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Ultrasound-assessed visceral fat and associations with glucose homeostasis and cardiovascular risk in clinical practice

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Abstract *Background and Aims:* Despite the lack of evidence that assessing the global cardiovascular risk leads to a decreased incidence of cardiovascular events, accurate patient profiling is paramount in preventive medicine. An excess of visceral fat (VF) is associated with an enhanced cardiovascular risk; importantly, VF is quantifiable rapidly, cheaply and safely by ultrasound, which makes it suitable for use in clinical practice. In the present study, we aimed to evaluate if US-measured VF (USVF) could be a better predictor of glucose homeostasis and cardiovascular risk than simple anthropometric measures.

Methods and Results: One-hundred sixty-two patients attending a Metabolic Disorders Clinic underwent a cross-sectional study for which USVF, anthropometric measures, a standard oral glucose tolerance test (OGTT), and calculation of cardiovascular Framingham score and vascular age were obtained. USVF was directly correlated with fasting and 2-h plasma glucose (respectively: $r = 0.26$, $p < 0.001$; $r = 0.28$, $p < 0.0001$), fasting and 2-h plasma insulin (for both: $r = 0.41$, $p < 0.0001$), homeostatic model assessment of insulin resistance (HOMA-IR; $r = 0.42$, $p < 0.0001$), cardiovascular Framingham score ($r = 0.44$ $p < 0.0001$) and vascular age ($r = 0.30$ $p < 0.001$). In receiver operator characteristic curves USVF had good diagnostic abilities for type 2 diabetes mellitus, fatty liver and metabolic syndrome, in both genders. At multivariate analysis, body mass index (BMI) outperformed USVF in the prediction of HOMA-IR; neverthless, USVF, not BMI, was an independent predictor of cardiovascular risk. Finally, models including USVF were the most parssimonious to predict Framingham score, vascular age and HOMA-IR.

Conclusion: In overweight and obese subjects, USVF could usefully complement other parameters for cardiovascular risk stratification.

Introduction

Obesity is a risk factor for type 2 diabetes mellitus (T2DM) [1], fatty liver [2] and cardiovascular diseases [3]. In adults, the definition of obesity is based on body mass index (BMI) [4], a measure directly related to all cause morbidity and mortality [5,6]. However, many studies have documented that this association is not linear [7,8], one of the

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explanations being that BMI does not distinguish lean from fat mass [9]. Visceral fat (VF), on the other hand, is a major determinant of insulin resistance, glucose intolerance, dyslipidemia, atherogenic lipid profile, systemic inflammation, endothelial damage and thrombophilia [10–13], which in turn are all known predictors of cardiovascular risk. This explains why 10–30% of obese patients, having a predominance of subcutaneous rather than visceral fat, are metabolically healthy [14]. On the contrary, a subgroup of non-obese subjects have an unfavorable cardiovascular and metabolic profile ("metabolically obese normal-weight" MONW), characterized by hyperinsulinemia, dyslipidemia, insulin resistance and arterial hypertension [15]. The two most commonly used tools to estimate central adiposity are the waist-to-hip ratio (WHR) and the waist circumference (WC) which, albeit directly related to VF, are indirect measurements, and as such are not reliable under all circumstances [16]. The waist-to-height ratio may represent a better screening tool than BMI for mortality risk [17], with the advantage that, by making allowance for height, the same boundary value, (0.5), can be used for everyone; however, it remains to large extent a proxy measure of VF. On the other hand, the direct measure of VF poses considerable difficulties in clinical practice. Computed tomography and magnetic resonance are the gold standard for the VF measurement, but cost, risks and/or availability limit their widespread use for this purpose [18].

In recent years, ultrasonographic assessment of VF (USVF) - specifically the distance between the internal face of the rectus abdominis muscle and the anterior wall of the aorta [19] - has emerged as a useful tool for measuring VF. In the present study we aimed to test the association between USVF and glucose metabolism, metabolic syndrome, fatty liver and estimates of cardiovascular risk in clinical practice.

Methods

We prospectively recruited along one year adult patients (older than 18), attending the Metabolic Disorders Clinic of a University Hospital in Northern Italy. We excluded patients with known T2DM, liver cirrhosis, severe chronic kidney disease, active cancer, pregnant women and those receiving antidiabetic drugs. The study was conducted in strict accordance with the principles of the Declaration of Helsinki.

The demographic and clinical data collected included age, gender, smoke and alcohol habits, past medical history, and concomitant treatment(s). Moreover, all patients underwent a thorough physical examination. The BMI was calculated as body weight in kg (taken with the patient wearing light underwear) divided by the square of the height in meters, and interpreted according to the World Health Organization classification [4]. The WC was measured midway between the lowest rib and the iliac crest when standing. Blood pressure was measured after a period of relaxation in the seated position using a manual sphygmomanometer.

Total cholesterol, high density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol and triglycerides, were measured by enzymatic methods (ADVIA, Siemens).

In agreement with the American Diabetes Association (ADA) 2003 Criteria [20], each patient underwent a standard Oral Glucose Tolerance Test (OGTT), after a 12-h fasting. This entails the ingestion of 75 gr of glucose and measurement of 2 glucose concentrations: Plasma glucose concentrations were measured by the hexokinase method (ADVIA, Siemens; detection limit 4 mg/dl), at fasting (FPG) and 2-h after the glucose challenge (2hPG). Plasma insulin concentrations were measured by chemiluminescence (Centaur, Siemens; detection limit 0.5μUI/ml) at the same times (FPI and 2hPI, respectively at fasting and at 2-h). In agreement with the ADA 2003 criteria, a patient was classified as having either a) normal glucose tolerance (NGT), when FPG was $<$100 mg/dl and 2hPG was $<$140 mg/dl; b) T2DM, when FPG was $\geq$126 and/or 2hPG was $\geq$200 mg/dl; c) impaired fasting glucose (IFG), when FPG was $\geq$100 but $<$126 mg/dl and 2hPG was $<$140 mg/dl; or d) impaired glucose tolerance (IGT), when FPG was $<$100 mg/dl and 2hPG was $\geq$140 but $<$200 mg/dl. For the purposes of the study, subjects with IFG and/or IGT were lumped into a single group called prediabetes (preDM).

For each patient we also calculated the homeostatic model assessment of insulin resistance (HOMA-IR) according to the following formula: (FPI μUI/ml $\times$ FPG mmol/L)/22.5 [21]. To complete the metabolic assessment, a lipid profile including total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides was obtained.

For each patient, we estimated the individual Cardiovascular Risk according to the Framingham score as well as the Vascular Age, using an online tool. Vascular age calculation requires the following data: age, gender, IMT. The following data have been used to calculate the Framingham score: age, gender, smoking history, total and HDL cholesterol, systolic blood pressure (SBP) and use of anti hypertensive drugs [22].

The diagnosis of metabolic syndrome (MS) was made according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria, considering WC, triglycerides plasma level, HDL cholesterol, FPG and SBP [23].

Ultrasonographic studies

US was performed with a GE Logiq S8 machine (GE Healthcare, Little Chalfont, UK):

- Both common carotid arteries were examined at 1- to 2-cm proximal site to the carotid bifurcation on a longitudinal 2-dimensional ultrasound image, with the patient lying supine. The intima media thickness (IMT) was measured by a linear probe (7.5 megahertz, MHz)in the posterior wall of the common carotid artery, as the distance from the leading edge of the first echogenic line (lumen-intima interface) to the leading edge of the second line (media-adventitia interface). We obtained 5 measurements for each side and IMT was derived as the

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