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Phenotypic characterization of normotolerant hypertensive patients

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ABSTRACT

Background: Normotolerant subjects (NGT) are considered at low risk, even if a plasma glucose value ≥155 mg/dl for the 1-hour post-load plasma glucose during an oral glucose tolerance test (OGTT) is able to identify NGT at high-risk for type-2 diabetes and subclinical organ damage. Insulin resistance (IR) contributes to the pathogenesis of impaired glucose tolerance and participates to the development of subclinical organ damage. However, it is unknown whether NGT<155 subjects are at low risk for the development of subclinical organ damage independently from other metabolic variables, such as IR/hyperinsulinemia.

Methods: From a large cohort of about 1200 uncomplicated hypertensive outpatients underwent to OGTT, we selected 645 NGT subjects, 319 men and 326 women aged 47.6±10.6. All subjects underwent standard echocardiography for measurement of left ventricular mass (LVM), and carotid ultrasonography for evaluation of intima media thickness (IMT). Finally, we estimated glomerular filtration rate (e-GFR) by using the new equation proposed by investigators in the chronic kidney disease epidemiology (CKD-EPI) collaboration.

Results: NGT<155 subjects into upper tertile of 1-h post-load insulin had a worse lipemic profile, a higher hs-CRP, creatinine, LVM, e-GFR and IMT. Comparing the NGT groups, we observed that metabolic and hemodynamic parameters of NGT<155 subjects into upper tertile of 1-h post-load insulin were similar to that observed in NGT≥155 subjects. Similarly, fasting and both 1-h and 2-h post-load insulin values were similar to that observed in NGT≥155.

Conclusions: We documented that hypertensive NGT subjects have different phenotypic patterns, particularly in their metabolic profile and in presence of subclinical organ damage.

1. Introduction

Diabetes mellitus is a powerful risk factor for cardiovascular disease associated with high morbidity and mortality rates. Diabetic patients also have an increased incidence of heart failure, which has been traditionally attributed to the development of ischemic complications and myocardial abnormalities, such as left ventricular hypertrophy (LVH) and impairment of cardiac function, that concur to define the diabetic cardiomyopathy. All these abnormalities contribute to the early appearance of diastolic dysfunction that leads to chronic heart failure, independently of other cardiovascular diseases. In addition, subjects with impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG) are characterized by an unfavorable cardiovascular risk profile [1], demonstrating that glucose metabolism worsening, tested by an oral glucose tolerance test (OGTT), is more strongly associated with both subclinical target organ damage and atherosclerotic disease.

Similarly, insulin resistance (IR) is another risk factor that is linked to the appearance and progression of cardiovascular disease, both as an independent risk factor as well as through its association with other risk factors such as obesity and hypertension [2,3]. Moreover, it is associated with left ventricular mass (LVM) increase, intima-media thickness (IMT), arterial stiffness and renal function, all independent predictors of subsequent cardiovascular events [1,4–6].

According to the molecular theory of diabetic cardiomyopathy, hyperglycemia seems to be the main pathogenetic factor, which causes abnormalities at the cardiac myocyte level, eventually leading to structural and functional abnormalities [7]. In keeping with this, we recently reported, in a large sample of newly diagnosed hypertensive patients, that normotolerant (NGT) subjects with 1-h post-load glucose ≥155 mg/dL (NGT≥155), compared with NGT with 1-h post-load glucose <155 mg/dL (NGT<155), have a higher LVM and a greater prevalence of LVH similar to that of IGT and diabetic patients [8]; in addition, they have higher IMT [9] and lower estimated glomerular filtration rate (e-GFR) [10] when compared with NGT<155. On the basis of these evidences, we suggested the usefulness to reconsider the concept that NGT subjects are a homogeneous group with a low cardiovascular risk. This recommendation has clinical relevance because emphasizes the importance of the phenotypic

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characterization in stratifying the profile of cardiovascular or cardio-metabolic risk in each subject. However, it is unknown whether NGT<155 subjects are at low risk for the development of subclinical organ damage independently from other metabolic variables, such as IR/hyperinsulinemia.

To evaluate whether cardio-metabolic factors may help to identify subjects with NGT<155 at enhanced risk for cardiovascular disease, we compared clinical characteristics, including IR/hyperinsulinemia and subclinical organ damage, in a group of newly diagnosed hypertensive subjects.

2. Materials and methods

2.1. Study population

From a large cohort of about 1200 uncomplicated hypertensive outpatients underwent to OGTT, we selected 645 NGT subjects, 319 men and 326 women aged 47.6 ± 10.6, participating to the CAtanzaro MEtabolic RIsk factors Study (CATAMERIS). All subjects were Caucasian and underwent physical examination and review of their medical history. Causes of secondary hypertension were excluded by appropriate clinical and biochemical tests. Other exclusion criteria were history or clinical evidence of coronary, valvular heart disease, congestive heart failure, hyperlipidemia, peripheral vascular disease, chronic gastrointestinal diseases associated with malabsorption, chronic pancreatitis, history of any malignant disease, history of alcohol or drug abuse, liver or kidney failure and treatments able to modify glucose metabolism. No subjects had ever been treated with antihypertensive drugs. All subjects underwent anthropometrical evaluation: weight, height and body mass index (BMI).

After 12-h fasting, a 75 g OGTT was performed with 0, 30, 60, 90 and 120 min sampling for plasma glucose and insulin. Glucose tolerance status was defined on the basis of OGTT using the World Health Organization (WHO) criteria. Insulin sensitivity was evaluated using the Matsuda index [insulin sensitivity index (ISI)], calculated as follows: 10,000/square root of [fasting glucose (mmol per liter) × fasting insulin (mU per liter)] × [mean glucose × mean insulin during OGTT]. The Matsuda index is strongly related to euglycemic hyperinsulinemic clamp that represents the gold standard test for measuring insulin sensitivity [11]. Baseline IR was estimated by HOMA-index. The Ethical Committee approved the protocol and informed written consent was obtained from all participants. All the investigations were performed in accordance with the principles of the Declaration of Helsinki.

2.2. Blood pressure measurements

Readings of clinic blood pressure (BP) were obtained in the left arm of the supine patients, after 5 min of quiet rest, with a mercury sphygmomanometer. Minimum three BP readings were taken on three separate occasions at least 2 weeks apart. Systolic and diastolic BP (SBP, DBP) were recorded at the first appearance (phase I) and the disappearance (phase V) of Korotkoff sounds. Baseline BP values were the average of the last two of the three consecutive measurements obtained at intervals of 3 min. Patients with a clinic SBP SBP >140 mmHg and/or DBP >90 mmHg were defined as hypertensive.

2.3. Laboratory determinations

All laboratory measurements were performed after at least 12 fasting hours. Plasma glucose was determined immediately by the glucose oxidase method [Glucose analyzer, Beckman Coulter, Milan; intra-assay coefficient of variation (CV) 2.2%, inter-assay CV 3.8%]. Triglyceride, total, low and high-density lipoprotein (LDL, HDL) cholesterol concentrations were measured by enzymatic methods (Roche Diagnostics GmbH, Mannheim, Germany). Serum insulin was determined in duplicate by a highly specific radioimmunoassay using two monoclonal antibodies; intra-assay CV 2.1%, inter-assay CV 2.9%. Circulating IGF-1 was obtained in duplicate using a site-specific (cross-reactivity: human insulin undetectable, intact proinsulin undetectable) and sensitive immunoradiometric assay (Nichols Advantage Kit from Nichols Institute Diagnostics, San Clemente, California, USA; intra-assay CV 5.2%, inter-assay CV 5.7%; internal reference values in healthy subjects 71–360 ng/ml).

2.4. Echocardiograms

Tracings were taken with the patient in partial left decubitus position, using a VIVID 7 Pro ultrasound machine (GE Technologies, Milwaukee, Wisconsin, USA) with an annular phased array 2.5 MHz transducer. Echocardiographic readings were made in random order by the investigator, who had no knowledge of patients' BP and other clinical data. Only frames with optimal visualization of cardiac structures were considered for reading. The mean values from at least five measurements of each parameter for each patient were computed. Having the same experienced sonographer (MS) perform all studies in a dimly lit and quiet room optimized the reproducibility of measurements. In our laboratory, the intra-observer CVs are 3.85% for posterior wall (PW) thickness, 3.70% for interventricular septal (IVS) thickness, 1.50% for left ventricular internal diameter (LVID) and 5.10% for left ventricular mass (LVM).

Tracings were recorded under two-dimensional guidance and M-mode measurements were taken at the tip of the mitral valve or just below. Measurements of IVS thickness, PW thickness and LVID were made at end-diastole and end-systole, as recommended by the American Society of Echocardiography [12]. LVM was calculated using the Devereux formula [13] and normalized by body surface area (LVMI).

2.5. Intima-media thickness measurements

Carotid ultrasonography was performed during the same echocardiographic examination, using linear probes of 7.5 to 10 MHz. Intima media thickness (IMT) was defined as the distance between the leading edge of the lumen-intima echo and the leading edge of the media adventitia echo [14]. Mean IMT was defined as the average of the IMT values of the near and far wall in the left and right carotid arteries, measured at a site free of plaque 10 to 15 mm proximal to the carotid bulb. Values are expressed in millimeters. Whenever a plaque was present, defined as a focal lesion >1.2 mm thick, measurements were performed before or after the plaque. All measurements were performed offline by a single experienced examiner who was unaware of the subjects' clinical and laboratory findings.

2.6. Renal function

Creatinine measurements were carried out by using Jaffe methodology and by the URICASE/POD (Boehringer Mannheim, Mannheim, Germany) method implemented in an auto-analyzer. Values of estimated glomerular filtration rate (e-GFR) (mL/min/1.73 m^2) were calculated by using the new equation proposed by investigators in the chronic kidney disease epidemiology (CKD-EPI) collaboration. This equation was developed from a much large cohort of patients, including both normal and CKD individuals, than the MDRD study. We preferred this equation because it is more accurate in subjects with GFR>60 mL/min/1.73 m^2, as our patients were supposed to have considering the creatinine value<1.5 mg/dL [15].

2.7. Statistical analysis

Data are expressed as mean ± SD, and comparisons among groups were made by Student's *t* test or the chi-squared test, as appropriate. Differences were assumed to be significant at $P<0.05$. All comparisons were performed using the statistical package SPSS 16.0 for Windows (SPSS Inc., Chicago, Illinois, USA).

3. Results

3.1. Study population

Subjects were divided into three tertiles on the basis of their 1-h post-load insulin, and then we compared subjects included in the first and upper tertile to better highlight the effects of hyperinsulinemia on metabolic parameters and subclinical organ damage. Demographic, clinical, and biochemical data of the study population, stratified according to 1-h post-load plasma glucose and by tertile of 1-h post-load insulin, are reported in Table 1. There were no significant differences between tertiles for gender distribution, age, BMI, fasting glucose, smokers and DBP both in NGT<155 and NGT≥155. On the contrary, subjects allocated into upper tertile of 1-h post-load insulin of both groups had higher values of fasting insulin, 2-h post-load insulin and HOMA-index in comparison with those in the first tertile; obviously, Matsuda index/ISI and IGF-1 values were significantly lower in the upper tertile when compared with that in the first tertile.

In NGT≥155 group, no significant differences between tertiles were observed for 1-h and 2-h post-load glucose, creatinine, total and LDL cholesterol, hs-CRP, LVMI, e-GFR and IMT. On the contrary, in NGT<155 group, subjects into upper tertile of insulin had a worse lipemic profile, a higher hs-CRP, creatinine, LVMI, IMT, and a lower e-GFR and IGF-1 values. Comparing the NGT groups, we observed that metabolic and hemodynamic parameters of NGT<155 subjects into upper tertile of 1-h post-load insulin were similar to that observed in NGT≥155 subjects. Similarly, fasting and both 1-h and 2-h post-load insulin values were similar to that observed in NGT≥155.

In Fig. 1 we report LVMI, IMT and e-GFR mean values stratified by tertiles of 1-h post-load insulin.