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Lipid accumulation product (LAP) is related to androgenicity and cardiovascular risk factors in postmenopausal women

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ABSTRACT

Objectives: To investigate whether lipid accumulation product (LAP) is related to androgen and sex hormone binding globulin (SHBG) levels and to cardiovascular risk factors in postmenopausal women with no evidence of established cardiovascular disease.
Study design: Cross-sectional study.
Main outcome measures: LAP (waist-58 × triglycerides [nmol/L]), LAP ≥ arbitrary cutoff point of 34.5, serum testosterone, SHBG, ultrasensitive C-reactive protein (us-CRP).
Results: Forty-nine women (mean age 55 ± 5 years; median amenorrhea time 5.5 years [3–8]) were studied: 14% had the metabolic syndrome and 24.5% were hypertensive. Compared with LAP < 34.5, LAP ≥ 34.5 ($n = 29$, 59%) was associated with higher testosterone ($p = 0.021$) and free androgen index (FAI) ($p = 0.003$) and lower SHBG levels ($p = 0.013$). Us-CRP ($p = 0.012$), total cholesterol ($p = 0.041$), glucose ($p = 0.020$) and homeostasis model assessment (HOMA) ($p = 0.019$) were higher, and high-density lipoprotein cholesterol (HDL-C) ($p = 0.001$) was lower with LAP ≥ 34.5. LAP was positively correlated with total testosterone ($r = 0.349$, $p = 0.014$), FAI (rs = 0.470, $p = 0.001$), us-CRP ($r = 0.315$, $p = 0.042$), systolic ($r = 0.318$, $p = 0.028$) and diastolic ($r = 0.327$, $p = 0.023$) blood pressure, total cholesterol ($r = 0.498$, $p < 0.001$) and glucose (rs = 0.319, $p = 0.026$). LAP was negatively correlated with SHBG (rs = −0.430, $p = 0.003$) and HDL-C ($r = -0.319$, $p = 0.026$).
Conclusions: LAP index seems to be associated with androgens and SHBG and with cardiovascular risk factors in postmenopausal women. Also, LAP seems to be a suitable method to screen for cardiovascular risk in postmenopause.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death among men and postmenopausal women worldwide [1]. Abdominal adiposity has been regarded as a marker of cardiovascular (CV) risk. While image tests are accurate to diagnose abdominal adiposity, their use is limited by high cost. Therefore, simple anthropometrical measures, such as waist circumference and waist-to-hip ratio, are widely employed in population and clinical studies [2–4]. Increased plasma triglycerides (TG) levels have also been associated with higher risk for CVD [5].

The lipid accumulation product (LAP), an estimate of lipid accumulation in adults, is based on a combination of two measurements that are safe and inexpensive to obtain: waist circumference (WC), a measure of truncal fat that includes the visceral depot, and the fasting concentration of circulating triglycerides (TG). LAP, which was first described by Kahn [6], was developed to express a continuous risk function. The population-based United States' National Health and Nutrition Examination Survey (NHANES III) concluded that LAP was superior to BMI for recognizing CV risk and diabetes [6,7]. Others have confirmed the LAP index as a marker of metabolic risk [8] and a tool to stratify the risk of unfavorable outcomes associated with obesity [9]. Our group has recently shown that using LAP as a categorical variable at a cutoff of 34.5 provides an accurate and simple tool to screen for insulin resistance, metabolic and CV risk in young women with polycystic ovary syndrome (PCOS) [10]. Another recent study comparing 392 women with PCOS and 140

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; ECLIA, electrochemiluminescence immunoassay; FAI, free androgen index; HDL-C, high-density lipoprotein cholesterol; HOMA, homeostasis model assessment; LDL-C, low-density lipoprotein cholesterol; NO, nitric oxide; PCOS, polycystic ovary syndrome; SBP, systolic blood pressure; SHBG, sex hormone binding globulin; TT, total testosterone; us-CRP, ultrasensitive C-reactive protein.

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controls confirmed the reliability of LAP as a marker of metabolic risk in PCOS patients and suggested a cutoff point of 44.1 for screening risk of impaired glucose tolerance in this population [11].

Some studies have related testosterone and sex hormone-binding globulin (SHBG) to CV risk and disease in women [12,13]. In postmenopausal women, cardiovascular risk factors such as central obesity, dyslipidemia, insulin resistance, hypertension, and endothelial dysfunction have been negatively associated with SHBG, and positively associated with androgens [12,14–18].

Therefore, the aim of the present study was to investigate if LAP is related to androgen and SHBG levels and to cardiovascular risk factors in postmenopausal women with no evidence of established cardiovascular disease.

2. Methods

2.1. Patients

The study was carried out with women consulting for climacteric symptoms at the Gynecological Endocrinology Unit at Hospital de Clínicas de Porto Alegre, Brazil. Inclusion criteria were as follows: (1) menopause, defined as last menstrual period at least 1 year before the beginning of the study plus follicle stimulating hormone (FSH) levels higher than 35 IU/L; (2) age > 40 years; (3) no use of any medication known to interfere with hormonal, glucose, or lipoprotein levels in the past 3 months; and (4) no use of steroidal or nonsteroidal anti-inflammatory drugs in the last 15 days. Diabetic patients or patients with thyroid, hepatic, or renal dysfunction were excluded. Forty-nine postmenopausal women fulfilling all the inclusion criteria were consecutively enrolled in the study. The study protocol was approved by the local Ethics Committee, and written informed consent was obtained from every subject.

2.2. Study protocol

Anthropometric measurements included body weight, height, waist circumference (waist measured at the midpoint between the lower rib margin and the iliac crest), and body mass index (BMI; current measured weight in kilograms divided by height in square meters), as previously reported [4]. Blood pressure was measured in the supine position after a 10-min rest. The same calibrated mercury manometer attached to a 12.5-cm × 23-cm inflatable cuff was used in all patients by the same operator, who adopted the fifth Korotkoff sound to determine diastolic pressure. Hypertension was defined as systolic blood pressure ≥ 130 mmHg, diastolic blood pressure ≥ 85 mmHg, or current use of antihypertensive drugs. FSH, estradiol, total testosterone (TT), SHBG, dehydroepiandrosterone sulfate, fibrinogen, ultrasensitive C-reactive protein (us-CRP), total and high-density lipoprotein (HDL) cholesterol, and TG were also determined using the fasting blood sample. All samples were obtained between 8 AM and 10 AM.

LAP (waist-58 × triglycerides [nmol/L]) was calculated after the clinical and laboratory evaluations. The patients were then stratified into two groups, with LAP ≥ or <34.5, a previously described arbitrary cutoff point [10].

The presence of cardiovascular risk factors and frequency of metabolic syndrome were evaluated according to the 2001 NCEP-ATPIII [5].

2.3. Assays

Total cholesterol, HDL cholesterol, triglycerides, and glucose were determined by colorimetric–enzymatic methods using the Bayer 1650 Advia System (Mannheim, Germany). Low-density lipoprotein (LDL) cholesterol was determined indirectly using the formula LDL = total cholesterol − (HDL + (triglycerides/5)). FSH was measured by electrochemiluminescence immunoassay (ECLIA), with intra and interassay coefficients of variation (CVs) of 1.8% and 3.3%, respectively. The sensitivity of the assays was 0.05 IU/L for FSH. The TT levels were measured with the radioimmunoassay method (ICM, Costa Mesa, CA, USA), with an assay sensitivity of 0.2 ng/mL and intra and interassay CVs of 10% and 11.3%, respectively. Ultrasensitive CRP was assayed using stored specimens, with a validated high-sensitivity nephelometric method (Dade Behring Marburg, Marburg, Germany). Sensitivity was 0.17 mg/L; and intra- and interassay CVs were 4.4% and 5.7%, respectively. For data analysis, individual results below the limit of sensitivity were considered as equal to 0.17 mg/L. Sex hormone-binding globulin was measured by chemiluminescence enzyme immunoassay (DPC, Los Angeles, CA, USA), with an assay sensitivity of 0.2 nmol/L and intra- and interassay CVs of 6.1% and 8.0%, respectively. Serum insulin levels were measured using ECLIA (Roche Diagnostics), with a sensitivity of 0.200 μIU/mL and intra- and interassay CVs of 2.0% and 4.3%, respectively. Free androgen index (FAI) was estimated by dividing TT (in nanomoles per liter) by SHBG (in nanomoles per liter) × 100. Homeostatic model assessment (HOMA) was calculated by multiplying insulin (μIU/ml) to glucose (mmol/l) and dividing this product by 22.5, as previously described [19].

2.4. Sample size estimation and statistical analysis

Sample size was estimated based on the results of our previous study [10], in which a difference of around 30 between women with LAP ≥ or <34.5 was found for PCOS patients and controls. Therefore, considering the same LAP difference, an alpha of 5% and a beta of 80%, the sample size was estimated as 44 women plus 10% of potential dropouts, giving a total of 49 participants.

Results are expressed as means ± SD or median and interquartile range. Comparisons between the 2 group means were analyzed by Student's *t* test; comparisons between median values were analyzed with the Mann–Whitney *U* test. Spearman's rank or Pearson's correlation coefficient was calculated between variables using a 2-tailed significance test for variables with a Gaussian or non-Gaussian distribution, respectively. Comparisons between ratios were carried out using the χ^2 test. us-CRP results were log-transformed for statistical analysis and back-transformed for data presentation. All analyses were performed using the Statistical Package for the Social Sciences 16 (SPSS, Chicago, IL, USA). Data were considered to be significant at $p < 0.05$.

3. Results

The mean age of participants was 55 (±5) years, the age at menopause was 48 (±3) years, and the median time since menopause was 5 (3–8) years. Metabolic syndrome, as defined by the National Cholesterol Education Program – Adult Treatment Panel III criteria [5] was diagnosed in 7 patients (14%). Twelve patients (24.5%) had hypertension.

The distribution of clinical, anthropometric and hormonal variables and us-CRP levels was analyzed in relation to the LAP cutoff point of 34.5 (Table 1). While both groups (LAP <34.5 or ≥34.5) were similar regarding age and time since menopause, the group with LAP ≥ 34.5 had greater waist, BMI, glucose, cholesterol, triglycerides and lower HDL-C. Although LDL-C and blood pressure levels were similar between the groups, the group with higher levels of LAP had higher prevalence of metabolic syndrome and higher us-CRP levels (Table 1).

SHBG levels were lower and androgens (TT and FAI) levels were greater in the group with LAP ≥ 34.5 (Fig. 1).

LAP was positively correlated with systolic and diastolic pressure, cholesterol, and fasting glucose, and negatively correlated