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Elevated glycated albumin and reduced endogenous secretory receptor for advanced glycation endproducts levels in serum predict major adverse cardio-cerebral events in patients with type 2 diabetes and stable coronary artery disease☆,☆☆

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ABSTRACT

Background and aim: Glycated albumin (GA) and the endogenous secretory receptor for advanced glycation endproducts (esRAGE) may modulate risk related to atherosclerosis. We tested the hypothesis that elevated GA and reduced esRAGE in serum are associated with adverse clinical outcomes in patients with type 2 diabetes and stable coronary artery disease (CAD).

Methods: We determined GA and esRAGE serum levels in 576 consecutive patients with type 2 diabetes and stable CAD undergoing sirolimus-eluting stent (SES)-PCI. The primary endpoint was the incidence of major adverse cardio-cerebral events (MACCE) including cardiac death, non-fatal myocardial infarction, and non-fatal stroke during a 2-year follow-up. The secondary endpoint was the occurrence of clinically driven repeat revascularization during a 2-year follow-up. The prognostic value of GA and esRAGE was determined with the Cox-proportional hazard model after adjustment for covariates.

Results: A total 40 patients (6.9%) experienced MACCE, and 108 (18.8%) patients underwent repeat coronary revascularization during the follow-up. Serum GA (HR = 1.22, 95% CI 1.16–1.28; HR = 1.15, 95% CI 1.11–1.19, respectively; for both $p < 0.001$) and esRAGE (HR = 0.60, 95% CI 0.40–0.87; HR = 0.75, 95% CI 0.61–0.92, respectively; for both $p < 0.01$) levels remained independent predictors of the primary and secondary endpoints after adjustment for possible confounders.

Conclusions: Serum GA and esRAGE are novel predictors of long-term clinical outcomes in patients with type 2 diabetes and stable CAD. Increased serum GA and decreased esRAGE are associated with a poor prognosis in such patients.

1. Introduction

In type 2 diabetes mellitus, hyperglycemia induces non-enzymatic glycation of proteins to form Amadori products, then undergoing further complex reactions leading to the formation of advanced glycation endproducts (AGEs) [1]. Glycated albumin (GA) – a predominant early Amadori-type glycation product – increases the expression of inflammatory cytokines and adhesion molecules, stimulates vascular smooth muscle cell growth, and promotes atherogenesis [2]. The main receptor for AGEs, RAGE – a member of the immunoglobulin superfamily of transmembrane cell surface molecules – binds a number of ligands, including AGEs [3]. Its endogenous secretory type (esRAGE) acts as a decoy for RAGE ligand without evoking a signaling cascade [4]. Both animal experiments and clinical studies have demonstrated that interaction between AGEs and RAGE alters gene expression as well as cell migration and proliferation, and plays an important role in the development and progression of diabetic micro- and macro-vascular complications [5–7]. Elevated GA and reduced esRAGE levels in serum have been frequently shown to be associated with the severity of coronary artery disease (CAD) and plaque progression, as well as with the occurrence of contrast-induced acute kidney injury and restenosis

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after percutaneous coronary intervention (PCI) in patients with type 2 diabetes [8–11]. However, the impact of these changes in AGEs on long-term prognosis in diabetic patients with CAD remains unclear. In the present study, we prospectively investigated whether serum elevated GA and reduced esRAGE levels are associated with the clinical outcomes during a 2-year follow-up after sirolimus-eluting stent (SES)-PCI in a large cohort of patients with type 2 diabetes and stable CAD.

2. Methods

2.1. Patient population

We screened a total of 1512 patients with type 2 diabetes undergoing PCI between January 2008 and June 2010 in the Shanghai Rui Jin Hospital PCI Outcomes Program. This program utilizes clinical and angiographic information for various cardiovascular diseases to estimate risk-adjusted outcomes. Data on patient demographics, clinical and angiographic features, and in-hospital management were collected retrospectively, whereas clinical outcomes during follow-up were identified prospectively. Because previous studies had shown that acute glycometabolic derangement was common in patients presenting acute coronary syndromes [12], and that plasma esRAGE was markedly affected by the presence of chronic kidney disease [13], for the purpose of this study and to avoid possible confounding variables, we excluded 474 patients with an acute coronary syndrome and 38 patients with markedly reduced renal function (estimated glomerular filtration rate [eGFR] <30 mL/min by the abbreviated MDRD equation — see below). We also excluded patients with major complications including death, acute myocardial infarction, or urgent target vessel revascularization (TVR) within one week after the procedure (n = 3), and those with previous history of coronary artery revascularization (n = 62), severe left ventricular dysfunction (ejection fraction <30%) (n = 9), or serious life-threatening disease implying an expected lifespan of <12 months (n = 3). One patient with type 1 diabetes was excluded by peptide C measurements. At the end of this selection, 625 patients with stable CAD were eligible to the study.

The diagnosis of type 2 diabetes was made according to the criteria of the American Diabetes Association: glycosylated hemoglobin (HbA1c) ≥6.5%, or fasting plasma glucose concentration ≥7.0 mmol/L, or 2-h postprandial glucose concentration ≥11.1 mmol/L, or a random plasma glucose ≥11.1 mmol/L in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis [14]. Stable CAD was defined according to the criteria recommended by the American College of Cardiology/American Heart Association [15]. Coronary angiography and interventional procedures were performed through the femoral or radial approach at the operator's discretion with implantation of SES. Quantitative coronary angiography (QCA) analysis was performed using the Cardiovascular Measurement System (QCA-CMS version 3.0, Medis, Nuenen, the Netherlands) by two interventional cardiologists blinded to the study protocol. A severity index was defined as the average of the most severe stenosis in the left main, left anterior descending, left circumflex, and right coronary arteries [16]. After the procedure, all patients received dual antiplatelet therapy with aspirin and clopidogrel for at least 12 months, and intensive medications (i.e., β-blockers, angiotensin converting enzyme inhibitors and statins) if not contraindicated. Written informed consent was obtained in 606 patients, and follow-up information was complete for 576 patients (95%) (Online Supplement Fig. 1). The protocol was approved by the Ethics Committee of the Shanghai Jiao Tong University School of Medicine, and all patients gave written informed consent. The trial was registered at ClinicalTrials.gov — identifier NCT02089360.

2.2. Biochemical investigations

Peripheral venous blood was collected on the day of angiography after an overnight fasting in all patients. Serum levels of fasting blood glucose, creatinine, total cholesterol, low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides were measured with standard laboratory techniques on a Hitachi 912 Analyzer (Roche Diagnostics, Germany). Two-h post-prandial glucose was also obtained just after a meal in all subjects. The abbreviated MDRD equation was used to calculate eGFR, where eGFR (mL/min) = 186 × (creatinine / 88.4) − 1.154 × (age) − 0.203 × (0.742 for female). Serum GA concentration was assayed with an improved bromocresol purple method using the Lucia TM glycated albumin-L assay kit (Asahi Kasel Pharma, Tokyo, Japan) with a linear range of 3.2%–68.1% and a maximum inter-assay coefficient of variation (CV) <3.0% [8,9,11]. Serum levels of esRAGE were measured by a commercial enzyme-linked immunosorbent assay (ELISA) kit (Phoenix Pharmaceuticals, Burlingame, CA, USA) as described previously, with a linear range of detection of 0.05–3.2 ng/L and an intra-assay CV of <10% [8–11]. Blood concentration of glycosylated hemoglobin (HbA1c) was assayed using ion-exchange high performance liquid chromatography with a Bio-Rad Variant Hemoglobin Testing System (Bio-Rad Laboratories, Hercules, CA, USA). Serum levels of high sensitivity C-reactive protein (hsCRP) were determined using a high-sensitivity ELISA kit (Biocheck Laboratories, Toledo, OH, USA).

2.3. Follow-up and study endpoints

After discharge, all patients were routinely followed-up every 3 months in a dedicated outpatient clinic or by telephone contact with either patients themselves or their relatives, and were advised to receive repeat angiography 12 months after PCI procedure, especially for those with recurrent ischemic symptoms.

The primary endpoint was a composite of major adverse cardiac and cerebrovascular events (MACCE) including cardiac death, non-fatal myocardial infarction, and non-fatal stroke during a 2-year follow-up. These hard outcome components were hypothesized to accurately reflect the prognostic significance of GA and esRAGE. All MACCE were reviewed and finally adjudicated by 2 experienced interventional cardiologists to guarantee rigorous data quality. Cardiac death was considered as any death with a demonstrable cardiac cause or any death that was not clearly attributable to a non-cardiac cause. Non-fatal myocardial infarction was defined as an episode of symptoms suspected for myocardial ischemia with electrocardiographic changes and a rise of biochemical markers suggesting myocardial necrosis. Non-fatal stroke was defined as the development of disabling neurological symptoms and objective findings confirmed by a neurologist and by imaging techniques.

The secondary endpoint was the occurrence of clinically driven repeat revascularization during a 2-year follow-up, including any clinically driven target or non-target vessel reintervention by either PCI or coronary artery bypass grafting (CABG). In-stent restenosis (ISR) was defined as the recurrence of luminal diameter stenosis of >50% within the stent or 5-mm proximal or distal segments adjacent to the stent at follow-up angiography. Atherosclerotic lesion progression was assessed at non-PCI intervened vessels, defined as the occurrence of at least one of the following criteria: (1) ≥10% diameter reduction of a pre-existing stenosis ≥50%; (2) ≥30% diameter reduction of a stenosis <50%; (3) - progression of any stenosis to total occlusion, or (4) development of a new stenosis ≥30% in a previously normal segment [10]. Definite and probable stent thrombosis was defined by Academic Research Consortium (ARC) [17].

2.4. Statistical analysis

We did not perform a formal a priori sample size estimate, due to the exploratory nature of the study. According to the final actual sample size achieved (576 patients), the corresponding power level calculated with NCSS-PASS versions 11.0 statistical software for Windows XP (Dawson edition; Kaysville, UT) was 88% and 81% for GA and esRAGE, respectively.

Categorical variables are summarized as frequencies and percentages, and were compared by the Chi-square test. Continuous variables are expressed as mean ± SD, and were compared using the one-way ANOVA. The associations of demographic characteristics, cardiovascular risk factors, severity of CAD, and use of medications with serum GA and esRAGE levels were quantified by means of the non-parametric Kruskal–Wallis test. Associations of GA and esRAGE with continuous variables, including blood lipids, systolic blood pressure, diastolic blood pressure, serum creatinine, fasting and 2-h postprandial serum glucose, GA, HbA1c, and hsCRP were analyzed by the Spearman's rank correlation test. The relation between serum GA and esRAGE levels and primary and secondary endpoints during the follow-up was evaluated with the Kaplan–Meier method with log-rank test. Prognostic variables for clinical outcomes were determined using univariable or multivariable Cox proportional hazards regression models. All variables at univariable analyses were chosen to enter the multivariable logistic regression analysis model. Significance tests were two-tailed, and probability values <0.05 were considered statistically significant. All statistical procedures were carried out with the SPSS versions 13.0 statistical software for Windows (SPSS, Inc., Chicago, IL, USA).

3. Results

3.1. Clinical characteristics of patients and outcomes

During a mean follow-up period of 2 years (range: 1.8 to 2.4 years), 40 patients (6.9%) experienced a MACCE, including cardiac death in 21 patients (3.6%), non-fatal acute myocardial infarction in 6 (1.0%), and non-fatal stroke in 13 (2.3%). One-hundred and eight patients (18.8%) underwent repeat coronary revascularization due to in-stent restenosis (n = 62; 57.4%), atherosclerotic lesion progression (n = 43; 39.8%), and definite or probable stent thrombosis (n = 3; 2.8%).

Patients experiencing a primary and/or secondary endpoint (n = 141, 24.5%) did not differ from those without with respect to demographic characteristics, cardiovascular risk factors, serum levels of creatinine, fasting and 2-h post-prandial glucose, HbA1c, and treatment of diabetes. Serum levels of GA (24.9 ± 3.6% vs 19.0 ± 4.0%) and hsCRP (14.5 ± 10.3 mg/L vs 9.7 ± 8.4 mg/L) were all significantly higher, and conversely esRAGE levels lower (0.17 ± 0.10 ng/mL vs 0.23 ± 0.14 ng/mL) in patients with study endpoints compared with those without (for all such comparisons, $p < 0.001$). The duration of diabetes was also longer (8.4 ± 7.2 years vs 6.8 ± 5.9 years, $p = 0.009$) and 3-vessel CAD more common (44.7% vs 26.7%, $p < 0.001$) in patients with study endpoints than in those without (Table 1).