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Carotid artery stiffness is related to hyperinsulinemia and insulin-resistance in middle-aged, non-diabetic hypertensive patients

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Oral glucose tolerance test;
HOMA-index

Abstract *Background and aims:* Glycometabolic abnormalities are frequently found in hypertension and could affect the mechanical properties of carotid arteries. The aim of the study was to investigate the relationship of glucose tolerance, plasma insulin, and insulin sensitivity with carotid distensibility in middle-aged, non-diabetic hypertensive patients free of cardiac and vascular complications.
Method and results: In 93 patients with grade 1–2, uncomplicated, primary hypertension and 68 matched normotensive controls we measured plasma glucose and insulin at fast and after an oral glucose load (OGTT), calculated the HOMA-index as a marker of insulin sensitivity, and assessed distensibility of common carotid arteries by B-mode ultrasonography. Hypertensive patients were hyperinsulinemic and insulin-resistant as compared to normotensive controls. Hypertensive patients with impaired fasting glucose and/or impaired glucose tolerance had comparable distensibility of carotid arteries. Patients with decreased carotid distensibility were older and had higher body mass, fasting and post-OGTT plasma insulin, HOMA-index, and carotid IMT than the remaining patients, but no differences in glycated hemoglobin, and fasting or post-OGTT plasma glucose. Carotid coefficient of distensibility was inversely related and β-stiffness directly related with fasting and post-OGTT plasma insulin, and HOMA-index. Multivariate logistic regression showed that age and post-OGTT plasma insulin levels predicted carotid artery stiffening independent of body mass index, sex, blood pressure, and plasma glucose levels.
Conclusions: The study demonstrates that decreased insulin sensitivity and the related hyperinsulinemia but not hyperglycemia could contribute to carotid artery stiffening in middle-aged, non-diabetic hypertensive patients free of cardiovascular complications.

Introduction

Substantial epidemiological evidence indicates that subclinical atherosclerosis of the carotid arteries is associated with increased cardiovascular risk in the general population [1]. The earliest stages of atherosclerosis are characterized by subtle mechanical and structural changes of blood vessels that can be assessed non-invasively by ultrasound examination of carotid arteries [2]. Carotid artery stiffness is estimated by measurement of reproducible markers that are found to be significantly worse in patients with hypertension as compared to normotensive controls [3]. In hypertensive patients, carotid artery stiffening predicts major cardiovascular events [2] and provides important information for stratification of cardiovascular risk [4].

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Hypertension is frequently associated with type-2 diabetes mellitus [5] and insulin resistance [6] and there is evidence supporting the view that decreased insulin sensitivity and/or compensatory hyperinsulinemia increase the cardiovascular risk of hypertensive patients [7]. A significant association between stiffening of central arteries and circulating levels of glucose and insulin has been reported in previous studies conducted in patients with type-2 diabetes and glucose intolerance [8] and even in normoglycemic, normotensive offspring of diabetic parents [9]. However, the relative contribution to this association of glucose intolerance or decreased insulin sensitivity with related hyperinsulinemia is still debated [10,11]. Increased carotid artery stiffness has also been reported in association with insulin resistance in elderly hypertensive patients [12] with left ventricular hypertrophy [13]. Because of the possible relevance of the combined effects of high blood pressure and glycometabolic abnormalities on mechanical properties of carotid arteries in the early stages of hypertension, we have examined the relationship of glucose tolerance, plasma insulin and insulin sensitivity with carotid distensibility in middle-aged, non-diabetic hypertensive patients free of cardiac and vascular complications.

Methods

Study population

Ninety-three patients (48 males, 45 females; age 48 $\pm$ 13 years) with grade 1–2 primary hypertension who were consecutively referred to the university clinic, were included in a cross-sectional study. All patients were white, lived in North-East of Italy, and were representative of the hypertensive population in this area [14]. Blood pressure was measured by an automated device (Omron M6, OMRON Healthcare Co., Kyoto, Japan) after each subject had been supine for 15 min and the average of three readings was recorded [15]. Diagnosis of hypertension was established in all patients according to current guidelines [4]. Patients younger of 18 years and older than 80 years and pregnant women were excluded, together with patients with body mass index (BMI) of more than 35, diabetes, 24 h creatinine clearance (GFR) of less than 30 ml/min/1.73 m^2, use of drugs that could interfere with glucose metabolism and insulin levels, and history of acute illness, stroke, transitory ischemic attack, ischemic heart, cardiac valve, or other types of heart disease, and peripheral artery disease. In all patients causes of secondary hypertension were excluded on the basis of extensive laboratory testing [4]. Patients with hypertension-related complications were excluded by laboratory tests that included ECG, echocardiography, ultrasound examination of aorta, carotid, iliac, and femoral arteries, and 24 h urinary albumin excretion. Additional tests including treadmill exercise testing, myocardial perfusion scan, and coronary, cerebral, and iliac-femoral angiography were done when indicated.

Thirty-eight (41%) of 93 patients had never been treated with anti-hypertensive drugs. Of the remaining patients, 31 (56%) were on angiotensin-converting enzyme inhibitors or angiotensin II-receptor blockers, 28 (51%) on calcium-channel blockers, 21 (38%) on diuretics, 18 (33%) on beta-blockers, and 6 (11%) on alpha-blockers. In these patients, drugs were withdrawn for a minimum of 2 weeks before the study and all patients were closely monitored during the wash-out period. Before evaluation, patients ate a standard diet for 7 days to keep a sodium intake of 150 mmol/day that was checked by measurement of 24 h urine sodium excretion. Patients were defined as smokers if they had smoked for at least 5 years and up to 1 year before the study and smoking habit was quantified by the average number of cigarettes smoked per day. Average alcohol intake was estimated by a questionnaire as grams/day.

Sixty-eight healthy subjects served as controls. These subjects were all normotensive and were selected from the general population of the same geographic areas as the hypertensive patients after specification of inclusion criteria to avoid age and gender as potential confounding variables. Normotensive controls were not taking any regular medications and did not have any concomitant disease. The study was performed in accordance with the principles of the Declaration of Helsinki and received approval from the local Institutional Review Board. Informed consent was obtained from all patients.

Laboratory measurements

A sample of venous blood was collected in the morning after an overnight fast with the patients in sitting position. Blood was collected into silicone-treated tubes containing trisodium-citrate and plasma was immediately separated and frozen at -80 °C until assaying. Plasma glucose was assayed using the glucose-oxidase method and plasma insulin was measured by RIA. The Homeostatic Model Assessment (HOMA) index was calculated as an index of insulin sensitivity from fasting plasma glucose (mmol/l) and insulin (μU/ml) using the formula: [(glucose $\times$ insulin)/22.5]. Glucose tolerance was evaluated with the use of a 180 min oral glucose tolerance test (OGTT) and the area under the curve for plasma glucose (G-AUC) and insulin (I-AUC) concentration during the OGTT was calculated by the trapezoidal rule as described previously [16]. According to the American Diabetes Association guidelines [17], patients were classified as having impaired fasting glucose (IFG) when fasting plasma glucose was between 100 mg/dl and 125 mg/dl and impaired glucose tolerance (IGT) when plasma glucose level at 120 min of the oral glucose load was between 140 and 199 mg/dl. GFR was assessed by duplicate measurement of 24 h creatinine clearance and normalized for body surface area.

Ultrasound assessment of carotid artery stiffness and intima-media thickness

Carotid arteries were examined with a duplex scanner (Toshiba Aplio CV, Japan) using a 7 MHz linear array transducer as described previously [18]. The same trained