Lipid accumulation product index: a reliable marker of cardiovascular risk in polycystic ovary syndrome

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Introduction

Polycystic ovary syndrome (PCOS), a disorder characterized by ovulatory dysfunction and hyperandrogenism, is the most prevalent endocrinopathy in women of reproductive age. PCOS is also considered a metabolic disorder, since insulin resistance (IR), an independent risk factor for cardiovascular disease, is a common feature in these patients (Dunaif et al., 1987; Ehrmann, 1997; Legro et al., 1999; Wild et al., 2000). The early recognition of an ‘insulin-resistant phenotype’ is important to prevent cardiovascular involvement in a subset of young and susceptible PCOS patients without other signs of IR.

Euglycemic hyperinsulinemic clamping is currently the gold standard for measuring IR. However, it is not suitable for clinical practice since it is complex, time-consuming and not feasible in large populations (DeFronzo et al., 1979). On the other hand, alternative methods for identifying IR that rely on the measurement of insulin itself may be misleading, due to substantial inter-assay and inter-laboratory variations (Laakso, 1993). Taking into consideration the practical and technical limitations of these methods, we hypothesized that the presence of IR, and therefore cardiovascular risk, could also be determined on the basis of variables associated with insulin action, rather than on direct insulin measurements. The lipid accumulation product (LAP) index (Kahn, 2005), which combines waist circumference (WC) and...
triglyceride concentration, could be useful in this situation. Therefore, the aim of this study was to verify the accuracy of LAP index as a marker of cardiovascular risk in PCOS patients.

Materials and Methods

Patients and controls

This is a case–control study carried out with women consulting at the Gynecological Endocrinology Unit at Hospital de Clínicas de Porto Alegre, Brazil. Fifty-one hirsute women aged between 14 and 35 years, oligo/amenorrheic cycles (<9 cycles/year), increased levels of serum testosterone and/or free androgen index (FAI), and absence of other disorders causing hirsutism (Spritzer et al., 1990) were enrolled in the study (The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2003; Azziz et al., 2006). Transabdominal or transvaginal ovarian ultrasound was performed in all patients. Enlarged, cystic ovaries were detected in most PCOS patients.

Forty-four BMI-matched, non-hirsute women in the same age range, with regular ovulatory cycles (luteal phase progesterone levels higher than 12 nmol/l), were included in the study as a control group. None of the women from either group had received any drugs known to interfere with hormone levels for at least 3 months before the study. Almost 95% of the sample were Caucasian. The remaining 5% were of mixed (African and European) descent. Women with BMI more than 40 kg/m² or type 2 diabetes were excluded. The study protocol was approved by the local Ethics Committee (Institutional Review Board-equivalent), and written informed consent was obtained from all subjects.

Study protocol

Anthropometric measurements were performed in duplicate by two investigators (W.D. and B.I.G.), and included body weight, height, BMI (current kg/m²) and WC (waist measured at the midpoint between the lower rib margin and the iliac crest in a plane that is perpendicular to the long axis of the body, with the subject standing balanced on both feet, approximately 20 cm apart, with both arms hanging freely) (World Health Organization, 1995; Donato et al., 2006; Toscani et al., 2007). Obesity was defined as BMI ≥ 30 kg/m². Hirsutism was defined as a modified Ferriman–Gallwey score of 8 or more (Ferriman and Gallwey, 1961). Blood pressure was measured after a 10-min rest in the supine position. The hormonal and metabolic evaluation was made between days 2 and 10 of the menstrual cycle or on any day if the patient was amenorrheic. After an overnight 12 h fast, blood samples were drawn from an antecubital vein for determination of plasma cholesterol, high-density lipoprotein (HDL)-cholesterol and triglycerides at baseline, and glucose and insulin before and 2 h after the ingestion of a 75 g oral glucose load. Impaired glucose tolerance was determined by glucose levels between 140 and 200 mg/ml, as defined by the World Health Organization (1999).

Blood samples were also drawn for measurement of sex hormone-binding globulin (SHBG) and total testosterone (TT). All samples were obtained between 8 and 10 a.m. FAI was estimated by dividing TT (nmol/l) by SHBG (nmol/l) × 100. Homeostasis model assessment (HOMA) index was calculated by multiplying insulin (μIU/ml) by glucose (mmol/l) and dividing this product by 22.5 (Wallace et al., 2004). The cutoff point to define IR was arbitrarily defined as a HOMA index ≥ 3.8 (Toscani et al., 2007). Metabolic syndrome was defined in accordance with National Cholesterol Education Program/Adult Treatment Panel III criteria (NCEP/ATPIII, 2001). The LAP index was calculated using the formula \(\text{waist (cm)} – 58 \times \text{triglyceride concentration (mmol/l)}\), as previously reported (Kahn, 2005).

Assays

Total cholesterol, HDL-cholesterol, triglycerides and glucose were determined by colorimetric-enzymatic methods using the Bayer 1650 Advia System (Mannheim, Germany). Non-HDL cholesterol (non-HDL-c) levels were calculated by subtracting HDL-cholesterol from total cholesterol values. Low-density lipoprotein (LDL) cholesterol was estimated indirectly using: \(\text{LDL} = \text{total cholesterol} – \text{HDL} – \text{triglycerides}/5\). Serum LH was measured by a specific immunometric assay (Diagnostic Products Corporation-DPC, Los Angeles, CA, USA) with sensitivity of 0.05 mIU/ml, and intra- and inter-assay coefficients of variation (CV) of 3.6 and 6.7%, respectively. TT levels were measured by radioimmunoassay (ICN, Costa Mesa, CA, USA) with an intra- and inter-assay CV of 10 and 11.6%, respectively. SHBG was measured by chemiluminescent enzyme immunoassay (DPC) with a sensitivity of 0.2 nmol/l, and intra- and inter-assay CV of 6.1 and 8.0%, respectively. Serum insulin levels were measured with an electrochemiluminescence immunoassay (Roche Diagnostics GmbH, D-68298 Mannheim, Germany) with sensitivity of 0.20 μIU/ml and intra- and inter-assay CV of 1.8 and 2.5%, respectively.

Statistical analysis

Results are presented as mean ± SD, or median and inter-quartile range. Log 10 transformation was used to normalize the distribution of non-Gaussian variables in order to allow comparisons between the groups using the Student’s t test. \(\chi^2\) was calculated for comparisons of dichotomous variables. Receiver operating characteristic (ROC) curves were generated for LAP index and non-HDL-c, WC and BMI using a HOMA index ≥ 3.8 as the reference value to define IR, as previously reported (Toscani et al., 2007). Sensitivity and specificity for LAP and non-HDL-c were calculated based on the point of inflection in these ROC curves. Sensitivity and specificity for BMI and WC were calculated using validated cutoffs (25 for BMI, 80 and 88 for WC). The correlation between variables was tested using the two-tailed Spearman rank correlation test considering the non-Gaussian distribution of variables. All analyses were performed using the Statistical Package for the Social Sciences (SPSS version 14.0, Chicago, IL, USA). Data were considered to be significant at \(P < 0.05\).

Results

Hirsutism score was 14.5 (ranging from 12 to 23) in the women with PCOS. Table I summarizes the clinical, hormonal and metabolic profile of both groups. Controls were older than PCOS patients. As expected, BMI was similar in both groups (normal 35.3 versus 25%; overweight 17.7 versus 22.7%; obese 47 versus 52.3%; respectively, in PCOS and controls, \(P = 0.429\)), but PCOS patients had a higher WC. The metabolic syndrome was about four times more frequent in PCOS. The groups had similar glucose levels, but other parameters, such as HOMA and LAP index (Fig. 1), were significantly higher in PCOS patients, even when adjusted for age (Table I). The frequency of hypertension was 19.6% in PCOS versus 9.1% in controls. Five (9.8%) PCOS patients and one (2.3%) control presented impaired glucose tolerance.

A positive and significant correlation was found between HOMA index and LAP \((r = 0.70; P < 0.001)\), WC \((r = 0.71; P < 0.001)\) and BMI \((r = 0.82; P < 0.001)\) in both the PCOS and control groups (Fig. 2).

ROC curve analysis revealed that the best cutoff values for LAP index and non-HDL-c to define the presence of IR were 34.5 (sensitivity: 84%; specificity 79%) and 3.02 mmol/l (sensitivity: 81%; specificity 63%), respectively (Fig. 3). ROC curves were also generated for BMI and
WC, using the standard cutoffs of 25 for BMI (sensitivity: 83%; specificity: 38%), and of 80 cm (sensitivity: 84%; specificity: 40%) and 88 cm (sensitivity: 71%; specificity: 61%) for WC (Fig. 3). Comparing all these ROC curves, we observed that an LAP index of 34.5 was the best marker of IR. This result was confirmed by analyzing the PCOS and control groups separately (Fig. 3).

Table II shows the predictive values for markers of central adiposity/IR according to HOMA index in PCOS patients. The positive and negative predictive values (PPV and NPV) for LAP ≥ 34.5 were 91 and 74%, respectively—again showing that LAP was more accurate than the other studied markers to determine the presence of IR (PPV of 73% and NPV of 61% for WC of 80 cm; PPV of 43% and NPV of 20% for WC of 88 cm; PPV of 76% and NPV of 68% for non-HDL-c of 3.02 mmol/l; and PPV of 72% and NPV of 66% for BMI 25).

**Discussion**

The present study shows that, despite being younger than controls, our PCOS patients had a worse metabolic profile and were more insulin resistant. The metabolic syndrome was also more prevalent in PCOS patients, even though they were in the same BMI range as controls.

While in the last years it has become clear that IR plays a central role in both the reproductive and metabolic disturbances observed in women with PCOS (Dunaif et al., 1987; Ehrmann, 1997; Legro et al., 1999; Wild et al., 2000), identification of IR in these patients is challenging. The gold standard, euglycemic hyperinsulinemic clamping, is clearly inadequate for clinical practice since it is expensive, time-consuming and requires complex technical skills, such as bilateral cannulation and arterIALIZATIONS of blood flow to the vein. In turn, simpler, alternative methods that use fasting insulin levels as a diagnostic tool can lead to misdiagnosis of IR. In addition to the large intra- and inter-assay variability that complicates direct insulin measurements, there is no reference range for normal insulin levels (Olefsky et al., 1973; Chevenne et al., 1999).
Therefore, indexes that have a good correlation with the clamp but which depend on fasting insulin levels are difficult to employ as a clinical test for predicting the IR of individual patients.

Previous studies have evaluated enlarged waist circumference and elevated triglycerides (EWET) in different populations as a surrogate marker of cardiovascular risk. Amongst the criteria that define the metabolic syndrome, the association of these two variables was more sensitive than the metabolic syndrome itself to demonstrate higher cardiovascular risk (Lemiex et al., 2000; Tankó et al., 2005). The presence of EWET was related to higher HOMA index at all ages, including in young women (Kahn and Valdez, 2003) and this dichotomous risk marker presented a moderate association with metabolic syndrome criteria in premenopausal women (Alhassan et al., 2008).

The LAP index, an ordinal scale combining WC and triglycerides, was first tested in 2005 in a study using data from National Health and Nutrition Examination Survey sample database (NHANES III). The authors compared the LAP index to BMI in terms of ability to identify cardiovascular risk in adults. The subpopulation with ordinal LAP quartile higher than BMI quartile (adjusted for sex, race-ethnicity and age) had more adverse levels in 9 out of the 11 cardiovascular risk factors assessed in the study, suggesting that LAP might be a better predictor of the incidence of cardiovascular disease (Kahn, 2005).

In the present study, we showed that the LAP index is highly correlated with HOMA index in PCOS patients and, in consequence, the LAP index may be useful to precociously screen a subset of young women who are susceptible to the development of diabetes and other IR-related comorbidities, including cardiovascular disease. The fact that PCOS patients have higher LAP index values compared with controls with the same BMI is further evidence of the potential metabolic implications of this disorder. In addition to the strong association with HOMA, the ROC curve showed that an LAP index \( \geq 34.5 \) had adequate sensitivity and specificity for detecting a state of IR. Similar to other multifactorial diseases with heterogeneous clinical manifestations, creating prediction diagrams based on tests with good predictive values should facilitate making clinical decisions in PCOS. In the present study, an LAP index of \( \geq 34.5 \) showed a better performance to accurately discriminate IR in PCOS women when compared with the cutoff points defined for BMI (25) and WC (80 and 88 cm) (NCEP/ATPII, 2001; Donato et al., 2006). Therefore, our results suggest that an LAP index of \( \geq 34.5 \) could be considered as a risk factor for metabolic disturbances and cardiovascular disease in PCOS patients and perhaps guide clinicians in the decision-making for treatment with insulin-sensitizer drugs.

As stated in the literature, the metabolic syndrome is closely related to IR; it is also more prevalent in PCOS patients than in women from the general population considering all age groups (Glueck et al., 2003; Apridonidze et al., 2005; Cussons et al., 2008). However, the syndrome is largely influenced by the presence of obesity, which means that young, non-obese PCOS women may present IR even without the metabolic syndrome. We have previously observed a 58.5% prevalence of IR, evaluated by HOMA index, versus 27.9% for the metabolic syndrome in a sample of PCOS patients that was similar to that of the present study (Spritzer and Wiltgen, 2007).

One limitation of the present study is the fact that euglycemic hyperinsulinemic clamping was not performed. However, previous studies in susceptible populations have shown that the HOMA index, used in our study as reference standard, is closely correlated with euglycemic hyperinsulinemic clamp results (Bonora et al., 2000). In addition, the HOMA index has been shown to predict cardiovascular disease in Caucasian individuals from the general population (Bonora et al., 2007).

![Figure 2](https://academic.oup.com/humrep/article-abstract/24/7/1726/2357415/17303165)
In conclusion, our results show that the LAP index, an easily obtainable measure, may be regarded as a reliable marker of risk for cardiovascular disease in PCOS. The early recognition of PCOS women who are prone to develop IR-related metabolic disturbances in the absence of other signs will allow the introduction of therapeutic interventions to ameliorate IR and probably reduce the risk of cardiovascular disease in the future.

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Table II Predictive values for markers of central adiposity/IR according to HOMA index in PCOS patients

<table>
<thead>
<tr>
<th>Cutoff point</th>
<th>HOMA index</th>
<th>Predictive value</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥3.8 (%)</td>
<td>&lt;3.8 (%)</td>
<td></td>
</tr>
<tr>
<td>LAP</td>
<td>≥34.54</td>
<td>82.1</td>
<td>12.5</td>
</tr>
<tr>
<td></td>
<td>&lt;34.54</td>
<td>17.9</td>
<td>87.5</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>≥88</td>
<td>31</td>
<td>68.7</td>
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<td></td>
<td>&lt;88</td>
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<td>31.3</td>
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<tr>
<td></td>
<td>≥80</td>
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<tr>
<td></td>
<td>&lt;80</td>
<td>17.2</td>
<td>50</td>
</tr>
<tr>
<td>Non-HDL-c</td>
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<td>79.3</td>
<td>35</td>
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<tr>
<td></td>
<td>&lt;3.02</td>
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<td>65</td>
</tr>
<tr>
<td>BMI</td>
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<td>80</td>
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<tr>
<td></td>
<td>&lt;25</td>
<td>20</td>
<td>57.1</td>
</tr>
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</table>

Figure 3 ROC curves for LAP index, non-HDL-c, WC and BMI with HOMA index of 3.8 as marker of IR.

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References


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