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Visceral adiposity index for the diagnosis of nonalcoholic fatty liver disease in premenopausal women with and without polycystic ovary syndrome

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ABSTRACT

Objective: Visceral adiposity index (VAI), initially developed for the assessment of cardiometabolic risk, has been also proposed for the detection of nonalcoholic fatty liver disease (NAFLD); however, its diagnostic performance for NAFLD is still under investigation. We evaluated VAI as a marker of NAFLD and compared its diagnostic performance with that of three other NAFLD indices – fatty liver index (FLI), lipid accumulation product (LAP) and hepatic steatosis index (HSI) – in premenopausal women with and without polycystic ovary syndrome (PCOS) assessed for NAFLD by ultrasonography.

Design: Cross-sectional case-control study.

Methods: Anthropometric measurements, biochemical testing and abdominal ultrasonography after excluding causes of secondary liver disease were performed in 145 premenopausal women with PCOS (Rotterdam criteria) and 145 healthy control women within the same age range and matched for body mass index (BMI). The diagnostic performance of the four indices was assessed with receiver operating characteristic (ROC) analysis.

Results: NAFLD by ultrasonography was detected in 132 of the total sample of 290 women (45.5%). VAI, FLI, LAP and HSI values were significantly higher in women with NAFLD than those without. The areas under the curve (AUROCs) for VAI, FLI, LAP and HSI were 0.77 ± 0.03, 0.87 ± 0.02, 0.84 ± 0.02 and 0.83 ± 0.02, respectively, in the whole group, showing an adequate discriminatory ability for NAFLD of the four indices. AUROCs of the four indices calculated separately for PCOS and control women showed a similar performance of all indices in the two groups.

Conclusions: These data show that VAI is useful for detecting NAFLD in premenopausal women with and without PCOS. However, VAI had a lower diagnostic performance in this cohort than FLI, LAP and HSI.

1. Introduction

Existing data support that enlarged visceral adipose tissue due to excess lipid storage is an important regulator of nonalcoholic fatty liver disease (NAFLD) [1–3]. Proposed mechanisms for this role of visceral adipose tissue are the increased portal free fatty acid flow to the liver, the increased insulin resistance of this tissue compared to other fat depots and the altered secretion of humoral factors from adipocytes which modulate insulin sensitivity [4]. Visceral adiposity can be assessed with various methods such as computed tomography (CT), magnetic resonance imaging (MRI) and dual energy x-ray absorptiometry (DXA) [4]. However, these methods are not applicable in everyday practice because of cost, routine availability and radiation in the case of CT and DXA. Thus, several surrogate markers for the assessment of visceral adiposity have been introduced in clinical practice, among them visceral adiposity index (VAI). This gender-specific index based on waist circumference measurement, body mass index calculation and triglyceride and HDL levels, was developed in 2010 and was proposed as an indicator of visceral adipose function and insulin sensitivity reflecting cardiometabolic risk [5]. In the original study VAI presented a significant correlation with visceral adipose tissue evaluated by MRI and was inversely correlated with insulin sensitivity assessed by euglycemic-hyperinsulinemic clamp [5]. In addition, VAI was independently associated with features of the metabolic syndrome and

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cardiovascular and cerebrovascular events in a cohort of primary care patients.

Although, liver biopsy is the gold standard for diagnosing and staging NAFLD and for assessing the efficacy of therapeutic interventions, its use is limited by cost, sampling errors and procedure-related morbidity and mortality [6]. Thus, the need for non-invasive, simple, reliable and cost-effective diagnostic tools has been raised. Imaging modalities are the most widely used non-invasive methods to detect hepatic steatosis and abdominal ultrasonography is recommended as a first-line diagnostic test [7]. In addition, several indices based on anthropometric measurements and biochemical parameters, have been proposed as hepatic steatosis biomarkers [8] and are considered as an acceptable alternative for the diagnosis of NAFLD [7]. The first study examining whether VAI could be used as an index of liver damage showed that it was independently associated with both steatosis and necroinflammatory severity in patients with genotype 1 chronic hepatitis C [9]. Another study by the same group of investigators showed that VAI was independently correlated with the severity of fibrosis in patients with biopsy-proven NAFLD [10]. At variance, ensuing studies in different patient populations showed that VAI could not predict liver damage severity [11–13], but it could predict hepatic steatosis diagnosis [11,14]. Regarding other indices, the fatty liver index (FLI) [15], the lipid accumulation product (LAP) [16] and the hepatic steatosis index (HSI) [17], all three validated using ultrasonography, have been shown to present an adequate performance in detecting hepatic steatosis, although mainly FLI has been used in epidemiological studies so far. In addition FLI, HSI and LAP have been shown efficient in detecting steatosis when validated with ^{1}H-magnetic resonance spectroscopy (^{1}H-MRS) [18,19]. Moreover, VAI, FLI and HSI have been shown with an adequate diagnostic accuracy for the presence of hepatic steatosis when using liver biopsy as reference standard [20].

In this study we aimed to 1) evaluate the ability of VAI to identify the presence of hepatic steatosis and to 2) compare diagnostic performance of VAI to the one of three other indices of hepatic steatosis FLI, LAP and HSI in a cohort of premenopausal women with and without polycystic ovary syndrome (PCOS) assessed for NAFLD by ultrasonography.

2. Subjects and methods

2.1. Subjects

For this study we used data which were prospectively collected based on the protocol of a previous study [21]. We studied 290 Caucasian premenopausal women aged 18–45 years, with a BMI 17.6–46.9 kg/m^2 (50 with a BMI < 25.1 kg/m2) - 145 with PCOS and 145 BMI-matched healthy controls – from March 2007 till July 2010. PCOS women were recruited prospectively from the outpatient endocrine clinic for obesity, hirsutism, menstrual disorders and subfertility of two centers (“Amalia Fleming” Hospital and “Red Cross” Hospital). PCOS was diagnosed according to the Rotterdam criteria [22], after exclusion of diseases with a similar clinical presentation, such as hyperprolactinemia, nonclassical adrenal 21-hydroxylase deficiency, Cushing’s syndrome and androgen secreting tumors by biochemical testing. Hundred and thirteen control women were recruited prospectively from the outpatient endocrine clinic for obesity or thyroid disorders in addition to 32 volunteers from the hospitals’ medical and paramedical staff. Controls reported normal menses and had no clinical signs of hyperandrogenism. The absence of PCOS in these women was confirmed by biochemical testing and pelvic ultrasound examination (transvaginal in the majority of participants). Inclusion criteria for all women were 1) maximum alcohol consumption 1 alcoholic drink per day, or less 2) no history of known autoimmune or genetic or other chronic liver disease 3) absence of viral liver disease by appropriate tests and 4) absence of known hypertension, hyperlipidemia, diabetes mellitus or other systemic diseases. No use of any medication for at least 3 months was required prior to participation in the study.

2.2. Study protocol

A detailed medical history was obtained from all women. Assessment of mean daily alcohol intake was based on self-reporting. Physical examination was performed, including measurements of weight, height, waist and hip circumference and blood pressure, as well as assessment of clinical signs of hyperandrogenism (hirsutism, acne).

Venous blood sample was drawn for biochemical evaluation after an overnight fast, in the early follicular phase of a spontaneous cycle or after progesterone induced bleeding in amenorrhoic patients. Biochemical evaluation comprised fasting glucose and insulin, serum aspartate (AST) and alanine aminotransferases (ALT), gamma-glutamyltranspeptidase (γGT), alkaline phosphatase (ALP), total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, total testosterone, dehydroepiandrosterone sulphate (DHEA-S) and sex hormone binding globulin (SHBG). Elevated aminotransferase and γGT levels were defined as values exceeding the upper normal level in our hospitals’ laboratory (ALT and AST ≥ 40 IU/land γGT > 36 IU/l).

The same day an abdominal ultrasound followed, using a B-mode scanner of General Electric Logiq 5, with a 3.5 MHz convex-array probe. Detection of HS was based on the assessment of the following ultrasonographic parameters, as previously described [21]: ultrasonographic contrast between hepatic and right renal parenchyma (hepatorenal echo contrast), abnormally intense high-level echoes arising from the hepatic parenchyma, echo penetration into the deep portion of the liver, intrahepatic vessel blurring and abnormal visualization of the diaphragm. Absence of HS was defined as equal echogenicity of hepatic parenchyma to that of the renal cortex with clear visualization of the intrahepatic vessels and the diaphragm [23].

The study protocol was approved by the Institutional Review Boards of “Amalia Fleming” Hospital and “Red Cross” Hospital and written informed consent was obtained from all participants before study commencement.

2.3. Calculations

FLI was calculated using BMI (kg/m^2), waist circumference (cm), serum triglyceride (mg/dl) and γGT (U/l) concentrations according to Bedogni et al. [15]. LAP was calculated using waist circumference (cm) and serum triglycerides (mmol/l) concentrations according to the formula for women by Bedogni et al. [16]. HSI was calculated using BMI (kg/m^2), serum ALT and AST (U/l) concentrations according to the formula for women by Lee et al [17]. VAI was calculated using BMI (kg/m^2), waist circumference (cm), serum triglyceride (mmol/l) and HDL cholesterol (mmol/l) concentrations according to the formula for women by Amato et al [5].

Free androgen index (FAI) was calculated as total testosterone (nmol/l) × 100 / SHBG (nmol/l).

Insulin resistance was estimated using the homeostasis model assessment (HOMA-IR) calculated as fasting insulin (μU/ml) × fasting glucose (mmol/l) / 22.5. Body mass index (BMI) was calculated as body weight (kg)/height^2 (m^2). The waist-to-hip ratio (WHR) was calculated as waist circumference (cm)/hip circumference (cm).

2.4. Assays

All hormones were measured with commercial kits. Serum testosterone was measured by electrochemiluminescence immunoassay (ECLIA; Roche Diagnostics GmbH, Mannheim, Germany). Serum SHBG and insulin were measured by immunoradiometric assay (IRMA; Biosource Europe SA, Nivelles, Belgium). Serum DHEA-S was measured by radioimmunoassay (RIA; Biosource Europe SA, Nivelles, Belgium). The intra- and interassay coefficients of variation for all these assays were less than 10%. Serum glucose was measured by the oxidase