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Original article

Assessment of epicardial adipose tissue and carotid/femoral intima media thickness in insulin resistance

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ABSTRACT

Background: Metabolic syndrome is a combination of multiple cardiovascular (CV) risk factors including insulin resistance (IR). Carotid, femoral intima media thickness (IMT), and epicardial fat thickness (EFT) are considered as novel cardiometabolic risk factors. We aimed to test the hypothesis that carotid, femoral IMT, and EFT are increased in patients with IR.
Methods: We enrolled consecutively and prospectively 113 patients with IR. Then we collected data from an age- and sex-matched control group of 112 individuals without IR. Homeostasis model assessment (HOMA) index value >2.5 was accepted as IR. Patients with diabetes mellitus, CV diseases, systolic heart failure, chronic liver or renal diseases were excluded. On B-mode duplex ultrasound the mean IMT at the far wall of both left and right common carotid/femoral arteries were measured manually. EFT was measured on the free wall of the right ventricle at end-diastole from the parasternal long-axis views by standard transthoracic 2D echocardiography.
Results: Both carotid IMT and EFT were significantly higher in patients with IR compared to controls (0.80 ± 0.21 mm *vs* 0.60 ± 0.21 mm; $p < 0.001$ and 7.34 ± 1.96 mm *vs* 5.22 ± 1.75 mm; $p < 0.001$, respectively). However, there were no significant differences in femoral IMT between the groups (0.74 ± 0.20 *vs* 0.69 ± 0.17; $p = 0.062$). In multivariate linear regression analysis age ($\beta = 0.223$, $p = 0.010$), 2-h blood glucose ($\beta = 0.198$, $p = 0.021$), and IR ($\beta = 0.369$, $p < 0.001$) were independent predictors of EFT. On the other hand age ($\beta = 0.363$, $p < 0.001$) and IR ($\beta = 0.321$, $p < 0.001$) were independent predictors of carotid IMT.
Conclusions: Patients with IR have increased carotid IMT and EFT, but not femoral IMT. This apparent incoherence may be due to the involvement of carotid arteries prior to femoral arteries in patients with IR.
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Introduction

Metabolic syndrome (MetS) is a combination of multiple cardiovascular (CV) risk factors including visceral obesity, hypertension, prediabetes, and atherogenic dyslipidemia [1]. Although there is still some debate about the nature of the MetS, insulin resistance (IR) is thought to be the primary cause of MetS. Hyperinsulinemia is a surrogate measure of IR which is associated with several clinical conditions including diabetes mellitus (DM), atherosclerosis, and cardiovascular diseases (CVD) [2,3].

Subclinical atherosclerosis develops several years before the clinical manifestation of CVD. If the patients are diagnosed at subclinical stages, preventive measures can be implemented. Carotid intima media thickness (IMT) is a well-known noninvasive independent predictor of subclinical atherosclerosis [4,5]. Epicardial fat thickness (EFT), which reflects cardiac and visceral adiposity, is suggested as a new cardiometabolic risk factor [6–8]. The associations between increased EFT and DM, hypertension, as well as CVD have been studied [6–11]. However assessment of femoral IMT as a predictor of subclinical atherosclerosis and intimal hyperplasia criteria for femoral artery are still unclear [3,12]. The purpose of our study was to test the hypothesis

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that EFT, carotid and femoral IMT, as markers of early atherosclerosis, are increased in patients with IR.

Materials and methods

We enrolled consecutively and prospectively 113 patients with IR who were referred to our cardiology department for CV risk screening from the internal medicine outpatient clinic between September 2013 and April 2015. Then we collected data from an age- and sex-matched control group of 112 individuals without IR.

A fasting blood sample was obtained from all participants, who signed the consent form, in order to measure biochemical parameters including plasma levels of fasting glucose, insulin, creatinine, transaminases, C-reactive protein (CRP), gamma-glutamyltransferase (GGT), hemoglobin A1c (HbA1c), and lipid profile. After 75 g oral glucose tolerance test (oGTT), 2-h plasma glucose levels were measured. oGTT was defined as a 2-h plasma glucose level after loading 75 g of anhydrous glucose in a total volume of 300 ml oral solution within 5 min. Then participants diagnosed with DM (defined as levels of fasting glucose ≥126 mg/dl or 2-h post-challenge plasma glucose ≥200 mg/dl) were excluded [13]. Homeostasis model assessment (HOMA) index for IR was calculated by using Matthew's equation which is fasting plasma insulin level (μ/L) × fasting glucose level (mg/dl)/405. HOMA index values higher than 2.5 are accepted as IR [14].

Demographic data, risk factors for CVD, medications, anthropometric measurements, and biochemical findings were recorded. Body mass index (BMI) was calculated as weight (kg)/height $(m)^2$. Waist circumference (WC) was measured at the midpoint between the lowest rib and the iliac crest while the patient was standing. Blood pressures (BP) were measured by standard sphygmomanometer after 5 min of rest.

Patients who were on hypoglycemic medication or diagnosed with DM, CVD, systolic heart failure, severe valvular disease, hypertrophic cardiomyopathy, stroke, chronic obstructive pulmonary disease, sepsis, chronic liver or renal diseases, peripheral arterial disease, and patients having atherosclerotic plaques in carotid arteries were excluded. To rule out CVD, all patients were examined by using electrocardiography, echocardiography, and stress tests. Coronary angiography was performed only if patients were at high risk for CVD or if they had a positive stress test. Patients were defined as having no CVD if none of the following were present: angina pectoris, ST-T wave changes, Q waves, left bundle branch block on electrocardiogram, regional wall motion abnormalities on echocardiogram, ischemia detected by non-invasive stress tests, history of myocardial infarction, coronary artery stenosis ≥50% on coronary angiography, or history of coronary revascularization.

Plaque in carotid and femoral arteries is defined as a focal structure of the inner vessel wall at least ≥0.5 mm (or 50%) of the surrounding IMT, or any IMT measurement ≥1.5 mm [15].

Carotid and femoral ultrasonography

A Logic 9 ultrasound machine (GE, Healthcare, Horten, Norway), equipped with a 9F linear array imaging probe, was used. Carotid IMT was measured manually from the far walls of left and right common carotid arteries, at a region 10 mm proximal to the carotid bifurcation. Measurements were made on B-mode duplex ultrasound in longitudinal plane. Carotid IMT was measured on this image at 3 adjacent sites 1 mm apart. In addition on B-mode duplex ultrasound (Logic 9) the mean femoral IMT at the far wall of both left and right common femoral arteries was measured manually at 3 adjacent sites 1 mm apart. The mean values of these 3 measurements were used for analyses (Fig. 1).

Routine two dimensional (2D), conventional spectral Doppler and epicardial fat thickness (EFT) data

A Vivid S5 ultrasound machine (GE Healthcare), equipped with a 3SRS broadband transducer, was used. All patients underwent standard 2D and Doppler echocardiography conforming to the American Society of Echocardiography and European Association of Cardiovascular Imaging (EACVI) recommendations [16]. Ejection fraction (EF) was calculated by the modified Simpson's method.

EFT was identified as the echo-free space between the outer wall of the myocardium and visceral layer of pericardium [6–8]. It was measured perpendicularly on the free wall of the right ventricle at end-diastole from the parasternal long-axis views of 3 cardiac cycles by standard transthoracic 2D echocardiography (Fig. 2) [8].

All measurements were performed and digitally stored conforming to EACVI recommendations [16] by the same investigator who was blinded to all clinical data of the patients, and then checked by an EACVI accredited senior echocardiographer who was also blinded.

Statistical analysis

SPSS 16.0 for Windows (Statistical Program for the Social Services Inc., Chicago, IL, USA) program was used for statistical analysis. Continuous variables were defined as mean ± standard deviation. Variables were tested for normal distribution by using the Kolmogorov–Smirnov test. Descriptive statistics were used for definition of demographic variables. Differences between the groups were assessed by using unpaired *t* test, or Mann–Whitney *U* test

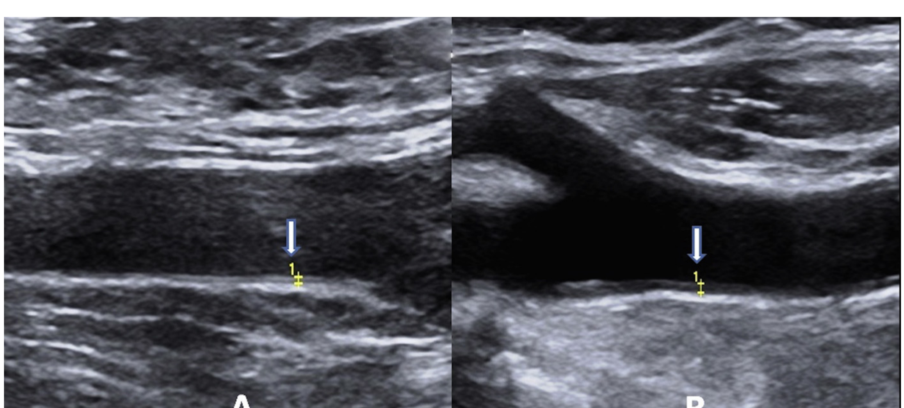

Fig. 1. Measurements of femoral (A) and carotid (B) intima media thickness at the far wall of common femoral/carotid arteries.

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