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Original Research Article

Evaluation of different biochemical markers in prediction of metabolic syndrome in polycystic ovary syndrome patients

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ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is the commonest cause of chronic hyperandrogenic anovulation. Insulin resistance and compensatory hyperinsulinemia are keys of the pathogenesis of PCOS. It is also considered as a metabolic disorder. Since the components of metabolic syndrome (MBS) namely obesity, glucose intolerance, dyslipidemia, and hypertension are the common features of this syndrome. The association between MBS and PCOS can be explained by different theories as insulin resistance, obesity, and related adipose tissue factors (adipocytokines) independent of insulin resistance are the main pathogenic contributors to both disorders.
Methods: A total of 143 women with PCOS were recruited as study subjects. All participants were subjected to anthropometric measurements, clinical assessment, and biochemical tests [fasting glucose, fasting insulin, and homeostatic model assessment-insulin resistance (HOMA-IR)]. Hormonal profile particularly leptin and homocysteine levels were also evaluated.
Results: 25 patients (17.4%) out of 143 women with PCOS met the criteria for MBS. Patients with MBS had significantly higher body mass index, blood pressure, HOMA-IR, leptin, and homocysteine levels compared to PCOS only patients. When HOMA-IR cut off was ≥4.3 sensitivity and specificity were 90%, 88.6%, but when leptin level was ≥34.5 the corresponding statistics were 79.6%, 75.5%.
Conclusions: Serum leptin, homocysteine, HOMA-IR as well as other biochemical markers are significantly higher in women with PCOS and MBS compared to PCOS only women. PCOS is associated with various factors like insulin resistance, obesity, and dyslipidemia. Consequently, adipocytokines and HOMA-IR play important role in the prediction of MBS in patients with PCOS.

Keywords: Homocysteine, Leptin, Polycystic ovary syndrome

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the commonest cause of chronic hyperandrogenic anovulation and one of the most common causes of infertility in young women.[1] It can be considered as a risk factor for metabolic syndrome-related comorbidities and for impaired well-being and mortality.[2]

Insulin resistance and compensatory hyperinsulinemia are keys of the pathogenesis of PCOS. Insulin effectiveness is through direct and/or indirect stimulation of the pituitary gland to stimulate ovarian androgen production.[3]

Hyperandrogenism, oligomenorrhea, chronic anovulation and hirsutism are the most common clinical manifestations of PCOS. It is also considered as a metabolic disorder where, the main components of metabolic syndrome (MBS) like obesity, glucose intolerance, atherogenic dyslipidemia and hypertension are the common associated features of PCO.[4,5]

A metabolic syndrome is a group of metabolic disorders. When a patient suffered from these conditions together, the chances for the future cardiovascular disease is greater than any one factor presenting alone. A number of proficient groups have developed clinical criteria for the metabolic syndrome. The most widely agreeable of these were produced by the European Group for the Study of Insulin Resistance (EGIR), the World Health Organization (WHO), and the National Cholesterol Education Program – Third Adult Treatment Panel (NCEP ATP III). All groups agreed on the basic components of the metabolic syndrome: insulin resistance,obesity, dyslipidemia and hypertension.[6,7] The National Cholesterol Education Program Adult Treatment Panel (NCEPATP III) which is the most widely agreeable guidelines define the MBS as having three or more of the following abnormalities: waist circumference ≥88 cm in women; Hypertriglyceridemia: ≥150 mg/dl; HDL-C <50 mg/dl in women; blood pressure >130/85 mmHg; and fasting glucose: >110 mg/dl.[8]

The association between MBS and PCOS can be explained by different theories include:

- insulin resistance underlies the pathogenesis of both MBS and PCOS,
- obesity and related adipose tissue factors (adipocytokines) independent of Insulin resistance are the main pathogenic contributors to both disorders.[9]

Leptin is mainly secreted by white adipose tissue and regulates energy homeostasis by inhibiting food intake and stimulating energy expenditure through its action in neuronal circuits in the brain, particularly in the hypothalamus.[10] Hyperleptinemia and raised free leptin index are discovered in women with PCOS compared with non-PCOS controls. Increased leptin levels may be associated with clinical and hormonal indices of insulin resistance, metabolic syndrome, infertility, and even cardiovascular disease risk in PCOS, which may participate in the etiology and progression of PCOS.[11,12]

Homocysteine (Hcy) is a sulfur-containing non-proteinogenic amino acid derived in methionine metabolism. Hyperhomocysteinemia, can be considered as independent risk factor for cardio and cerebrovascular disorders as well as other morbidities. Also, Insulin resistance and hyperinsulinaemia in patients with PCOS is associated with elevated plasma homocysteine, regardless of body weight.[13,14]

The aim of the present study is to evaluate the predictive value of insulin resistance, serum leptin and other biochemical markers in the assessment of MBS in women with PCOS.

METHODS

This cross-sectional study was conducted at IBN Sina College Hospital, Jeddah, Saudi Arabia, from August 2014 to October 2016. A total of 143 women with PCOS were recruited for the study. The diagnosis of PCOS was done according to Rotterdam PCOS consensus (Rott – PCOS) criteria.[15] This study was approved by the Hospital Research Ethics Committee and has been performed in accordance with the ethical standards as in Declaration of Helsinki (1964) and its latter amendments, and a written informed consent was obtained from each participant prior to the study.

Inclusion criteria

PCOS was diagnosed if at least two out of three criteria were present: oligo/amenorrhea, clinical or biochemical hyperandrogenism, and PCO picture on ultrasonography. Clinical hyperandrogenism was defined as the presence of hirsutism (Ferriman-Galwey score >8) and /or acne. Biochemical hyperandrogenism was defined as elevated total testosterone >2nmol/L. Ultrasonographic PCO was defined as the presence of at least one ovary with 12 or more follicles measuring 2-9 mm in diameter.[16]

Exclusion criteria

Excluding other etiologies mimic PCOS, such as cushing syndrome, thyroid dysfunction, hyperprolactinemia, drug or alcohol abuse, adrenal hyperplasia or androgen producing neoplasm. The use of hormonal treatment was prohibited for 2 months prior to study entry.

MBS was defined according to NCEP ATP III guidelines.[8] Insulin resistance (IR) was assessed using the homeostatic model assessment (HOMA-IR: fasting Insulin (uU/ml) x fasting glucose (mg/dL)/405.[17]

History, physical examination, ultrasound and laboratory analysis

Questionnaire was designed for demographic data, complaints and duration of disorder, menstrual history, medical history, family history (diabetes, hypertension, obesity, and ischemic heart disease), signs of hyperandrogenism (hirsutism, acne, and alopecia)

Anthropometric measurements included waist circumference which is measured in centimeters at the narrowest circumference, midway between the upper border of iliac crest and the lower rib margin, while the hip circumference measured as the widest length at the level of the greater trochanters.

Height was recorded in centimeters and weight in kilograms. Body mass index (BMI) was calculated by dividing weight in kilograms per the square of height in meters (kg/m^2). Overweight was defined as a BMI between 25.0 and 29.9, and obese as 30.0 or higher according to World Health Organzation categories. Sitting blood pressure was measured after a 10-min. rest using standard sphygmomanometer. Hisutism was diagnosed by using the Ferriman-Gallwey score (9 body areas each rated from 0-4).[18] Transvaginal ultrasonography was done by the same investigator using the 4 MHz transvaginal probe for imaging of PCO.

Overnight 8-10 hours fasting blood specimens were obtained from all participants for measurement of fasting blood glucose, insulin, total cholesterol (TC), triglycerides (TG), low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL), leptin, and homocysteine. Serum luteinizing hormone (LH), follicle-stimulating hormone (FSH), and total testosterone concentrations were measured on the third day of either spontaneous or progesterone–induced menstruation. Blood samples were collected in Plain tube (Red Top). After clot formation, blood samples were centrifuged for 15 minutes at 2000xg. Fasting blood glucose levels and Lipid profile were determined immediately using Vitros 350 Biochemistry Analyzer using dry chemistry technique (Ortho Clinical Diagnostics, USA). FSH, LH, total testosterone and fasting Insulin levels were determined on the same day using Architect i1000 analyzer by Chemiluminescence immunoassay technology (Abbott Diagnostics, Germany). Homocysteine levels were determined by Siemens Immulite 2000 Chemiluminescence immunoassay system (Siemens Healthcare Diagnostics, USA). Serum Leptin levels were measured using DRG leptin (Sandwich) ELISA Kit (EIA-2395) purchased from DRG instruments (GmbH, Germany) following the manufacturer's recommendations. Aliquots of serum samples were stored at -80°C for future use.

Statistical analysis

The data was collected and entered into the personal computer. Statistical analysis was done using Statistical Package for Social Sciences (SPSS/version 20) software. Arithmetic mean, standard deviation, for categorized variables Chi-square test was used, while for numerical data t-test was used to compare two groups. The correlation was analyzed by Spearman correlation coefficients. Receiver operating characteristic (ROC) curve was done to determine the cut off value of the different markers and its sensitivity, specificity and accuracy at this point in predict the disease. The level of significance was 0.05.

RESULTS

In this cross-sectional study 143 PCOS women were recruited, only 25 patients (17.4%) met the criteria for MBS. The demographic and clinical characteristics of the study participants are illustrated in Table 1.

Table 1: The demographic data and clinical characteristic of PCOS patients (group A), and PCOS patients with MBS (group B).

Variables	Group (A) PCOS N=118	Group (B) PCOS+MBS N=25	P
Age (Year)	25.48 ±3.566	27.22±4.64	0.062
Height (cm)	159.92±6.209	157.52±6.99	0.452
Weight (kg)	61.90±5.881	79.64±7.06	0.0021*
BMI (kg/m^2)	24.29±2.759	32.30±4.26	0.0012*
WC (cm)	76.83±3.349	91.24±3.88	0.001*
SBP (mmHg)	112.34±4.700	126.12±5.96	0.001*
DBP (mmHg)	71.53±4.086	83.16±3.30	0.001*

Data are presented as mean±SD; MBS (metabolic syndrome); BMI (body mass index); WC (waist circumference); SBP (systolic blood pressure); DBP (diastolic blood pressure); *Significant.

There were no statistically significant differences between the two groups for maternal age, and height. The mean BMI was significantly higher in MBS group compared to PCOS group (32.30±4.26 vs 24.29±2.75, p =0.001). Also, waist circumference in patients with MBS (91.24±3.88 cm) was significantly more than subjects without this disorder (76.83±3.34 cm, p=0.001). Moreover, the mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) in MBS women showed a significant increase compared to PCOS women (126.12±5.96 vs. 112.34±4.70, p=0.001; 83.16±3.30 vs 71.53±4.08, p= 0.001 respectively) (Table 1).

Table 2: The biochemical variables of PCOS patients (group A), and PCOS patients with MBS (group B).

Variables	Group(A) PCOS N=118	Group(B) PCOS+MBS N=25	P
FBS (mg/dL)	82.08±3.078	105.32±3.44	0.001*
Fasting insulin (mU/L)	14.78±2.737	20.72±3.03	0.001*
HOMA- IR	3.00±0.564	5.34±0.86	0.001*
Total cholesterol (mg/dL)	167.29±3.588	181.68±3.98	0.001*
HDL (mg/dL)	44.46±2.893	38.48±3.22	0.001*
LDL (mg/dL)	103.43±3.497	136.96±2.44	0.001*
Triglycerides (mg/dL)	99.54±3.734	163.72±3.36	0.001*

Data are presented as mean±SD; MBS (metabolic syndrome); FBS (fasting blood sugar); HOMA-IR (homeostatic model assessment of insulin resistance); LDL (low density lipoprotein); HDL (high density lipoprotein); *Significant.

Compared with PCOS patient, MBS women had significantly higher fasting glucose (105.32±3.44 vs

82.08±3.078mg/ml, p=0.001), fasting insulin (20.72±3.03 vs 14.78±2.737mg/ml, p=0.001) and HOMA –IR (5.34±0.86 vs 3.00±0.564, p=0.001).

Table 3: The hormonal profile of PCOS patients (group A), and PCOS patients with MBS (group B).

Variables	Group (A) PCOS N=118	Group (B) PCOS+MBS N=25	P
FSH (mIU/mL)	3.98±0.638	4.488±0.49	0.072
LH (mIU/mL)	6.97±1.198	7.812±1.64	0.069
Total testosterone (ng/mL)	79.38±3.827	82.76±2.37	0.107
Leptin (ng/mL)	31.72±7.447	41.584±13.06	0.001*
Homocysteine (µmol/L)	14.96±5.426	21.76±8.84	0.001*

Data are presented as mean±SD; MBS (metabolic syndrome); FSH follicle-stimulating hormone, LH luteinizing hormone; *Significant.

Furthermore, PCOS women with MBS showed significantly higher levels of total cholesterol (181.68±3.98vs. 167.29±3.588 mg/dl, p=0.001), triglycerides (163.72±3.36 vs 99.54±3.734mg/dl, p=0.001), low density lipoprotein cholesterol (136.96±2.44 vs 103.43±3.497 mg/dl, P=0.001) than those in women without MBS. On the other hand, high density lipoprotein cholesterol was significantly lower in PCOS women with MBS compared with those with PCOS only (38.48±3.22 vs 44.46±2.893 mg/dl, P=0.001) (Table 2).

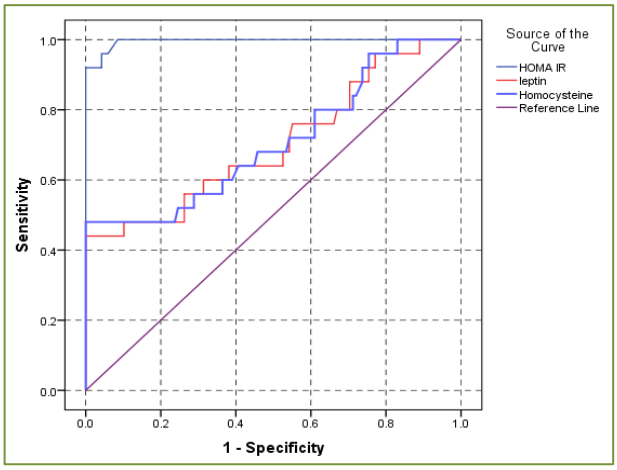

Figure 1: ROC curve to determine the sensitivity, specificity and accuracy of HOMA-IR, leptin and homocytesine in prediction of MBS.

Table 4: Correlation between HOMA- IR, leptin and homocysteine and other variables.

		HOMA-IR	Leptin	Homocysteine
leptin	r	0.297**		
	p	0.000		
Homocysteine	r	0.352**	0.069	
	p	0.0001	0.411	
BMI	r	0.621**	0.286**	0.278**
	p	0.000	0.001	0.001
FBS	r	0.809**	0.341**	0.414**
	p	0.000	0.000	0.000
Fasting insulin	r	0.941**	0.231**	0.256**
	p	0.000	0.005	0.002
Total cholesterol	r	0.736**	0.302**	0.305**
	p	0.000	0.000	0.000
HDL	r	-0.522-**	-0.173-*	-0.210-*
	p	0.000	0.039	0.012
LDL	r	0.800**	0.395**	0.361**
	p	0.000	0.000	0.000
Triglycerides	r	0.802**	0.392**	0.359**
	p	0.000	0.000	0.000
FSH	r	0.190*	0.018	0.026
	p	0.021	0.827	0.760
LH	r	0.253**	0.301**	0.057
	p	0.004	0.000	0.502
Testosterone	r	0.342**	0.137	0.099
	p	0.000	0.103	0.239

r (correlation); BMI (body mass index); FBS (fasting blood sugar); HDL (high density lipoprotein); LDL (low density lipoprotein); FSH (follicle-stimulating hormone); LH luteinizing hormone; *Significant at level 0.05, ** Significant at level 0.01

Regarding the hormonal profile, FSH, LH, and total testosterone did not show any significant differences between both groups. On the other hand, leptin and homocysteine were significantly higher in PCOS with MBS group compared to PCOS only group (41.584±13.06 vs 31.72±7.447, p=0.001; 21.76±8.84 vs 14.96±5.426, p=0.001 respectively) (Table 3).

For the prediction of MBS, cut off points for HOMA-IR, leptin, and homocystiene were determined. When HOMA-IR was ≥4.3, sensitivity and specificity were 90 %, 88.6%, while positive predictive value (PPV) and negative predictive value (NPV) were 89.1%, 88.7%, respectively. When leptin level was ≥34.5 the corresponding statistics were 79.6%, 75.5%, and 78.0%, 73.5%, but when homocysteine level was ≥16.0 they were 82.0%, 83.6%, and 81.0%, 86.2% respectively. (Figure 1) Correlation between HOMA- IR, leptin and homocysteine and other variables are illustrated in Table 4.

DISCUSSION

In the present study, the most notable finding is that 17.4% of women with PCOS have developed MBS before the end of their fourth decade of life. This prevalence is markedly higher than the 6.7% prevalence of MBS reported in women between ages of 20 and 30 years and the 15% prevalence reported in women between ages 30 and 40 years from the Third National and Nutrition Examination Survey (NHANES III).[19]

Usually the most likely pathogenic link between PCOS and MBS is insulin resistance and compensatory hyperinsulinism. Sharaf et al showed the prevalence of insulin resistance was 32% among women with PCOS.[20] However hyperinsulinemic euglycemic clamp technique is the gold standard for measuring insulin sensitivity, but it is expensive, invasive, and time consuming.[21] Moreover, HOMA-IR is a simple and non-invasive method for measuring insulin sensitivity through the glucose and insulin concentrations measured under fasting conditions. Therefore, in this study we used HOMA-IR as a marker of insulin resistance, and we postulated that women with concomitant PCOS and MBS would have more insulin resistance than women with PCOS only. We found HOMA-IR values of those two groups 5.34±0.86 versus 3.00±0.564, respectively (p=0.001). This finding agrees with other previous studies who have found that all markers of reduced insulin sensitivity are more obvious in women with concomitant PCOS and MBS rather than women without MBS.[22-24]

Women with PCOS had a higher prevalence of MBS at all ranges of BMI compared with women in general population. This may suggest that the presence of PCOS by itself increases risk of the MBS, perhaps secondary to the intrinsic insulin resistance of PCOS. Women with concurrent PCOS and MBS present more frequently with phenotypic feature of acanthosis nigricans, a biomarker of insulin resistance, than women with PCOS only. They also suffer from hyperandrogenemia, in the form of higher serum free testosterone and lower serum Sex hormone-binding globulin (SHBG) concentrations, than PCOS women without the MBS. Notably, this may reflect severe insulin resistance in the women with MBS, as SHBG has been noted to correlate inversely with insulin sensitivity. However, in our study, women with PCOS only and women with PCOS+MBS did not show any significant differences in total testosterone. These data are consistent with some studies in the literatures and in contrast with others.[23-25]

Usually, serum leptin concentrations rise in proportion to the body adiposity. Consequently, obese individuals with MBS generally have higher circulating leptin concentrations. However, obese individuals are resistant to the hypothalamic effects of leptin, and the catabolic pathways designed to reduce appetite and increase energy expenditure are not activated. Therefore, excess body weight is maintained. The role of high leptin level in women with PCOS is not clear yet, but there is a possibility that woman with PCOS are leptin resistant.[26] In the present study leptin levels in women with concomitant PCOS and MBS were significantly higher than women with PCOS only. We found leptin values of those two groups 41.584±13.06 versus 31.72±7.447, respectively (p=0.001). In our work, serum homocysteine levels were significantly higher in PCOS+MBS than women with PCOS, present findings are in line with previous studies by Mancini et al, Loverro et al, and Badawy et al.[26-28]

Goverde et al found that a combination of waist circumference and free androgen index (FAI) may offer a selection criterion for the presence of either MBS or IR.[29] Another study suggested use of triglyceride/HDL-cholesterol ratio (TG/HDL-C ratio) >3.2 as a criterion to screen for MBS in hyperandrogenic women.[24] In this study, HOMA-IR and leptin were found to be suitable for diagnosis of MBS.

CONCLUSION

Serum leptin, homocysteine and HOMA-IR levels are significantly different between women with PCOS only and women with PCOS + MBS as well as other biochemical markers. PCOS is associated with various factors like insulin resistance, obesity, oxidative stress, dyslipidemia which are aggravated by hyperhomocysteinemia that may have more pronounced risk. Consequently, adipose tissue factors and HOMA-IR play important role in the prediction of MBS in patients with PCOS. The present study highlights the need for comprehensive screening for metabolic syndrome in women with PCOS attending infertility clinic. However, these markers are very expensive and impractical for clinical use. Further studies are required to find the optimum clinical and biochemical markers for prediction

of MBS in PCOS patients, and clarify the role of homocysteine in human reproductive physiology.

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