormone [LH], follicle-stimulating hormone, and testosterone) were compared between the three groups. **Results:** Mean age of all the groups was comparable. A significantly higher waist circumference was seen in Group I; however, waist-hip ratio (WHR) was comparable between obese and nonobese PCOS groups. Between Groups I and II, mean fasting blood sugar, mean values of impaired glucose tolerance (IGT), and clinical hyperandrogenism were statistically comparable. Degree of insulin resistance (IR) in Group I versus Group II (44% vs. 36%) and of metabolic syndrome in Group I (20%) versus Group II (8%) was statistically comparable. Degree of hypertension (P = 0.001), IGT (P = 0.001), and dyslipidemia were higher in nonobese PCOS group versus normal group. Mean values of serum LH, serum fasting insulin, and serum testosterone were significantly different in nonobese PCOS women when compared with normal. Prevalence of IR (36% vs. 8%; P < 0.01) and metabolic syndrome was significantly higher in nonobese PCOS than normal controls. **Conclusion:** PCOS *per se* has evolved as a risk factor for endocrinal and metabolic derangements irrespective of the BMI status. Prevalence of IR and metabolic syndrome is high in nonobese PCOS as compared to normal controls, risks being as high as that in obese PCOS.

Keywords: Insulin resistance, metabolic syndrome, polycystic ovarian syndrome

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is a multifaceted heterogeneous endocrine disorder affecting 5-10% of women in the reproductive age group,[1] with a reported incidence of 11-26% even in adolescents.[2] While the index of suspicion of PCOS remains high in the presence of obesity, the diagnosis may be missed, as nearly 50% cases occur in women who are normal weight.[3] Although association of insulin resistance (IR) and other metabolic derangements have been observed in PCOS,[4] there is scant available literature regarding the prevalence of these conditions in India (especially in the normal weight or lean

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PCOS women) where the burden of diabetes mellitus (DM) in general population is high.[5] Here, in this study, we report the prevalence of glucose intolerance and IR and comparison of metabolic and endocrinal parameters of obese and nonobese women with PCOS with normal controls.

MATERIALS AND METHODS

The present study was a cross-sectional comparative study conducted in Infertility Clinic of Department of Obstetrics and Gynaecology, and Endocrine and Metabolic Clinic of Department of Medicine, University College of Medical Sciences and Guru Teg Bahadur Hospital, Delhi.

One-hundred fifty patients, in the age group 18-35 years, were recruited for the study, of which 100 cases of PCOS, diagnosed as per Rotterdam *et al*. criteria 2003,[6] formed the study group and 50 non-PCOS normal weight formed the controls. The PCOS group was further divided into obese and nonobese PCOS groups. The body mass index (BMI) cutoff[7] was taken as ≤23 kg/m^2. Patients with DM, hyperprolactinemia, thyroid dysfunction, Cushing's syndrome, and androgen-secreting tumors and those on medical treatment for PCOS or women using exogenous hormones in the last 3 months were excluded from the study.

History included pattern of menstrual cycle, duration and extent of hair growth, voice changes, acne and weight gain, and family history of hypertension, DM, and coronary artery disease. Oligomenorrhea was defined as an intermenstrual interval of ≥35 days or a total of ≤8 menses/year. Anthropometric assessments such as measurement of height, weight, waist circumference, WHR, blood pressure (BP), and detailed systemic examination were carried out. BMI was calculated by the formula weight (kg)/height (m^2). Clinical hyperandrogenism was diagnosed by the presence of hirsutism and/or alopecia and/or acne vulgaris. Hirsutism was objectively scored by Ferriman-Gallwey (FG) score. A score of ≥8 of 36 was considered statistically significant.[8] Biochemical hyperandrogenism was defined as a total serum testosterone level of >1 ng/ml. Polycystic ovaries were diagnosed by ultrasonography (USG) using Wipro GE LOGIQ 500 (GE Healthcare) by 4.0 MHz abdominal transducer/7 MHz vaginal transducer on day 2/3 of menstrual cycle in menstruating women or on any day in patients with amenorrhea. In married women, transvaginal sonography was performed using 7.0 MHz vaginal transducer to demonstrate >12 follicles measuring 2-9 mm in each ovary/ovarian volume of >10cc using the simplified formula for prolate ellipsoid (0.5 × length × width × thickness).[2] Hormonal evaluation was done after an overnight fasting on day 2/day 3 of cycle or on any day in amenorrheic women for pooled levels of serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin, thyroid-stimulating hormone, testosterone and serum fasting insulin (FI), fasting blood sugar, and lipid profile using commercial kits in our endocrine laboratory. Oral glucose tolerance test (OGTT) was done 2 h after 75 g oral glucose load. Samples were stored at −20°C until the assay.

Metabolic syndrome diagnosed as per the National Cholesterol Education Program-Adult Treatment Panel-III criteria 2005,[9] requiring the presence of any three of the criteria which include waist circumference >88 cm; elevated triglycerides ≥150 mg/dl or on drug treatment for this lipid abnormality; reduced high-density lipoprotein cholesterol (HDL-C) <50 mg/dl in females or on drug treatment for this lipid abnormality; hypertension: Systolic BP ≥135 mmHg and or diastolic BP ≥85 mmHg or on drug treatment for hypertension; fasting plasma glucose ≥100 mg/dl.

IR[10] was defined by either increased FI (>20 U/ml) or fasting blood sugar:FI ratio of <4.5 or abnormal OGTT, i.e., impaired glucose tolerance (IGT) of 140-199 mg/dl or DM with blood sugar levels of >200 mg/dl.

This study was approved by and conducted according to the guidelines of the Institutional Ethical Committee. A written informed consent was taken from all the women enrolled for the study and confidentiality was maintained.

Statistical analysis

Data were analyzed by SPSS version 17 (Chicago IL) of statistical software. Quantitative variables were analyzed by *t*-test and one-way ANOVA followed by *post hoc* Tukey's test. For qualitative data, Chi-square test/Fisher's exact test was used wherever applicable. $P < 0.05$ was considered statistically significant.

RESULTS

Clinical and anthropometric variables in all the subjects studied showed the mean age in all the three groups was comparable ($P = 0.227$). Majority of the patients presented in the age group of 21-30 years. The mean ages of the patients were 27.5 ± 10.3, 24.2 ± 9.8, and 25.8 ± 8.4 years in obese, nonobese, and normal controls, respectively. The mean ovarian volume in both the PCOS groups was comparable ($P = 0.715$) and was significantly higher than that of controls ($P < 0.01$). A number of patients with clinical hyperandrogenism were comparable in the obese and nonobese PCOS group. The mean FG score was comparable in the two study groups ($P = 0.465$). There were no features of seborrhea and male pattern balding in either group.

BMI ranged from 24 to 45 kg/m² with a mean of 28.73 ± 3.76 in the obese group and 19.96 ± 2.36 in the nonobese group. WHR >0.85 was comparable in the both obese and nonobese groups ($P = 0.001$) whereas a significantly high WHR >0.85 was seen in nonobese PCOS when compared to the normal controls ($P = 0.001$).

Metabolic parameters

Metabolic variables, namely, mean fetal bovine serum (FBS), OGTT mean, mean HDL-C, and mean triglyceride levels were statistically comparable between obese PCOS and nonobese PCOS groups. Mean value of HDL-C was significantly higher ($P = 0.005$) in nonobese PCOS when compared to control group [Table 1]. Hypertension was observed in 20% of obese PCOS and 10% of nonobese PCOS subjects. The two groups also had comparable number of women with abnormal fasting blood glucose of >100 mg/dl ($P = 0.161$) and dyslipidemia. The prevalence of metabolic syndrome in obese and nonobese group was 20% versus 8%, respectively, and this difference was statistically nonsignificant ($P = 0.084$). None in the control group had metabolic syndrome, and hence a statistically significant difference between nonobese PCOS and normal controls was observed in all the metabolic parameters such as hypertension,

fasting blood sugar, and dyslipidemia ($P < 0.001$). Prevalence of IR was comparable in both the obese and nonobese groups. Percentage of women with serum FI >20 μIU/ml, fasting blood glucose:FI ratio <4.5, IGT, and DM was higher in obese group as compared to the nonobese Group II, but this difference was not statistically significant [Table 2]. Prevalence of IR was significantly higher in the nonobese PCOS women than normal controls. All the parameters of IR were significantly abnormal in nonobese PCOS group as compared to normal controls.

Endocrinal parameters

Mean values of serum FSH, LH, and FI between obese and nonobese were statistically comparable. Serum testosterone levels were significantly higher in nonobese as compared to obese groups [Figure 1]. The mean value of serum LH, serum FI, and serum testosterone was high nonobese PCOS when compared with normal women and was statistically significant.

Table 1: Distribution of metabolic parameters in three groups

Variables	Groups	Mean ± SD	*P* (one-way ANOVA test)	Post hoc Tukey's test (*P*)
FBS (mg/dl)	Group I	91.96±16.50	0.004	0.380
	Group II	86.92±8.66		
	Group I	91.96±16.50		0.003
	Group III	81.2±6.02		
	Group II	86.92±8.66		0.117
	Group III	81.2±6.02		
OGTT (mg/dl)	Group I	120.16±23.67	0.029	0.736
	Group II	107.05±21.04		
	Group I	120.16±23.67		0.026
	Group III	100.92±12.38		
	Group II	107.05±21.04		
	Group III	100.92±12.38		
HDL-C (mg/dl)	Group I	40.64±9.49	0.008	0.340
	Group II	45.51±6.81		
	Group I	40.64±9.49		0.187
	Group III	33.9±8.10		
	Group II	45.51±6.81		0.005
	Group III	33.9±8.10		
Triglyceride (mg/dl)	Group I	95.58±48.14	0.008	0.125
	Group II	101.91±36.37		
	Group I	95.58±48.14		0.006
	Group III	79.84±22.31		
	Group II	101.91±36.37		0.468
	Group III	79.84±22.31		

FBS: Fasting blood sugar, OGTT: Oral glucose tolerance test, HDL-C: High-density lipoprotein-cholesterol, SD: Standard deviation

Table 2: Comparison of number of women with insulin resistance between obese polycystic ovarian syndrome and nonobese polycystic ovarian syndrome

Variable	Group I (obese) ($n = 50$) (%)	Group II (nonobese) ($n = 50$) (%)	*P*
Degree of insulin resistance	22 (44)	18 (36)	0.414*
Serum FI >20 μIU/ml	17 (34)	10 (20)	0.115*
Fasting blood glucose:FI ratio <4.5	20 (40)	14 (28)	0.205*
Abnormal OGTT			
IGT (140–199 mg/dl)	6 (12)	4 (8)	0.505*
DM (>200 mg/dl)	1 (2)	0	1.000#

*Chi-square test ($P < 0.05$-significant), #Fisher's exact ($P < 0.05$-significant). OGTT: Oral glucose tolerance test, FI: Fasting insulin, IGT: Impaired glucose tolerance, DM: Diabetes mellitus

DISCUSSION

A relatively young population of PCOS women were enrolled in the present study with a majority of them presenting in the age group of 21-30 years. A BMI cutoff ≤23 kg/m^2 was taken for the upper limit of normal as per WHO recommendation for Asia-Pacific region.[7] Oligo-anovulation (Oligomenorrhea/amenorrhea) and USG evidence of polycystic ovaries were observed in 70% of obese PCOS and 72% of nonobese whereas varying degrees of hirsutism were seen in 26% of obese and 34% of nonobese PCOS women and this distribution was statistically comparable, in contrast to a significantly higher prevalence of both menstrual irregularities (79.2% vs. 44%) and clinical hyperandrogenism (74.2% vs. 50.6%) in the obese versus lean PCOS women as reported by Majumdar *et al*.[12] in their study of 450 PCOS women with a BMI cutoff of 23 kg/m^2. Despite the significant difference in BMI and WHR, a marker of android obesity was comparable in both obese and nonobese PCOS women (62% vs. 54%; $P = 0.418$). The control group, on the other hand, had a significantly lower incidence (6%) of WHR >0.85. Similar observations were noted in a study conducted on 120 PCO women by Ezeh *et al*.[11] FG score was similar in both obese and nonobese PCOS groups. Comparable prevalence of hirsutism was observed in both groups of PCOS women. This is in contrast to the study by Majumdar and Singh,[12] who reported a significantly higher hirsutism in obese PCOS as compared to the normal population with a BMI cutoff of 23 kg/m^2. Mean serum testosterone levels were significantly higher in nonobese PCOS subjects (32% vs. 20%) when compared with obese PCOS. Similar observations of high testosterone values have been documented in the PCOS women in a study by Diamanti-Kandarakis *et al*.,[13] and more so in the lean PCOS by Somani *et al*.[14]

The general incidence of hypertension reported in Northern Indian Urban women of all ages is about 22-29%.[15,16] The present study showed a similar frequency of hypertension in obese and nonobese PCOS women, which was higher than that in the normal women. Similar distribution of hypertension has been reported by Majumdar and Singh[12] in 450 PCOS women. On the contrary, Conway *et al*.[17] reported higher systolic BP only in obese PCOS as compared to the lean group. Holte *et al*.[18] reported an increased prevalence of labile hypertension indicating a prehypertensive state in women with PCOS, which

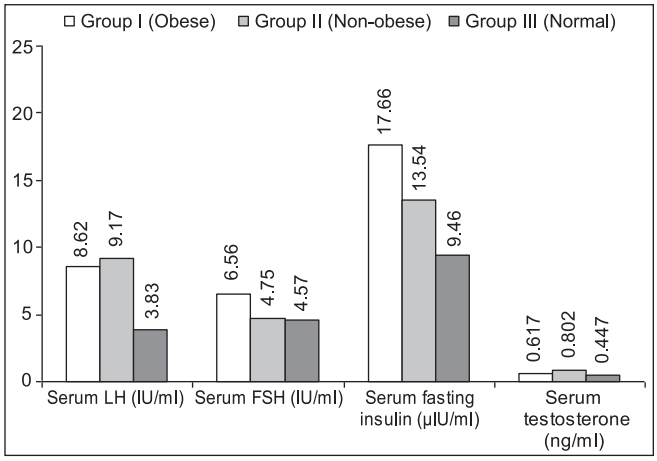

Figure 1: Comparison of hormonal parameters between the three groups

adds a further risk factor for profound metabolic aberrations. Elting *et al*.[19] have reported a high prevalence of DM (4 times) and hypertension (2.5 times) in 346 lean PCOS as compared to general Dutch female population. In the present study, fasting blood sugar of >100 mg% was seen in 20% and 14%, respectively, in obese and nonobese PCOS groups and this difference was statistically insignificant. Similar observation of comparable FBS between lean PCOS and normal controls has been reported by Vrbíková *et al*.[20] Higher FBS in PCOS women has also been documented by studies by Apridonidze *et al*.[21] in 2005 on 106 PCOS patients and Dokras *et al*.[22] on 129 PCOS patients as compared with normal controls. In contrast to these studies, Taponen *et al*.[23] in 2004 reported no difference in fasting blood glucose and triglyceride values between obese PCOS women and normal controls. Talbott *et al*.[24] noted in a review that women with PCOS had dyslipidemia, increased BP, plasminogen activator inhibitor, and coronary artery calcification. An interesting observation they made was that abnormal lipid profile difference between PCOS cases and controls was mainly seen in women aged <45 years while carotid artery changes were seen in PCOS women after 45 years. This indicates that dyslipidemia occurring at a younger age translates into atherosclerosis and cardiovascular disease later in life. However, Vural *et al*.[25] comparing 43 PCOS patients with 43 normal controls reported no difference in fasting blood glucose, LDL, and triglyceride levels in nonobese and normal controls.

Vrbíková *et al*.[20] reported lower HDL-C levels in lean PCOS as compared to normal controls. However, there were no differences in triglyceride levels between the two groups.

The mean serum FI in Group I (obese PCOS), Group II (nonobese PCOS), and Group III (control) were 17.66 ± 8.95, 13.54 ± 6.40, and 9.46 ± 3.84, respectively. Both the PCOS groups had significantly higher FI levels than the controls, but within the PCOS groups, the levels were comparable. However, Yildirim *et al*.[26] reported higher FI levels in nonobese PCOS women as compared to the normal controls and Silfen *et al*.[3] reported more than 2-fold increase in FI levels and a significant decrease in estimations of insulin sensitivity in overweight as compared to normal weight adolescents with PCOS. FG:FI ratio <4.5 was seen in 40% and 28% of obese and nonobese PCOS, respectively.

An IGT of 12% and 8% of obese and nonobese group, respectively, in the present study is similar to that of Gambineri *et al*.,[27] who reported 15.7% and 2.5% IGT and type-2 diabetes, respectively, in PCOS subjects screened from Mediterranean region. A National Survey[28] of Diabetes and IGT conducted in the year 2000 in six major cities of India showed a 13.1% prevalence of IGT and 5% prevalence of diabetes in the younger age group (20-40 years) of the general population. Majumdar *et al*.[12] reported a higher prevalence of IGT and type-2 DM in obese PCOS women with respect to lean ones. Legro *et al*.[29] reported 31% IGT and 7.5% type-2 DM in obese PCOS patients and 10.3% IGT and 1.5% DM in nonobese PCOS which was 3 times that of general population. They found that PCOS women are at a significantly higher risk for IGT and type-2 DM at all weights and at a younger age. Ehrmann *et al*. found IGT in 35% of women with PCOS and diabetes in 10%.[30]

In our study, a higher IR was seen between both obese and nonobese PCOS (44% and 36%) as compared to normal controls. Morales *et al*.[31] reported reduced insulin sensitivity by 50% in lean PCOS from that of normal controls. There was a further decrease in obese controls and a 2-fold greater reduction in obese PCOS than in obese controls, suggesting that IR is a common feature in PCOS, and that obesity contributes an additional component to IR in obese PCOS.

Higher prevalence of IR has been reported by Grulet *et al*.[32] The prevalence of insulin resistance was 63% in lean PCOS and 51% in obese PCOS $P<0.01$. However, Silfen *et al*.[3] reported a more than 2-fold increase in FI levels and a significant decrease in estimations of insulin sensitivity in overweight (>25 kg/m^2) as compared to normal weight adolescents with PCOS. Vrbíková *et al*.[33] reported that lean PCOS women are not more insulin resistant when compared with healthy controls. In a recent 12-year follow-up study conducted on 637 subjects, authors concluded a high prevalence of IR in PCO women.[34]

In the present study, the prevalence of metabolic syndrome in obese PCOS women was higher than nonobese PCOS women (20% vs. 8%), though this difference was not statistically significant. Coviello *et al*.[35] conducted a cross-sectional case-control study in 49 adolescent girls with PCOS to see the prevalence of metabolic syndrome in adolescent girls with PCOS. They reported that 11% overweight non-PCOS and 63% PCOS had metabolic syndrome. No case of metabolic syndrome was reported in the lean PCOS group.

CONCLUSION

The absence of hypertension, dyslipidemia, and metabolic syndrome in the control group in the present study is probably due to the small number of cases combined with the fact that the control group was normal weight young women. However, IR was observed in 4% of controls. The distribution of cases with hypertension, IR, and metabolic syndrome was nonsignificantly higher in the obese PCOS when compared to their nonobese counterparts. Irrespective of the BMI status, PCOS group as a whole had a significantly higher incidence of abnormal values of all the endocrinal and metabolic parameters evaluated in the study. Early modification of lifestyle even in the nonobese PCOS women can delay the onset of disease. Indian PCOS women have a very high prevalence of glucose intolerance, DM, and IR and the constellation starts at early age. All nonobese PCOS women should be screened for metabolic abnormalities with at least a simple 2 h OGTT at first detection. Although there is no recommendation of frequency of screening if initial reports are normal, a time line of at least 1-3 years may be appropriate.

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Conflicts of interest
There are no conflicts of interest.

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