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Original Article

Association of Metabolic Syndrome in Polycystic Ovarian Syndrome : an Observational Study

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Abstract

Objectives: To find out the prevalence of metabolic syndrome (MBS) in women with PCOS and assess their strength of association. Methods: Total 50 apparently healthy non-pregnant PCOS subjects of 15 to 35 years were studied for having the features of MBS from May 2006 to April 2007. MBS was diagnosed by National Cholesterol Education Program's Adult Treatment Panel III 2001 criteria. Student's t test & Mann-Whitney U test were used for statistical analysis. *Results:* 21 subjects out of 50 (42%) met criteria for the MBS. 15(71.5%) belonged to 26-35 years and six (20.7%) in 15-25 years. Prevalence of waist circumference > 88 cm were noted in 34%, HDL cholesterol< 50 mg/dl in 50%, triglycerides ≥ 150 mg/dl in 40%, BP ≥130/85 mm Hg in 50% and FBS≥ 110 mg/dl in 16%. Women with higher insulin resistance and free testosterone levels significantly (P<0.01) correlated with higher prevalence of MBS. *Conclusion:* The metabolic syndrome and its individual components are common in PCOS, particularly among women with hyperinsulinemia and hyperandrogenism.

Key Words : PCOS, metabolic syndrome, hyperinsulinemia.

Introduction

Polycystic ovarian syndrome (PCOS) is an ill-defined heterogenous condition with a complex pathophysiology. It is one of the most common endocrine disorders affecting approximately 5–8% women of reproductive age group[1]. After the joint consensus, held at Rotterdam by ESHRE/ASRM in May 2003, the criteria for diagnosis of PCOS, has been well established[2]. Insulin resistance, being the main etiological factor, contributes to overall hyperandrogenemia, leading to hirsutism, menstrual problems and anovulation. This is also the main responsible factor linking PCOS with hypertension, dyslipidemia, impaired glucose tolerance and type 2 diabetes mellitus (DM), central obesity and sub clinical carotid atherosclerosis[3,4] . PCOS has a speculative relationship with two major morbid diseases i.e. coronary heart disease (CHD) and type 2 DM, as long term sequel[5]. Insulin resistance per se is commonly associated with a group of cardio-vascular risk factors known as "Insulin resistance syndrome" or "metabolic syndrome" [6] characterized by the presence of compensatory hyperinsulinemia resulting in varying degree of glucose intolerance, dyslipidemia, central obesity and hypertension. It was suggested that the metabolic and haemodynamic abnormalities associated with Syndrome X constitute a major role in the etiopathogenesis of coro-

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nary heart disease [7]. The National Cholesterol Education Program's Adult Treatment Panel III (NCEPATP III) in 2001,[8] defines metabolic syndrome (MBS)as the presence of at least three of the following five criteria.1] Abdominal/central obesity (waist circumference >88cms), 2] Serum triglycerides 150mg/dl or greater, 3] Serum HDL cholesterol less than 50 mg/dl, 4] BP 130/85 or greater, 5] Fasting blood sugar (FBS) 110mg/dl or more. Later The International Diabetes Federation (IDF) in April 2005 nearly reiterates the NCEPATPIII definition, yet it takes the emphasis on central obesity even further by requiring an enlarged waist circumference for diagnosis[9]. Thus NCEPATP III criteria were revised and FBS was taken more than or equal to 100 mg/dl and waist circumference >80cm. Therefore much overlapping is observed between PCOS and MBS. Both are common risk factor for CHD and type 2 DM. This background knowledge demands the necessity to work out the prevalence of MBS in women with PCOS in our society and to measure the strength of their association in the Indian scenario.

Material and Methods

The study was an observational study approved by the Hospital Ethics Committee and conducted at the Department of Gynecology & Obstetrics, Institute of Post Graduate Medical Education & Research, Kolkata during the period of May 2006 to April 2007. Fifty, apparently healthy non-pregnant females 15-35 years with normal thyroid profile and prolactin levels, having documented features of PCOS (according to Rotterdam criteria, 2003) were selected from those attending the out patient department (OPD) of our hospital and assessed for presence of metabolic syndrome and clinical or laboratory evidence of hyperandrogenism (Ferrymen - Galaway score ≥ 7 was taken as cut off value for assessing hirsutism and elevated free testosterone > 2.57pg/ml). They were sub-divided in two age groups; 15-25years [Group 1] and 26 -35 years [Group 2] for proper age matched association. Each patient had undergone a detailed clinical examination and a relevant laboratory evaluation. Metabolic syndrome was diagnosed according to NCEPATP III 2001 criteria for the presence of at least three of the five criteria . Ultrasonography – Trans abdominal (TAS) and or Trans vaginal (TVS) was done. Most of the unmarried women had TAS. Blood samples for LH, FSH were taken thrice at 30 minutes interval in early follicular phase (day 2 – day 3) and the mean level measured. Fasting blood sugar, fasting Insulin (FI -normal values ranges from 2.6- 24.9μU/ml), free Testosterone (normal range between 0.15- 2.57pg/ml), TSH and Prolactin (for exclusion) were assayed by chemiluminescence's immunoassay method in the Biochemistry Department laboratory of our hospital. The Student's t test and Mann-Whitney U test were used for between-group comparisons of continuous variables. Statistical significance for all analyses was defined as a two-tailed P value of less than 0.05. Results were expressed as mean ± SD (standard deviation).

Results:

In this study complete data were available for 50 diagnosed women with PCOS. The median age of women with PCOS was 25 years (range 15–35 years). Among the 50 women with PCOS, 21 met criteria for the metabolic syndrome. It had been observed that more women at higher age group (71.5%) were suffering from features of MBS in comparison to only 20.7% in younger age group and there was a significant age difference in prevalence of MBS in women with PCOS ($P< 0.01$) (Table I).

Table-I

Prevalence of the metabolic syndrome and age distribution among women with PCOS:

Age	With metabolic syndrome (n=21)	Without metabolic syndrome (n=29)
15-25yr.(n=29)	6(20.7%)	23(79.3%)
25- 35yr.(n=21)	15(71.4%)	6(28.6%)
Total (n=50)	21 (42%)	29(58%)

P value < 0.01

On comparing different variables (Table II), women with and without MBS significantly differed ($p <0.001$) in there distribution of age (28.2 ± 5.8 vs. 22.1 ± 4.3 yr) and FBS/FI ratio ($p=0.001$) but did not differ significantly in their levels of either TSH (3.0 ± 1.4 vs. 2.8 ± 1.2 μIU/ml) or Prolactin (18.4 ± 5.7 vs. 20.5 ± 10.6 ng/ml). As expected, compared with women who did not meet criteria for MBS, those with the MBS had a significantly higher BMI (29.6 ± 3.2 vs. 24 ± 5.2 kg/m2), waist circumference (92.4 ± 4.9 vs. 82 ± 3.5

Table-II

Comparison of different variables in PCOS women with and without the metabolic syndrome:

Variables	With Metabolic syndrome	Without Metabolic s syndrome	P value
Number (%) of subjects	21(42%)	29(58%)	
Age (yr)	28.2±5.8	22.1±4.3	<0.001
BMI(kg/m2)	29.6±3.2	24.0±5.2	<0.001
Waist circumference(cm)	92.4±4.9	82.0±3.5	<0.001
Systolic BP(mmHg)	130±0.0	119.8±5.6	<0.001
Diastolic BP(mmHg)	87.8±3.3	79.3±6.2	<0.001
TSH (μIU/ml)	3.0±1.4	2.8±1.2	0.51
Prolactin (ng/ml)	18.4±5.7	20.5±10.6	0.41
LH/FSH ratio	2.6±1.0	2.5±1.4	0.82
FBS(mg/dl)	99.3±20.4	83.1±8.6	<0.001
Fasting Insulin(μIU/ml)	17.9±7.4	10.3±5.1	<0.001
FBS/fasting Insulin ratio	6.3±2.3	10.0±4.5	= 0.001
Free testosterone(pg/ml)	2.2±0.7	1.0±0.6	<0.001
Triglycerides (mg/dl)	167.7±29.4	107.6±27.2	<0.001
HDL-C (mg/dl)	42.6±6.8	53.8±7.2	<0.001
Total cholesterol (mg/dl)	197.3±22.4	163.2±30.5	<0.001

Data are mean±SD (standard deviation). Student t test used.

cm), systolic (130 ± 0.0 vs. 119.8 ± 5.6 mm Hg) and diastolic (87.8 ± 3.3 vs. 79.3 ± 6.27 mm Hg) blood pressures. In addition, the fasting glucose (99.3 ± 20.4 vs. 83.1 ± 8.6 mg/dl) and insulin (17.9 ± 7.4 vs. 10.3 ± 5.1 μU/ml) concentrations were significantly higher in those with MBS. Finally, total cholesterol (197.3±22.4 vs. 163.2±30.5mg/dl), triglycerides levels (163.2±30.5 vs.107.6±27.2mg/dl) both were significantly higher in those with the MBS. HDL cholesterol levels were significantly lower in women with MBS (42.6 ± 6.8 vs.53.8 ± 7.2 mg/dl).

The age-adjusted prevalence of each component of MBS were worked out. Within the entire cohort of subjects, the waist circumference (WC) exceeded 88 cm in 34%, HDL cholesterol was less than 50 mg/dl in 50%, triglycerides were 150 mg/dl or greater in 40%, whereas blood pressure was 130/85 mm Hg or greater in 50% and fasting glucose concentrations were 110 mg/dl or greater in 16% (Table III).If the cut-off value for WC was taken >80cm, according to the definition of International Diabetic Federation then prevalence of WC exceeding 80 cm would have been 82% instead of 34% (according to NCEP-ATP III criteria i.e. WC > 88cm).Lowering the cut-off value, the prevalence of WC of 'at risk' patients increased from 34% to as high as 82%.

Each individual component of the metabolic syndrome was assessed to determine its ability to predict the presence (positive predictive value) or absence (negative predictive value) of the requisite number of remaining components needed to establish the diagnosis of the MBS. The presence of a fasting plasma glucose of 110 mg/dl or greater had the highest positive predictive value (100%) for the presence of the MBS. However,

Table-III

Prevalence of individual components of the metabolic syndrome in PCOS women:

Components of MBS	Subjects with MBS	Percentage (%)
Waist circumference ≥88cm	17	34%
HDL-cholesterol <50mg/dl	25	50%
Triglycerides ≥ 150mg/dl	20	40%
Hypertension≥ 130/85	25	50%
FBS ≥ 110mg/dl	8	16%

Table-IV

Positive and Negative Predictive values of each components of the metabolic syndrome in PCOS women:

Components of the MBS	No. of subjects with criterion	No. of subjects with criterion and atleast three total croteroa	Percentage of subjects with positive predictive value	No. of subjects without criterion	No. of subjects without criterion and less than total croteroa	Percentage of subjects with negative predictive value
Waist circumference >88cm	17	17	100%	33	29	87%
HDL-C < 50 mg/dl	25	21	84%	25	25	100%
Triglycerides 150 mg/dl	20	20	100%	30	29	96%
Hypertension 130 mm Hg systolic or 85 mm Hg diastolic	25	21	84%	25	25	100%
Fasting glucose 110 mg/dl	8	8	100%	42	29	69%

only eight subjects met this criterion. Elevated triglycerides, a much more common finding, also had highest-positive predictive value for the presence of the metabolic syndrome noted in 100% (20 out of the 20 women) having triglyceride level greater than or equal to 150 mg/dl. Then 84% of those with a systolic blood pressure greater than or equal to 130 mm Hg or diastolic blood pressure greater than or equal to 85 mm Hg met criteria for the metabolic syndrome. Similarly, 84% of women with HDL cholesterol less than 50 mg/dl met the criteria of MBS. Curiously, waist circumference greater than or equal to 88 cm had 100% predictive value, though only 17 subjects had the findings. WC, HDL cholesterol, and triglycerides and blood pressure each had high-negative predictive values. Of the 33 women whose WC was less than 88 cm, 29 (87%) did not meet the criteria for the metabolic syndrome. Of the 25 women with an HDL more than 50

Table V.

Comparison of Hirsutism score in women with or without MBS among women with PCOS:

Metabolic syndrome	F-G score ≥ 7 (n-34)	F-G score < 7 (n=16)
With MBS (n=21)	19(56%)	2(12.5%)
Without MBS (n=29)	15(44%)	14(87.5)

P value-0.005 by Mann-Whitney U test
(F-G score=Farrymen-Galaway score)

mg/dl, all (100%) did not meet the criteria for the metabolic syndrome. Finally, 29 of the 30 (96%) women with a triglyceride level less than 150 mg/dl, did not meet criteria for the metabolic syndrome. The negative predictive values for hypertension were also 100% but that of elevated fasting glucose was 69% only (table IV).

The hirsutism score as measured by Farrymen-Galaway scoring method, had shown that 56% patients with metabolic syndrome and PCOS were having score ≥ 7, while majority (87.5%) of the women without MBS had < 7 scoring value. Comparison of this variable between two groups i.e. with MBS and without MBS by Mann-Whitney U test have shown a P value = 0.005. So hirsutism score significantly differ in women with or without MBS and are more prevalent in women with MBS (tableV).In this study, family history of CHD and diabetes did not significantly correlate with metabolic syndrome with PCOS. Among the total subjects, eight had FBS/FI ratio ≤ 4.5 and seven out of eight had features of MBS. So FBS/FI ratio had a significant (P = 0.001) correlation with MBS. The concentration of free testosterone was also significantly (P = 0.004) related to women with the MBS. 82% subjects with the MBS have high free testosterone level in comparison to only 18% in women without MBS.

Discussion :

The result of our study indicate 42% prevalence of metabolic syndrome in PCOS. This is closely related to the observations of 33.4% and 47.3% prevalence made by Ehrmann et al[10] and Dokras et al[11] respectively. Two other studies [12,13] had also shown the prevalence of MBS 44% and 43% respectively among sampled women with PCOS. The age adjusted prevalence of MBS has shown that women in between 26-35yrs have higher prevalence (71.5%) of MBS, in comparison to only 20.7% in 15-25yrs age group. Comparing the mean [± SD] data for different variables, it was noted that WC, systolic and diastolic blood pressures, fasting glucose and fasting insulin had a significantly higher value among those with MBS in comparison to those without the MBS. In addition HDL cholesterol and triglycerides levels were significantly (P<0.01) different in women who met the criteria for the metabolic syndrome which are corroborative of the study of Ehrmann et al[10].

Each defining criterion was evaluated for its value to either confirm or exclude chances of MBS. In our study WC above the threshold of 88 cm was found only in 34% cases which differs from study done by Ehrmam et al[10] which supports high value of waist circumference by citing 80% of subjects above 88cm. But such a huge difference in our study may be because of the study population selected and the cut off value chosen at lower level. If 80 cm, would had been taken as the cut-off value for WC the result would have been 82% using International Diabetic Federation (IDF) definition. The same had been claimed by Misra et al[14] who had opined that lower cut-off points of WC for defining abdominal obesity might be more suitable for Asians than those suggested by NCEP. In case of other components like HDL-C, triglycerides, blood pressure, fasting glucose concentrations individual prevalence corroborated with that observed by Ehrmann etal[10]. Presence of a fasting plasma glucose of 110 mg/dl or greater had the highest positive predictive value (100%) which is in concordance with the study done by Ehrmann etal[10] having 84% positive predictive value of FBS. HDL cholesterol less than 50 mg/dl had 84% positive predictive value for the metabolic syndrome which is supported by the study of Dokras et al[11] showing triglycerides/HDL–C ratio > 3, having high

positive predictive value of 85.5%. Similarly waist circumference greater than or equal to 88 cm had 100% predictive value according to our study. This suggests that Indian women rather should have a different cut-off value for WC.[14] In our study none of the 13 women with a BMI less than 25 kg/m^2 met criteria for the MBS. The study by Ehrmann DA et al[10], had no woman with BMI less than or equal to 27.0 kg/m^2 meeting the criteria for the MBS. This difference of cut-off margin may be due to the reason that south Asians or Indians are having more subcutaneous fat in spite of same BMI with the Western population. Misra A et al[14] had shown that the exact cut-off for normal BMI in Indian women should be less than 23 kg/m^2.Though family history of diabetes did not significantly correlate with MBS with PCOS (P=0.76), the fasting insulin level and FBS/FI ratio $\leq$ 4.5 or insulin resistance had a significant (P < 0.01) difference among women with MBS in comparison to those without MBS. This had been supported by the study of Dokras et al[11] and et al[10] who had shown a significant (P < 0.001) increasing trend in the proportion of women with the metabolic syndrome as related to the fasting insulin concentration. This trend remained significant (P = 0.001) even after adjusting for BMI. In our study the concentration of free testosterone was also significantly (P < 0.001) increased with the metabolic syndrome though it differs from the finding of et al[10] & Dokras et al[11] who observed no significant difference in serum androgen levels in PCOS women with or without MBS. But the present study was supported by Apridonidze et al[13] who observed that PCOS women with MBS had significantly higher levels of serum free testosterone (P = 0.002) than those without MBS.

Conclusion :

It is observed from the study that the metabolic syndrome manifests at an early age in women with PCOS. Hyperinsulinemia, a central factor in the pathogenesis of PCOS, also appears to be a critical link between PCOS and the metabolic syndrome. Thus there is an urgent necessity to asses the rising trend of MBS among the women with PCOS and to take early measures for primary prevention of its long term sequel. However, a large prospective multicentric control trial has to be designed.

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