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Relationships of plasma lipoprotein(a) levels with insulin resistance in hypertensive patients

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ABSTRACT

Background. Lipoprotein(a) [Lp(a)] is an emergent cardiovascular risk factor that is related to the presence and severity of cardiovascular damage in hypertensive patients. In these patients, insulin resistance is frequently detected but its relationship with plasma Lp(a) is not clear. The aim of this study was to examine the relationships between Lp(a) and variables of glucose metabolism in hypertension.

Methods. In 527 consecutive, non-diabetic, middle-aged hypertensive patients we measured anthropometric indexes, 24-hour creatinine clearance, lipid profile including Lp (a) levels, fasting glucose, insulin and C-peptide, and calculated the Homeostatic Model Assessment (HOMA) index.

Results. Lp(a) levels were significantly and progressively lower with increasing HOMA-index values. Lp(a) was inversely related to fasting glucose, insulin, and C-peptide, HOMA-index, and creatinine clearance and directly related to LDL-cholesterol. Multiple regression analysis adjusted for age, sex, body mass index, blood pressure, smoking habit, alcohol intake, renal function, lipid profile, history of cardiovascular events, and drug use showed that HOMA-index and creatinine clearance were inversely and independently associated to Lp(a) levels.

Conclusions. Insulin resistance and higher fasting insulin levels are associated with lower plasma Lp(a) in hypertensive patients. This association might be relevant in the assessment of cardiovascular risk in these patients.

1. Introduction

Lipoprotein(a) [Lp(a)] is a heterogeneous lipoprotein that shares many properties with low-density lipoproteins (LDL), but is metabolically distinct from LDL because it contains a structurally unique protein, apolipoprotein(a) [apo(a)], the size of which is genetically determined and highly variable [1]. It's commonly accepted that plasma Lp(a) levels are largely determined on a genetic basis and remain relatively stable over an individual's lifetime [2]. Lp(a) is synthesized by the liver and partly disposed of by the kidneys [2,3]. Although the relevance of this lipoprotein as a cardiovascular risk factor is debated, case-control and prospective trials have reported a significant relationship of Lp(a) levels with cardiovascular

Abbreviations: Lp(a), lipoprotein(a); LDL, low-density lipoproteins; Apo(a), apolipoprotein(a); BMI, body mass index; TIA, transitory ischemic attack; ELISA, enzyme linked immunosorbent assay; HOMA, homeostatic model assessment; G-AUC, area under the curve for glucose response to oral glucose test; I-AUC, area under the curve for insulin response to oral glucose test; LSD, least significance difference; VIF, variance inflation factor; CVD, cardiovascular disease; CRP, C-reactive protein; HDL, high-density lipoproteins; CVE, cardiovascular events; ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blockers.

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events [4–6] and presence and severity of clinical and subclinical organ damage in hypertensive patients [7,8].

Insulin resistance is frequent in patients with hypertension [9] and there is substantial evidence supporting the view that insulin resistance and/or compensatory hyperinsulinemia contribute to the cardiovascular risk in these patients [10]. Past investigations have suggested an inverse relationship of Lp(a) levels with circulating insulin and insulin resistance in diabetic and non-diabetic subjects [11–13], but so far no studies have addressed this relationship in hypertension. The aim of this study was therefore to investigate the relationships between plasma Lp(a) levels and variables of glucose metabolism and insulin sensitivity in a large group of patients with primary hypertension.

2. Methods

2.1. Study population

In a cross-sectional study, we included 527 hypertensive patients who were consecutively referred to the hypertension unit of our university clinic. Blood pressure was measured by an automated device (Omron M6; Omron Healthcare, Kyoto, Japan) after each subject had been supine for 15 min, and the average of 3 readings obtained in 5 min was recorded. Increased blood pressure (systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg) was detected at least twice on 2 different occasions and subsequently confirmed on at least 2 more visits during the 4 weeks that followed. The patients seen at our clinic include individuals with all grades of hypertension who live in the northeast of Italy and are representative of the hypertensive population of this geographical area [14]. Exclusion criteria were: age of less than 18 or more than 80 years; pregnancy; body mass index (BMI) of more than 35; secondary forms of hypertension which have been excluded by exhaustive laboratory testing as described previously [15]; diabetes mellitus; history of major cardiovascular events in the last 12 months; renal failure with 24-hour creatinine clearance of less than 60 ml/min/1.73 m^2 body surface area; and presence of other diseases or treatments that might interfere with glucose metabolism. Prevalence of hypertension-related cardiovascular events (coronary artery disease, stroke or transitory ischemic attack, atrial fibrillation, peripheral arterial disease) and, history of menopause or use of hormonal replacement therapy were assessed in all study patients by analysis of clinical records, clinical examination, and laboratory tests that included electrocardiography, echocardiography, and ultrasound examination of carotid, iliac, and femoral arteries. Additional laboratory tests, including exercise testing, myocardial perfusion scan, and coronary, cerebral, and iliac-femoral angiography, and cerebral computerized tomography or magnetic resonance imaging were performed when appropriate.

A venous blood sample was drawn without venous stasis between 8:00 and 9:00 AM after an overnight fast. Plasma concentrations of Lp(a) were determined by the Macra® Lp(a) Enzyme Linked Immunosorbent Assay (ELISA) kit (Trinity Biotech PLC, Bray, Ireland) a method that is highly correlated with the reference method used by the WHO for the standardization of the lipoprotein(a) assay [16]. The intra- and inter-assay coefficients of variation for Lp(a) measurements were from 2 to 7% and from 6 to 9%, respectively. Plasma glucose was assayed by the glucose-oxidase method. Plasma insulin and C-peptide levels were measured by radioimmunoassay. 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 × insulin)/22.5]. In all patients, an oral glucose tolerance test was performed with a standard load (75 g of glucose) and measurement of plasma glucose and insulin at 30, 60, 90, 120, and 180 min. The area under the curve for glucose (G-AUC) and insulin (I-AUC) response to the glucose load was calculated by the trapezoidal rule [17]. Cardiovascular risk was assessed by the Framingham score [18] and presence of the metabolic syndrome by the National Cholesterol Education Program-Adult Treatment Panel III criteria [19]. The study was approved by the local institutional review board, and informed consent was obtained from all patients.

2.2. Statistical analysis

To investigate the relationship between plasma Lp(a) levels and insulin sensitivity the population was divided according to quartiles of the HOMA-index. The Kolmogorov–Smirnov test was used to assess normality of distribution of continuous variables. Normally distributed variables are presented as mean and standard deviation and variables with skewed distribution as median and interquartile ranges. One-way analysis of variance with post-hoc t-test with Bonferroni correction for multiple comparisons was used to compare normally distributed variables. The Mann–Whitney test was used for comparisons of variables with skewed distribution between two independent groups and the Kruskal–Wallis test for multiple comparisons with post-hoc Mann–Whitney tests for adjustment (alpha criterion: 0.05/number of comparisons). Differences between group frequencies were assessed with the Pearson χ^2 test. Relationships between continuously distributed values were examined by the Spearman's correlation coefficient (ρ). In multivariate regression analysis, covariates were selected based upon their relationship with either Lp(a) levels or HOMA-index on univariate analysis. Variables with skewed distribution were normalized by log transformation and dichotomous variables were converted to dummy variables. In different multiple regression models, sensitivity analysis was performed after exclusion of patients taking antihypertensive agents, lipid-lowering drugs, and aspirin. Multicollinearity was assessed by calculating for each variable in the model a variance inflation factor (VIF). A P value <5% was considered to indicate statistical significance. Data analyses were done with the software Statistica® 8.0 (StatSoft, Tulsa, OK).

3. Results

At the time of the study, 255 (48%) of the 527 hypertensive patients were untreated and 272 (52%) were taking antihypertensive agents, 100 (19%) of whom were taking one drug,