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Original article

The relationship of angiographically defined coronary artery disease with insulin sensitivity and secretion in subjects with different glucose tolerance

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ABSTRACT

Background: Most studies pay attention to the relationship between insulin resistance and coronary artery disease (CAD) in patients with abnormal glucose tolerance. But few studies have focused on the role of insulin secretion. The aim of this study was to investigate the association between insulin sensitivity, insulin secretion, and CAD in patients with different glucose metabolic status.

Methods: 316 newly diagnosed patients with different glucose metabolic status (according to the results of oral glucose tolerance test) were included in this study. The homeostasis model assessment of insulin resistance ($HOMA_{IR}$) and Matsuda index were used to estimate insulin sensitivity; the insulin secretion was assessed using the HOMA-β, insulinogenic index, area under the curve – insulin/glucose (AUC-Ins/Glu). CAD was defined as ≥50% of luminal stenosis in at least one major coronary vessel through coronary angiography.

Results: Univariate analysis revealed that $HOMA_{IR}$ and Matsuda index were significantly different between the CAD group and the non-CAD group in all patients. Logistic analysis revealed that Matsuda index was an independent risk factor for the presence of CAD in all patients, and $HOMA_{IR}$ was an independent risk factor for the presence of CAD in normal glucose tolerance patients. Moreover, in the CAD group compared to the non-CAD group, there was no significant difference in the HOMA-β, insulinogenic index, and AUC-Ins/Glu in all patients.

Conclusions: Insulin resistance is closely related to the presence of CAD in newly diagnosed patients with different glucose metabolic status. The insulin secretion may not be closely related to the presence of CAD.

Introduction

In the *Euro Heart Survey* Study [1], a total of 4196 patients with coronary heart disease combined with glucose metabolism disorders (including impaired glucose regulation and diabetes mellitus) constituted almost 67% of the subjects in the study. However, it is more serious in China. The total prevalence of abnormal glucose metabolism was 76.9% in in-patients with coronary artery disease (CAD) according to the results of the *China Heart Survey* [2]. It is well-known that diabetes mellitus (DM) is one of the classic risk factors for CAD. It is also well known that insulin resistance and (or) hyperinsulinemia is one of the major candidates that contribute to the development of atherosclerosis in patients with different glucose tolerance [3,4]. Then does the insulin secretion play an important role in coronary atherosclerosis as well as insulin resistance? But few studies have focused on the role of insulin secretion during the development of atherosclerosis with different glucose tolerance [5–7]. Fujiwara et al. [5] reported that the elevation of plasma insulin concentrations in both the sum and the early phase to an oral glucose load were significantly higher in the CAD group than in the normal group with different glucose tolerance. Therefore our study chose several indices of insulin sensitivity and insulin secretion from oral glucose tolerance test (OGTT) to investigate the relationship between CAD and insulin sensitivity as well as insulin secretion in patients with different glucose tolerance.

Materials and methods

Subjects

A total of 493 Chinese patients with known or suspected CAD were submitted to coronary angiography at Shanghai East Hospital

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between February 2009 and October 2009. "Suspected CAD" means that a patient's symptoms or other clinical characteristics suggest a high likelihood for significant CAD and its related adverse outcomes but that clinical evidence has not yet been documented as defined CAD [8]. A total of 39 patients were excluded because of severe congestive heart failure (New York Heart Association class III–IV), liver dysfunction (aspartate aminotransferase and/or alanine aminotransferase > 1.5 × upper limit of normal), and renal dysfunction (creatinine clearance < 60 ml/min, creatinine clearance was estimated from serum creatinine concentration using the Cockcroft–Gault formula). Except for 138 patients having a history of type 2 DM, the remaining 316 patients were enrolled and underwent 75 g OGTT. According to the results of OGTT (1999 WHO criteria), the patients were divided into three groups: normal glucose tolerance (NGT), impaired glucose regulation (IGR, including impaired glucose tolerance and impaired fasting glucose), type 2 DM. No patient enrolled in this study was diagnosed with type 1 DM. The study protocol was approved by the ethics review board of Tongji University. Written informed consent was obtained from all participants, and all the procedures were done in accordance with the Declaration of Helsinki and relevant policies in China.

Biochemical methods

All patients were evaluated considering classic risk factors for CAD throughout a medical-oriented questionnaire, physical examination, and laboratory assessment. Clinical data included: age, gender, body mass index (BMI), waist circumference, hypertension [systolic blood pressure (SBP)/diastolic blood pressure (DBP) ≥ 140/90 mmHg or history of hypertension], dyslipidemia [total cholesterol (TC) ≥ 5.17 mmol/l; triglycerides (TG) ≥ 1.70 mmol/l; low density lipoprotein cholesterol (LDL-C) ≥ 3.10 mmol/l; high density lipoprotein cholesterol (HDL-C) < 1.03 mmol/l or history of dyslipidemia], and smoker ("yes" or "no", yes smoker defined as having smoked more than three cigarettes a day for at least one year), etc. Blood samples were collected at 0 min, 30 min, 60 min, 120 min, and 180 min for plasma glucose (Glu0, Glu30, Glu60, Glu120, Glu180), insulin (Ins0, Ins30, Ins60, Ins120, Ins180), and C-peptide measurements (C-pep0, C-pep30, C-pep60, C-pep120, C-pep180) in OGTT. Insulin and C-peptide measurements were analyzed by radio-immuno-assay (RIA). Glycosylated hemoglobin (HbA_1c) was analyzed by high performance liquid chromatography (HPLC).

Coronary angiography

Coronary angiography was performed via the radial or femoral artery. All the angiographies were interpreted by the consensus of two independent observers blinded to the results of analysis. The extent of lumen narrowing was measured and recorded as a percentage loss of lumen diameter in the narrowing area of the epicardial coronary artery compared to the proximal normal coronary artery. CAD was defined as ≥50% of luminal stenosis in at least one major coronary vessel. Based on clinical manifestations, laboratory tests, and coronary angiography, 61 patients were diagnosed with acute myocardial infarction, 48 patients were diagnosed with stable angina, 102 patients were diagnosed with unstable angina, and 105 patients were diagnosed with no CAD [those with mild stenosis (<50%) in their coronary arteries were considered to be non-CAD].

Insulin sensitivity indices

The following two OGTT-based indices of insulin sensitivity were studied: (1) homeostasis model assessment of insulin resistance ($HOMA_{IR}$) = Ins0 × Glu0/22.5; (2) Matsuda index [9] = 10,000/(Glu0 × Ins0 × mean glucose × mean insulin)$^{0.5}$.

Insulin secretion indices

The following three OGTT-based measures of insulin secretion were studied: (1) HOMA-β; (2) insulinogenic index; (3) ratio of the total area-under-the-insulin-curve to the total area-under-the-glucose-curve (AUC-Ins/Glu). Insulin secretion index was calculated as follows: HOMA-β = 20 × Ins0/(Glu0 − 3.5); insulinogenic index = (Ins30 − Ins0)/(Glu30 − Glu0); AUC-Ins/Glu was calculated using the trapezoidal rule applied to the insulin and glucose curves, AUC-Ins/Glu = AUC-Ins/AUC-Glu = (0.5 × Ins0 + Ins30 + Ins60 + Ins120 + 0.5 × Ins180)/(0.5 × Glu0 + Glu30 + Glu60 + Glu120 + 0.5 × Glu180) [9,10].

Statistical analysis

Data are presented as mean ± SD, median (minimum–maximum), or as percentages, as appropriate. Quantitative data are presented as mean ± standard deviation or median (minimum–maximum), and compared by *t*-test or one-way ANOVA or Mann–Whitney *U* test between groups, whichever was appropriate. Categorical data were expressed as rate and compared by Chi-square test. Spearman's correlation analysis was conducted for the variables with the trend of correlation. The forward conditional method was used in multivariate logistic regression models. Statistical analyses were performed using the SPSS package (SPSS for Windows, version 13.0; IBM, Armonk, NY, USA). A *p*-value < 0.05 was considered statistically significant.

Results

Compared with the non-CAD group in NGT patients, the CAD group showed statistically significant differences in hypertension ($p = 0.018$), waist circumference ($p = 0.001$), SBP ($p = 0.026$), fasting insulin ($p = 0.005$), $HOMA_{IR}$ ($p = 0.002$), Matsuda index ($p = 0.004$), LDL-C ($p = 0.002$), and hs-CRP ($p = 0.032$). Compared with the non-CAD group in newly diagnosed IGR patients, the CAD group showed statistically significant differences in hypertension ($p = 0.019$), smokers ($p = 0.031$), BMI ($p = 0.040$), waist circumference ($p = 0.016$), SBP ($p = 0.015$), fasting insulin ($p = 0.041$), $HOMA_{IR}$ ($p = 0.034$), Matsuda index ($p = 0.006$), and hs-CRP ($p = 0.007$). Compared with the non-CAD group in newly diagnosed DM patients, the CAD group showed statistically significant differences in hypertension ($p = 0.036$), smokers ($p = 0.011$), $HOMA_{IR}$ ($p = 0.048$), Matsuda index ($p = 0.007$), TG ($p = 0.003$), LDL-C ($p = 0.001$), and hs-CRP ($p = 0.028$) (Table 1).

When the levels of plasma glucose, insulin, and C-peptide were compared according to OGTT in newly diagnosed NGT, IGR, and DM groups, there were significant or no significant differences in the results between the CAD and non-CAD groups for AUC-Glu ($p = 0.007$), AUC-Ins ($p = 0.121$), and AUC-Cp (AUC-Cp = 0.5 × C-pep0 + C-pep30 + C-pep60 + C-pep120 + 0.5 × C-pep180, $p = 0.223$) in NGT patients. There were no significant differences between the CAD and non-CAD groups for AUC-Glu ($p = 0.163$), AUC-Ins ($p = 0.061$), and AUC-Cp ($p = 0.452$) in newly diagnosed IGR patients. Comparing results between the CAD and non-CAD groups, there were no significant differences for AUC-Glu ($p = 0.438$), AUC-Ins ($p = 0.073$), and AUC-Cp ($p = 0.054$) in newly diagnosed DM patients (Fig. 1).

After adjustment for gender, age, BMI, DBP, fasting glucose, HbA_1c, TC, TG, and HDL-C, multivariate logistic regression analysis showed that smoking (OR 2.537 95%CI 1.056–6.093), waist circumference (OR 1.053 95%CI 1.010–1.098), SBP (OR 1.033 95%CI 1.008–1.058), $HOMA_{IR}$ (OR 2.221 95%CI 1.166–4.231), and LDL-C