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Separate impact of metabolic syndrome and altered glucose tolerance on early markers of vascular injuries

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ABSTRACT

Objective: We investigated the separate impact of metabolic syndrome (MS) and altered glucose tolerance on early markers of vascular injuries.
Methods: Intima-media thickness (IMT) and Pulse Wave Analysis (PWA), were evaluated in 132 overweight or obese subjects, with (MS^+) or without (MS^-) MS; subjects were further classified as normotolerant (NT) or with altered glucose tolerance (AGT) according to a 2 h oral glucose tolerance test (OGTT).
Results: In MS^+ patients, IMT was higher than in the MS^- group, and PWA revealed higher Augmentation Pressure (Aug, the contribution that wave reflection makes to systolic arterial pressure) and lower subendocardial viability ratio (SEVR, an estimate of myocardial perfusion). When analyzed according to glucose tolerance, IMT was higher in MS^+NT subjects and AGT patients with and without MS, vs. MS^-NT subjects. Logistic regression modeling showed that both AGT and MS were independently associated with increased IMT. However, only MS remained associated with IMT after adjustment for age. SEVR was reduced only in MS^+ patients, independently of glucose tolerance. In both groups, Aug and AugI were higher in the AGT group, but the correlation with 2 h-plasma glucose disappeared when corrected for age.
Conclusion: Both MS and AGT altered IMT, but the effect of AGT disappears when age is added to the multiple regression model. In contrast, arterial stiffness was affected differently in the two categories: in subjects with MS, the subendocardial viability ratio (an estimate of myocardial perfusion) was impaired, while in subjects with AGT, both Aug and AugI were increased. These data suggest that applying the definition of MS might help to better characterize cardiovascular risk in subjects with altered glucose tolerance or obesity.

1. Introduction

Metabolic syndrome (MS), a cluster of interrelated metabolic disorders and vascular risk factors closely linked to insulin resistance, is associated with a 2-fold increase in risk of cardiovascular diseases (CVD), CVD mortality, and stroke, and a 1,5 fold increase in risk from all causes of mortality [1,2]. The mechanism through which this syndrome increases cardiovascular risk is under debate, but may involve defects in vascular structure and function.

Morphological and functional alterations of the arterial wall, including increased intima-media thickness (IMT) and vascular wall stiffness, are associated with the presence of CV risk factors and atherosclerotic disease, and are recognized as significant independent predictors of adverse cardiovascular outcomes [3,4]. Previous studies have shown, using different techniques, including ultrasound and pulse wave velocity, reduced large artery elasticity in subjects with individual components of metabolic syndrome such as dyslipidemia, high blood pressure, and abdominal fat [3,5–7]. In addition, MS has been reported to be associated with increased aortic stiffness in patients at high risk for diabetes, and in groups with uncomplicated, untreated essential hypertension [8]; moreover, the clustering of multiple components of MS has been reported to have a greater impact on vascular parameters than individual components of MS [8,9].

In addition, altered glucose tolerance and type 2 diabetes likely cluster with classic cardiovascular risk factors, and are associated with a two-to seven-fold increased risk for cardiovascular disease [10]. This excessive risk is not fully explained by risk factors such as high levels of LDL cholesterol or blood pressure; several studies

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have shown an increase in peripheral arterial stiffness, and a greater thickness of the carotid artery in type 2 diabetes mellitus (T2DM), independent of other established risk factors for atherosclerosis [11,12].

This study was undertaken to examine the respective roles of MS and altered glucose tolerance on intima-media thickness, measured by ultrasonography, and arterial stiffness and subendocardial viability ratio (SEVR), an index of diastolic cardiac function, meausured by pulse wave analysis (PWA).

2. Materials and methods

2.1. Study subjects

Subjects were consecutively recruited among overweight or obese patients attending our University Hospital for cardiovascular risk evaluation. Inclusion criteria were an age range of 18–65 years and body mass index (BMI) $\geq$ 25 kg/m^2. Exclusion criteria were: previous history of overt diabetes, use of medications known to affect glucose metabolism, previous cardiovascular events, active smoking, clinical evidence of advanced liver or renal disease, rheumatic diseases and/or recent history of acute illness. Subjects were divided into two groups, with or without metabolic syndrome, according to National Cholesterol Education Program: Adult Treatment Panel III (NCEP-ATP III) criteria [2]. The NCEP defines metabolic syndrome as having three or more of the following five cardiovascular risk factors: waist circumference (WC) of >102 for men and >88 cm for women for abdominal obesity, triglycerides >150 mg/dl, HDL cholesterol <40 mg/dl for men or >50 mg/dl for women, blood pressure $\geq$130/$\geq$85 mmHg, and fasting glucose $\geq$100 mg/dl.

Body weight and height were measured, and body mass index (BMI) was calculated as weight (kg)/[height (m)]^2. Waist circumference was measured in a standing position at the level of the umbilicus. Blood pressure (BP) was measured with a calibrated mercury sphygmomanometer after the subject had rested in the supine position for 10 min.

Venous blood samples were drawn from the antecubital vein the morning after an overnight fast. Baseline venous blood samples were obtained for measurements of plasma glucose, total cholesterol, HDL cholesterol, and triglycerides. LDL cholesterol concentrations were estimated by using the Friedewald formula. All subjects underwent a 75 g oral glucose tolerance test (OGTT): samples for glucose measurement were drawn at baseline after glucose ingestion and up to 120 min. Subjects were classified according to their 2-h glucose levels into categories of normal glucose tolerance (NT), impaired glucose tolerance (IGT) or diabetic (DM). NT was defined as a 2 h plasma glucose level <140 mg/dl. IGT was defined as a 2 h plasma glucose level of 140–200 mg/dl. Type 2 diabetes was defined as a 2 h plasma glucose level $\geq$200 mg/dl [13].

2.2. Biochemical analyses

Plasma glucose, serum total cholesterol, triglycerides, high density lipoprotein cholesterol (HDL), and high sensitivity C-reactive protein (hs-CRP) were measured by available enzymatic methods, as previously described [14]. ICAM-1 was measured by an ELISA method according to a protocol supplied by the manufacturer (Millipore, Bellerica; MA, USA).

2.3. Carotid ultrasound examinations

Ultrasound scans were performed with a GE Medical System Vivid Pro 3 ultrasound system equipped with a 7.5-MHz linear array transducer as previously described in detail [5]. A single physician carried out all ultrasound examinations. Subjects were examined in the supine position. Longitudinal images from the angle with the best visibility were displayed bilaterally for the common carotid artery, carotid bulb, and internal carotid artery. Scans were performed and measurements carried out at a total of ten sites: both the far wall (the carotid wall farthest from the probe) and the near wall (the carotid wall closest to the probe) of the common carotid and bulb; right and left distal 10 mm of common carotid and bulb, and far wall of the proximal 10 mm of internal carotid. All measurements were taken in the diastole, assessed as the phase when the lumen diameter is at its smallest and IMT is at its largest. From each measurement, the maximum IMT was derived as the maximum IMT assessed in the ten sites [5].

2.4. Pulse-wave analysis

The technique of pulse-wave analysis was used to evaluate central aortic pressure and the augmentation index, as previously described [5]. All measurements were made from the right radial artery by applanation tonometry using a Millar tonometer (SPC-301; Millar Instruments, Houston, TX) by a single investigator with the subject in supine position, by applying a tonometer to the radial artery and compressing the vessel wall sufficiently to record the pulse trace. Data were collected directly into a desk-top computer and processed with the SphygmoCor Px (Sydney, Australia), which allows continuous on-line recording of the radial artery pressure waveform. The integral system software was used to calculate an average radial artery waveform, and generate the corresponding ascending aortic pressure waveform using a previously validated transfer factor. The aortic waveform has two systolic pressure peaks, the latter of which is caused by wave reflection from the periphery. With arterial stiffening, both the pulse-wave velocity and the amplitude of the reflected wave increase, such that the reflected wave arrives back earlier, and adds to (or augments) central systolic pressure. The aortic waveform in pulse-wave analysis was subjected to further analysis for calculation of aortic pressure augmentation (Aug), the augmentation index (AugI, calculated by dividing augmentation by pulse pressure), central blood pressure, ejection duration (duration of systolic period in milliseconds), and Buckberg's subendocardial viability ratio (SEVR, area of diastole divided by area of systole during one cardiac cycle in the aorta). The timing of the reflected wave was analyzed to estimate the aortic pulse-wave velocity. Pulse pressure is the difference between systolic and diastolic blood pressures.

The study was approved by the local ethics committee. Informed consent was obtained from each participant.

2.5. Statistical analyses

The sample size has been calculated based on subendocardial viability ratio (SEVR) according to effect size (Cohen d) using medium effect size (0.5). Statistical comparisons of clinical and biomedical parameters were performed using Stat View 6.0 for Windows. Data are given as means $\pm$ SE. Each variable's distribution characteristics including normality were assessed by the Kolmogorov–Smirnov test. Statistical analysis included the unpaired t test and ANOVA for continuous variables, and χ^2 test for non continuous variables. A p value less than 0.05 was considered statistically significant. When necessary, numerical variables were logarithmically transformed to reduce skewness, and values were expressed as arithmetic means.

Pearson's and Spearman's correlations were used as appropriate. Multiple regression and logistic regression analyses were performed for continuous and binary outcomes, respectively.