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Research paper

Lipid accumulation product is associated with metabolic syndrome in women with polycystic ovary syndrome

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ABSTRACT

OBJECTIVE: There is a need for a simple and accurate method for the assessment of cardiovascular risk in polycystic ovary syndrome (PCOS). Lipid accumulation product (LAP) is based on the assessment of waist circumference and serum triglycerides that yield an estimation of lipid overaccumulation. We aimed to determine whether LAP is associated with metabolic syndrome (MetS) in Caucasian women with PCOS. DESIGN: We studied 222 women with PCOS who were diagnosed using the Rotterdam criteria. In all the subjects and controls, LAP was determined and the MetS was assessed using three different international criteria, NCEP-ATP III, IDF, and JIS. ROC curve and logistic regression analyses were performed to determine and analyze associations with the MetS. RESULTS: In the study population the prevalence of MetS was 16.2-19.4%. The cut-off value of 25.9 determined that LAP has the strongest association with MetS whichever international criteria are used, followed by HDL (NCEP-ATP III and JIS) and glucose (IDF). CONCLUSIONS: LAP is used as an independent clinical indicator for MetS in our PCOS women of Caucasian origin. The high diagnostic accuracy of LAP is superseding the need for the use of multiple clinical indicators for the assessment of lipid accumulation as a prerequisite for diagnosis of metabolic and cardiovascular diseases in PCOS women.

Key words: Lipid accumulation product, Metabolic syndrome, Polycystic ovary syndrome, Triglycerides, Waist circumference

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common endocrinopathy in women of reproductive age, with a prevalence of 6-10%, which is characterized by hyperandrogenic features and chronic oligo-anovulation.[1-3] Meanwhile, most women with PCOS are also characterized by metabolic abnormalities like insulin resistance, hyperinsulinemia, abdominal obesity, these forming the risk factors for the metabolic syndrome (MetS).[4] Therefore, PCOS is considered to be a metabolic disorder with a number of obesity-related cardiovascular risk factors, specifically insulin resistance, type 2 diabetes, proatherogenic lipid profile, and therefore influencing the susceptibility of those women to develop possible cardiovascular disease later in life.[5-7]

A significant proportion of women of Caucasian origin with PCOS fulfill the criteria for the MetS irrespectively of the international definition used. However, analyzed PCOS subjects were predominantly overweight or obese.[8-10] Although excessive weight predominates among PCOS women assessed for the presence of MetS, it is assumed that PCOS women have an increased risk for the metabolic syndrome that is independent of insulin resistance or obesity.[10,11]

As the diagnosis of MetS is established from the combination of anthropometric and laboratory measures, there is a need for the simplest and the most accurate method of assessment of risk factors to which PCOS women are exposed during the long period of transition from subclinical to overt cardiovascular disease.[12] Therefore, lipid accumulation product (LAP) was proposed in an attempt to develop an easy predictor of cardiovascular disease.[13] This simple clinical index is based on the assessment of waist circumference (WC) and serum triglycerides (TG), yielding an estimation for lipid overaccumulation in adults. LAP was confirmed to be a powerful marker of MetS[14] and diabetes[13] in the general population. Recently, LAP was suggested as being associated with impaired glucose tolerance[15] and MetS[16] in women with PCOS.

The aim of our study was to determine the level of LAP and analyze its association with MetS in a cohort of Caucasian origin women with PCOS.

SUBJECTS AND METHODOLOGY

Subjects

We analyzed 222 women with PCOS (age: 25.01±4.89 years, BMI: 22.99±4.57 kg/m^2) and 45 healthy women (age: 28.58±4.91 years, BMI: 21.62±3.88 kg/m^2). Subjects were recruited from the outpatient endocrine clinics where they were referred for investigation of oligo- or amenorrhea, fertility problems, hirsutism or acne. PCOS was defined according to the revised 2003 Rotterdam Consensus conference on diagnostic criteria for polycystic ovary syndrome that requires the presence at least two of the following three criteria: (i) oligomenorrhea or anovulation; (ii) clinical and/or biochemical signs of hyperandrogenemia; and (iii) polycystic ovaries on ultrasound.[17] Besides moderate oligo/amenorrhea, our patients had elevated serum testosterone concentrations and appearance of polycystic ovaries. Hyperandrogenemia was defined by serum total testosterone >2 nmol/L, which was based on examination of 56 nonselected women presenting for routine controls who were not hirsute, had regular cycles, and had received no hormonal therapy.[12] None of the examined patients had non-classical 21-hydroxylase deficiency, hyperprolactinemia, Cushing's disease, impaired fasting glucose (fasting venous glucose ≥6 mmol/L), untreated hypothyroidism or history of drug or alcohol abuse before the diagnosis of PCOS. No patients had received any hormone treatment for at least three months before the study.

The control group consisted of healthy volunteers without any signs of hyperandrogenism, with normal ovulating cycles confirmed by plasma progesterone during the luteal phase of the cycle, and with normal ultrasound appearance of the ovaries.

The study was approved by the Institutional Ethical Committees and written consent was obtained from all subjects.

Methodology

In all subjects, body mass index (BMI), waist circumference (WC), and systolic and diastolic blood pressure (SBP and DBP, respectively) were determined. BMI (kg/m^2) was calculated by dividing weight (kg) by height (m) squared, while WC (cm) represented the smallest circumference at the level of the umbilicus.

Baseline blood samples were drawn in all subjects

for determination of total cholesterol (TC), high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides (TG), fasting plasma glucose (FPG), insulin, testosterone, sex-hormone binding protein (SHBG). All subjects were investigated in the follicular phase of the menstrual cycle (between days 3 and 7), and after a 12h overnight fast. Samples for hormonal analyses were frozen at -80°C until measurement.

Total cholesterol (mmol/L) and triglycerides (mmol/L) were determined using standard enzymatic methods (cholesterol: cholesterol oxidase, Randox, UK; triglycerides: glycerol-3-phosphat oxidase, Randox, UK). HDL (mmol/L) was measured by direct method (Randox, UK), and LDL (mmol/L) determined by the Friedewald formula.[18] Serum insulin (mU/L) concentrations were determined by radioimmunoassay [RIA INSULIN (PEG), INEP, Belgrade, Serbia; intra- and inter-assay CV were 2.5 and 7.7%, respectively]. Serum testosterone (nmol/L) was measured by radioimmunoassay (TESTOCT2, CIS bio international, Gif-Sur-Yvette Cedex, France; intra- and inter-assay CV were 4.5 and 5.1%, respectively). SHBG (nmol/L) was measured by radioimmunoassay (SHBG-RIACT, CIS bio international, Gif-Sur-Yvette Cedex, France; intra- and inter-assay CV were 3.9 and 4.7%, respectively). Free androgen index (FAI) was calculated by the formula [(testosterone × 100) / SHBG] with both testosterone and SHBG expressed in nmol/L.[19] FAI >8 was considered as positive for hyperandrogenemia. Insulin resistance was estimated by the homeostasis model assessment of IR (HOMA-IR) method using the formula [HOMA-IR= insulin (mIU/L) × glucose (mmol/L)/22.5].[20] LAP was defined as [(WC – 58) × tryglicerides].[13] The formula includes the minimum WC values used to define sex-specific origin points (58 cm for women) in the Third National Health and Nutrition Examination Survey (NHANES III).[13] Both in PCOS and the controls groups the minimum WC value (60 cm) was quite similar to those used in the original equation for the definition of LAP. The adjustment of the LAP formula according to the minimum WC values of subjects did not change findings (data not shown). For the purpose of comparison we used the original formula.

All subjects were assessed as having MetS using three different international criteria: NCEP-ATP III,[21] IDF,[22] and Joint Interim Statement (JIS) criteria.[23] According to NCEP-ATP III, the diagnosis of MetS was established if any three or more of the following criteria were satisfied: 1) WC: ≥88cm, 2) tryglicerides (TG) ≥1.7mmol/L, 3) SBP ≥130 and/or DBP ≥85 mmHg, 4) fasting HDL <1.3mmol/L, and 5) fasting plasma glucose (FPG) ≥6.1 mmol/l. The IDF definition of the MetS for the Europid population considered central adiposity (defined as WC 80 cm) as a prerequisite factor for the diagnosis of the MetS, plus two of the following criteria: TG ≥1.7mmol/L, or specific treatment, low HDL (<1.3mmol/L) or specific treatment, high blood pressure (SBP >130 and/or DBP ≥85mmHg) or treatment of diagnosed hypertension, and FPG ≥5.6mmol/L or type 2 diabetes. According to the JIS criteria, the diagnosis of MetS was established as the presence of any three of the following criteria: 1) central adiposity (WC ≥80cm), 2) TG ≥1.7mmol/L, or specific treatment, 3) HDL <1.3mmol/L or specific treatment, 4) SBP ≥130 and/or DBP ≥85 mmHg or treatment of diagnosed hypertension, and 5) FPG ≥5.6 mmol/l or previously diagnosed type 2 diabetes that is under treatment.

Statistical analyses

Statistical analysis was performed using the Statistical Package for the Social Sciences software (SPSS, version 17.0; SPSS Inc, Chicago, IL, USA). Results are presented as mean ± standard deviation (SD). Normality of data distribution of continuous variables was tested by the Kolmogorov-Smirnov test. In order to achieve normal distribution, all skewed or kurtic data were logarithmically transformed. Differences between groups were analyzed by Student's T test and univariate analysis of variance (ANOVA) as appropriate. As our women with PCOS were younger than the respective controls, we introduced age as a covariate in all comparisons among groups (ANCOVA). Post hoc Bonferroni adjustment was performed for multiple comparisons. A *P* value less than 0.05 was considered as statistically significant.

Receiver operating characteristic (ROC) curves were generated for each continuous variable to identify the indicators of MetS defined by NCEP-ATP III, IDF, and JIS criteria. The areas under the curves (AUCs) are provided with standard error of mean (S.E.M.) and 95% confidence intervals (95%CI). ROC curves, a plot of the sensitivity (SEN) (true positive) versus 1-specificity (SP) (false positive) for each potential indicator tested, determine the ability of a screening

measure to correctly identify individuals based on their classification by a reference test. Values for each AUC can be between 0 and 1, with a value of 0.5 indicating that the diagnostic test is no better than chance. We considered that the parameters possessed an accurate diagnostic sensitivity when the AUC value was >0.75.[24] We defined the best cut-off value as the value with the highest proportion of positives and negatives classified correctly by the test. For all variables that are determinants of MetS we used their principal already known cut-off values (or approximate cut-off values if the principal values were not shown) in order to analyze their sensitivity and specificity and compare them to the sensitivity and specificity of the LAP cut-off value. Correlations were analyzed by performing Pearson's correlation test. Binary logistic regression was performed in order to analyze the determinants of MetS. Univariate logistic regression analyses were performed for LAP and all other known determinants of MetS. All significant determinants from univariate logistic regression analyses were entered into multivariate logistic regression analysis in order to discover indices that were independently associated with MetS in our PCOS population and to analyze if LAP could be one of the established determinants of MetS.

RESULTS

Comparison of clinical characteristics between PCOS and controls and in relation to the presence of MetS

Anthropometric and metabolic characteristics of the women with PCOS and the healthy control women are presented in Table 1. As the PCOS women were younger than the controls, all the comparisons were age adjusted. In comparison to controls, the whole group of PCOS women had significantly higher LAP, WC, DBP, basal insulin and HOMA-IR index, total and LDL cholesterol, triglycerides as well total testosterone and FAI. The prevalence of the MetS according to the NCEP-ATP III, IDF, and JIS criteria for the whole group of PCOS women was 16.2% (36/222), 18.5% (41/222), and 19.4% (43/222), respectively, and for the control group 6.7% (3/45).

In the next step, the women with PCOS were sub-

Table 1. Clinical characteristics of women in PCOS and control groups

Analyses	PCOS (N=222)	Controls (N=45)	p	Age adjusted p
Age (years)	25.01 ± 4.89	28.58 ± 4.91	**<0.001**	-
BMI (kg/m^2)	22.99 ± 4.57	21.62 ± 3.88	0.061	**<0.001**
WC (cm)	78.12 ± 12.77	75.72 ± 10.51	0.258	**0.027**
SBP (mmHg)	118.63 ± 12.03	116.67 ± 8.86	0.356	0.128
DBP (mmHg)	77.73 ± 9.34	75.33 ± 7.64	0.135	**0.037**
Glucose (mmol/L)	4.66 ± 0.52	4.63 ± 0.50	0.697	0.313
Insulin (mU/L)	17.71 ± 17.02	13.35 ± 7.37	**0.018**	**0.035**
HOMA-IR	3.75 ± 4.12	2.79 ± 1.61	**0.022**	**0.034**
TC (mmol/L)	5.11 ± 1.13	4.86 ± 0.79	0.200	**0.017**
HDL (mmol/L)	1.37 ± 0.31	1.47 ± 0.33	0.069	**0.024**
LDL (mmol/L)	3.20 ± 1.03	2.95 ± 0.70	0.171	**0.022**
TG (mmol/L)	1.17 ± 0.75	0.97 ± 0.65	**0.025**	**<0.001**
Testosterone (nmol/L)	2.64 ± 1.16	1.79 ± 0.89	**<0.001**	**<0.001**
SHBG (nmol/L)	41.02 ± 23.24	62.76 ± 28.19	**<0.001**	**<0.001**
FAI (%)	8.70 ± 7.27	3.24 ± 1.37	**<0.001**	**<0.001**
LAP	28.94 ± 38.37	18.59 ± 23.47	**0.047**	**< 0.001**

BMI: body mass index; LAP: lipid accumulation product; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; HOMA-IR: homeostatic model of insulin resistance; TC: total cholesterol; HDL: high density lipoprotein; LDL: low density lipoprotein; TG: triglycerides; SHBG: sex hormone binding protein; FAI: free androgen index.

classified into six groups related to the presence of MetS using the three international criteria. Because only three women in the control group had MetS, they were not considered for further analyses and the 42 control subjects without MetS were used as a control group for all multiple comparisons. The clinical characteristics of the six groups (PCOS with and without MetS and controls without MetS) are presented in Table 2. Multiple comparisons between PCOS with MetS, PCOS without MetS, and controls were performed for each of the three international critera used: they showed the same level of significant differences of the analyzed parameters, which did not change after age adjustment (data not shown). LAP was significantly higher in PCOS with MetS in comparison to both PCOS without MetS and controls,

Table 2. Clinical characteristics of PCOS with and without MetS according to NCEP-ATP III, IDF, and JIS criteria

		NCEP-ATP III			IDF			JIS		
Analyses	**Controls (N=42)**	**PCOS with MetS (N=36)**	**PCOS without MetS (N=186)**	**P**	**PCOS with MetS (N=41)**	**PCOS without MetS (N=181)**	**P**	**PCOS with MetS-JIS (N=43)**	**PCOS without MetS-JIS (N=179)**	**p**
Age (years)	28.1±4.4	27.4±6.7[a]	24.5±4.2[b]	**<0.001**	27.7±6.6[a]	24.3±4.1[b]	**<0.001**	27.7±6.5[c]	24.3±4.13[b]	**<0.001**
BMI (kg/m^2)	21.1±3	30.3±3.8[c,d]	21.5±3.1	**<0.001**	30.1±3.3[c,d]	21.3±3	**<0.001**	29.7±3.9[c,d]	21.3±3	**<0.001**
WC (cm)	74.0±8.4	97.1±10[c,d]	74.4±9.6	**<0.001**	96.2±9.4[c,d]	73.9±9.4	**<0.001**	95.1±10.4[c,d]	73.9±9.4	**<0.001**
SBP (mmHg)	116.1±8.6	128.1±15[c,d]	116.7±10.3	**<0.001**	128.6±14.8[c,d]	116.3±10	**<0.001**	128.9±14.9[c,d]	116.1±9.7	**<0.001**
DBP (mmHg)	74.8±7.5	85.0±9.9[c,d]	76.2±8.5	**<0.001**	84.8±9.5[c,d]	76.1±8.5	**<0.001**	85.0±9.3[c,d]	75.9±8.4	**<0.001**
Glucose (mmol/l)	4.5±0.4	4.8±0.5	4.6±0.5	0.080	4.9±0.5[a,e]	4.6±0.4	**0.003**	4.8±0.5[a,e]	4.6±0.4	**0.004**
Insulin (mU/L)	12.1±4.8	20.5±6.7[a,d]	17.1±18.3[f]	**<0.001**	19.4±7.2[a,d]	17.3±18.5[f]	**0.001**	19.1±7.1[a,d]	17.3±18.6[f]	**0.001**
HOMA-IR	2.5±1	4.3±1.4[a,d]	3.6±4.4[f]	**<0.001**	4.1±1.5[a,d]	3.6±4.5[f]	**<0.001**	4.1±1.4[a,d]	3.6±4.5[f]	**<0.001**
TC (mmol/L)	4.8±0.7	5.9±1.5[c,d]	4.9±0.9	**<0.001**	5.9±1.1[c,d]	4.9±1	**<0.001**	6.0±1.4[c,d]	4.9±0.9	**<0.001**
HDL (mmol/L)	1.5±0.3	1.0±0.1[c,d]	1.4±0.3	**<0.001**	1.0±0.1[c,d]	1.4±0.3	**<0.001**	1.0±0.1[c,d]	1.4±0.2	**<0.001**
LDL (mmol/L)	2.9±0.6	3.9±1.6[c,d]	3.0±0.8	**<0.001**	3.8±1.3[c,d]	3.0±0.9	**<0.001**	3.9±1.4[c,d]	3.0±0.7	**<0.001**
TG (mmol/L)	0.8±0.3	2.2±1[c,d]	0.9±0.4	**<0.001**	2.1±1[c,d]	0.9±0.3	**<0.001**	2.1±1[c,d]	0.9±0.3	**<0.001**
Testosterone (nmol/L)	1.8±0.8	2.9±1.5[d]	2.5±1[b]	**<0.001**	2.9±1.4[d]	2.5±1[b]	**<0.001**	2.9±1.4[d]	2.5±1[b]	**<0.001**
SHBG (nmol/L)	64.4±27.6	26.8±25.1[c,d]	43.7±21.9[b]	**<0.001**	27.8±24.1[c,d]	43.9±22[b]	**<0.001**	28.1±23.6[c,d]	44.0±22.1[f]	**<0.001**
FAI (%)	3.1±1.3	15.6±12.6[c,d]	7.3±4.7[b]	**<0.001**	15.1±12[c,d]	7.2±4.6[b]	**<0.001**	14.7±11.8[c,d]	7.2±4.6[b]	**<0.001**
LAP	13.4±8.5	91.8±56.7[c,d]	16.7±15.4	**<0.001**	87.1±55.1[c,d]	15.7±14	**<0.001**	84.4±55.1[c,d]	15.6±14.1	**<0.001**

BMI: body mass index, LAP: lipid accumulation product, WC: waist circuference, SBP: systolic blood pressure, DBP: diastolic blood pressure, HOMA-IR: homeostatic model of insulin resistance, TC: total cholesterol, HDL: high density lipoprotein, LDL: low density lipoprotein, TG: triglycerides, SHBG: sex hormone binding protein, FAI: free androgen inde x.

a = PCOS with MetS vs PCOS without MetS $p<0.05$; b= PCOS without MetS vs Controls $p<0.001$; c = PCOS with MetS vs PCOS without MetS $p<0.001$; d = PCOS with MetS vs Controls $p<0.001$; e = PCOS with MetS vs Controls $p<0.05$; f = PCOS without MetS vs Controls $p<0.05$.

irrespectively of the criteria for the MetS used. All differences are presented in Table 2.

As expected, LAP significantly correlated with BMI, WC, and tryglicerides in all PCOS groups with and without MetS and in controls (data not shown). In PCOS women with MetS, LAP had a significant positive correlation with insulin (NCEP ATP III; IDF and JIS: r=0.391, p=0.025; r=0.470, p=0.003 and r=0.469, p=0.003, respectively), and HOMA-IR (IDF and JIS: r=0.416, p=0.012 and r=0.430, p=0.007, respectively). In PCOS women without MetS, LAP has a significant positive correlation with TC (NCEP-ATP III: r=0.344, p<0.001) and LDL (NCEP-ATP III; IDF and JIS: r=0.354, p<0.001; r=0.314, p<0.001 and r=0.302, p<0.001, respectively), and significant negative correlation with HDL (NCEP-ATP III; IDF and JIS: r= -0.356, p<0.001; r= -0.357, p<0.001 and r= -0.343, p<0.001, respectively).

Analyses of determinants of MetS in women with PCOS

By means of the ROC curve analyses, we identified and test diagnostic accuracy of the MetS determinants within our PCOS women and as related to the specific international criteria. The following cut-off values were identified for: LAP 25.9, WC 88.5 cm, BMI 25 kg/m^2, HDL 1.3 mmol/L, HOMA-IR 3.3, glucose 6.1 mmol/L (for NCEP-ATPIII) and 5.6 mmol/L (for IDF and JIS), TG 1.7 mmol/L, SBP 137.5 mmHg, DBP 87.5 mmHg. LAP exhibited high diagnostic accuracy irrespectively of the definition for the MetS used [NCEP-ATP III, IDF and JIS: AUC_{LAP} 0.97 ± 0.01 (95% CI 0.95-0.99), SEN: 81.4%, 93%, 93%, respectively, and SP: 91.3%, 85%, 86%, respectively]. Other predictors for the MetS, namely WC, BMI, HDL cholesterol, and HOMA-IR, are presented in Table 3. Glucose, tryglicerides, systolic and diastolic blood pressure had low diagnostic accuracy for previously defined cut-off values.

LAP cut-off value 25.9 had higher negative predictive value (NPV) than positive predictive value (PPV) irrespectively of the definition for MetS used (NPV for NCEP-ATP III, IDF and JIS: 99.4%, 98%, 98%, respectively, and PPV for NCEP-ATP III, IDF and JIS: 53.8%, 58.5% and 61.5%, respectively).

Logistic regression

Univariate binary logistic regression showed that LAP was significantly associated with MetS irrespectively of the international criteria used. In univariate analysis, significant determinants of MetS were also HDL and TG for all international criteria used, while an additional indicator was WC in NCEP-ATP III and JIS, and glucose in IDF and JIS (Table 4).

In order to avoid any problems with multi-collinearity, we omitted WC in IDF from univariate logistic

Table 3. Area under ROC for identification of determinants for MetS using different international criteria

	NCEP-ATPIII				IDF				JIS			
Determinant	**AUC**	**95% CI**	**SEN (%)**	**SP (%)**	**AUC**	**95% CI**	**SEN (%)**	**SP (%)**	**AUC**	**95% CI**	**SEN (%)**	**SP (%)**
LAP	0.97±0.01	0.95-0.99	81	91	0.97±0.01	0.95-0.99	93	85	0.97±0.01	0.94-0.99	93	86
WC	0.94±0.02	0.89-0.98	89	94	0.96±0.01	0.93-0.98	98	83	0.93±0.02	0.89-0.97	93	83
BMI	0.94±0.03	0.89-0.99	91	87	0.97±0.01	0.94-0.99	93	88	0.94±0.02	0.90-0.98	88	88
TG	0.93±0.02	0.89-0.97	67	95	0.91±0.03	0.87-0.96	63	96	0.92±0.02	0.88-0.97	65	97
HDL	0.90±0.02	0.85-0.94	63	97	0.87±0.03	0.81-0.93	63	97	0.87±0.03	0.81-0.93	66	91
DBP	0.76±0.05	0.66-0.85	33	91	0.76±0.04	0.67-0.85	35	92	0.77±0.04	0.69-0.86	36	92
SBP	0.75±0.05	0.65-0.85	28	97	0.77±0.05	0.67-0.86	28	97	0.77±0.05	0.68-0.86	29	98
HOMA-IR	0.73±0.04	0.65-0.81	75	62	0.69±0.05	0.60-0.78	69	62	0.69±0.04	0.60-0.77	68	62
Glucose	0.59±0.05	0.48-0.69	6	99	0.65±0.05	0.55-0.75	13	98	0.64±0.05	0.55-0.74	12	98

Evaluated by ROC with following cut-off values: LAP: Lipid accumulation product=25.94, WC: Waist circumference=88.5cm for NCEP/ATP III and WC=80.5cm for IDF; BMI: Body mass index=25 kg/m^2; TG: Tryglicerides=1.7mmol/L; HDL: High density lipoprotein=1.3mmol/L; DBP: Diastolic blood pressure=87.5mmHg, SBP: Systolic blood pressure=137.5mmHg: HOMA-IR=3.30; Glucose=6.1mmol/L for NCEP/ATP III and glucose=5.6cm for IDF and JIS.

regression analysis and WC and TG (for all international criteria) from multivariate logistic regression analysis. Thus, only LAP and HDL (in NCEP-ATP III), or LAP, HDL, and glucose (in IDF and JIS) entered the analysis performed with blocks (in NCEP-ATP III firstly LAP entered analysis, and then HDL; in IDF and JIS firstly LAP entered analysis, and then HDL and glucose together). In the final model, LAP and HDL remained significantly associated with MetS defined by NCEP-ATP III and JIS criteria, while LAP, HDL, and glucose remained significantly associated with MetS defined by IDF criteria (Table 4). LAP was a more potent indicator than either HDL or glucose in respective international criteria used, but models were stronger when all parameters were present.

DISCUSSION

The results of our study confirmed for the first time a strong association between lipid accumulation product and metabolic syndrome in a selected Europid population of women with PCOS. We found the highest diagnostic accuracy for LAP among other known or related determinants for the MetS and irrespectively of the three international criteria (NCEP-ATP III, IDF or JIS) used.

MetS has a varying frequency of up to 50% among PCOS women, this being mainly related to geographical and racial differences.[9,10,25-27] Prevalence of the MetS using three criteria within our PCOS women was in the range of 16.2 to 19.4% and is similar to the prevalence in other Europid populations.[10,26,28] There is a universally established relationship obesity and the MetS. The prevalence of obesity is rising worldwide and is considered to be contributing directly to the current high prevalence of the MetS.[29] It is assumed that the increased prevalence of abdominal obesity and MetS among women with PCOS is directly linked[30] and that even after adjustment for BMI, PCOS did not persist as an independent indicator of MetS in those women.[8,10] On the other hand, obesity denotes excess fat with consequent dysfunctions that are related to the anatomical regions.[31,32] In 2005, Henry Kahn proposed a simple index named lipid accumulation index, or LAP, based on the measurement of WC, an indicator of intra-abdominal fat depots, and the fasting concentration of triglycerides, a marker of circulating lipoprotein content. Hence, LAP expresses a continuous metabolic and cardiovascular risk function associated with lipid overaccumulation in adults.[13] Besides the confirmed diagnostic accuracy of LAP in predicting MetS among non-diabetic adults in a Europid population,[14] in PCOS women this novel index was shown to be associated with HOMA index[33] and impaired glucose tolerance,[15] mostly in Caucasian women, and MetS was defined by IDF criteria in

Table 4. Determinants of MetS in PCOS using different international criteria

	NCEP/ATP III			IDF			JIS		
Variable	**RR**	**95%CI**	**p**	**RR**	**95%CI**	**p**	**RR**	**95%CI**	**P**
Univariate binary logistic regression									
LAP	182.00	24.00-1379.96	**<0.001**	72.25	20.81-250.79	**<0.001**	82.13	23.60-285.83	**<0.001**
WC	159.50	42.66-596.33	**<0.001**	NA	NA	NA	87.43	20.15-379.33	**<0.001**
HDL	0.02	0.002-0.116	**<0.001**	0.06	0.02-0.17	**<0.001**	0.05	0.02-0.16	**<0.001**
TG	35.20	13.73-90.23	**<0.001**	37.48	14.47-97.11	**<0.001**	53.82	19.26-150.38	**<0.001**
Glucose	5.46	0.74-40.09	0.096	4.67	1.68-13.00	**0.003**	4.34	1.56-12.05	**0.005**
Multivariate binary logistic regression									
LAP	92.01	11.82-716.11	**<0.001**	36.24	9.93-132.30	**<0.001**	41.32	11.34-150.45	**<0.001**
HDL	0.05	0.01-0.37	**0.004**	0.15	0.04-0.56	**0.005**	0.13	0.04-0.50	**0.003**
Glucose	-	-	-	6.10	1.07-34.74	**0.042**	5.61	0.94-33.39	0.058
R^2	**85.94**			**103.57**			**101.39**		

Evaluated by binary logistic regression with following cut-off values: LAP: Lipid accumulation product=25.94, WC: Waist circumference=88cm for NCEP/ATP III and WC=80cm for IDF; WC not included in analysis for IDF; HDL=1.3mmol/L; TG=1.7mmol/L; glucose=6.1mmol/L for NCEP/ATP III and glucose= 5.6cm for IDF and JIS. NA: not analysed.

Chinese women.[16] However, a study by Xiang et al is the only one demonstrating the relation between LAP and MetS in PCOS, and even though without data for the respective controls, this could account for the high prevalence of MetS shown in this selected Chinese population.[16] Our mean value for LAP of 28.9 in the whole group of PCOS women is similar to the values shown in the other Europid-based study on PCOS women.[15] When we used the cut-off value of 25.9 for LAP in the multivariate analyses for each of the three international criteria for the MetS used, the same five indicators for the MetS were fully validated. We showed for the first time in the selected Europid population of women with PCOS that LAP among assessed variables had the strongest association with MetS, and irrespectively of the international definition used (AUC_{LAP} 0.97 ± 0.01, respectively). Other indices of the MetS from the ROC analyses, namely WC, BMI, HDL, and HOMA-IR, had lower diagnostic accuracy (Table 3).

The second highest diagnostic accuracy was shared between WC and BMI. It was considered with regard to Europid females that central obesity is present when WC is ≥80 cm,[29] and that it is related to BMI ≥25 kg/m^2.[34] Moreover, in comparison to BMI, which can often mask remarkable heterogeneity among subjects of similar BMI values, WC assessment provides an effective measure of visceral fat and, if conjuncted with fasting triglyceridemia, represents a useful marker of visceral fat accumulation.[35] If we take into consideration that BMI was not shown to be an accurate predictor of the risk of obesity-related diseases,[36] our results are in line with other studies that found WC to be an important clinical predictor of the MetS in respective PCOS populations.[10,16] Our results, obtained three international criteria for the MetS, are in line with the results of other authors attributing to the WC a high accuracy of prediction of MetS irrespectively of the cut-off values for WC. Although our data showed that WC and BMI shared the same level of accuracy, WC had higher sensitivity in predicting MetS, particularly when the IDF and JIS criteria are used. Moreover, our results on prediction power of WC, using the cut-off value of 80 cm as obligatory or not obligatory in the IDF and JIS criteria for the definition of MetS, supported the view that accepted WC for Europid women[29] is more appropriate for our group of Caucasian-origin PCOS women.

Low HDL-cholesterol is an established clinical indicator for the diagnosis of the MetS in the general population.[21,23,29] Among women with PCOS, low HDL was confirmed in many studies and shown to be one of the most frequent among single abnormalities in MetS.[9,15,16,25,28,37] Our results confirmed an abnormal HDL concentration within a selected cohort of Europid women with PCOS and MetS. Furthermore, HDL was shown to be an accurate marker, and together with LAP, the one most powerfully associated with MetS using either NCEP-ATP III, IDF or JIS criteria. Recently it was suggested that HDL may induce nitric oxide dependent vasorelaxation and consequent cardiovascular protection.[38] Therefore, it was hypothesized that low HDL might be considered the most important factor associating PCOS with a disposition to cardiovascular diseases.[9]

Insulin resistance is a prevalent metabolic condition in the vast majority of subjects with multiple metabolic disorders and can be easily estimated using HOMA-IR index.[39] Via this simple method, the degree of insulin resistance is correlated with other metabolic abnormalities.[40] It was shown that women with PCOS are at increased risk for the spectrum of disorders associated with insulin resistance, including MetS.[41] Although direct measure of insulin resistance is not included in any of the criteria for the MetS used in this study, the cut-off value of HOMA-IR appeared to attain a significant level of diagnostic accuracy for the presence of MetS by all three international criteria used. Even more, it was shown that the assessment of insulin resistance, given as basal insulin concentrations or calculation of HOMA-IR, had a significant positive correlation with LAP in PCOS women who had MetS. Our results are in accordance with a study by Wiltgen et al[33] showing an association of LAP with HOMA-IR. However, this study was performed on a smaller group of predominantly overweight/obese Caucasian PCOS women.

A limitation of our study is the relatively small control group for comparison with the whole group of PCOS. However, this difference was reduced or non-existent when the analysis of PCOS women was performed in relation to the presence of MetS. Another limitation could be the relatively younger

age of the PCOS women in relation to the controls. This limitation was also considered in our recent study,[10] and hence all the analyses between groups were undertaken with the age adjustment. We are also aware that our PCOS women were enrolled from a population referred to the health care center and not from the general population, therefore, our results cannot be extrapolated to the general population. The method used for the measurement of androgens in the blood could be another limitation as we did not measure free testosterone but rather calculated FAI. Direct measurement of free testosterone concentration is related to technical difficulties with different assays that are not easily feasible.[42] However, calculated FAI was proven to be of high diagnostic accuracy for diagnosing hyperandrogenemia.[43]

In conclusion, LAP is shown to be a simple and independent clinical indicator for the assessment of MetS in PCOS women of Caucasian origin. The high diagnostic accuracy of LAP that implies determination of WC and serum triglycerides is superseding the need for the use of multiple clinical indicators for the assessment of lipid accumulation as a prerequisite for diagnosis of metabolic syndrome and consequent prediction of cardiovascular diseases in PCOS women.

GRANT

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DISCLOSURE SUMMARY

The authors have nothing to disclose.

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