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Impact of elevated serum glycated albumin levels on contrast-induced acute kidney injury in diabetic patients with moderate to severe renal insufficiency undergoing coronary angiography

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ABSTRACT

Background: Glycated albumin (GA) has been shown to be a better indicator than glycosylated hemoglobin A1c (HbA1c) in terms of severity of renal impairment in patients with type 2 diabetes mellitus (T2DM). This study aimed to determine whether elevated serum GA levels are associated with an increased risk for contrast-induced acute kidney injury (CI-AKI) and worse clinical outcome in patients with T2DM and at least moderate renal insufficiency (RI) undergoing coronary angiography.

Methods: Serum levels of fasting blood glucose (FBG), HbA1c and GA were measured in 1030 patients with T2DM and moderate to severe RI (eGFR 15–59 mL/min/1.73 m^2). CI-AKI was defined as ≥25% increase in serum creatinine within 72 h after the procedure. Receiver-operating characteristic curve was constructed to assess the predictive value of GA, HbA1c and FBG for CI-AKI. Multivariable logistic regression model was developed to identify risk factors for CI-AKI, and Kaplan–Meier curve analysis was used to compare the rates of dialysis and major adverse cardiac events (MACE) during one-year follow-up.

Results: The overall rate of CI-AKI was 11.1%. GA was significantly higher in patients with CI-AKI than in those without, and correlated positively with changes of renal function after the procedure. After adjusting for age, sex, left ventricular ejection fraction, multi-vessel disease, type and volume of contrast media, FBG, and HbA1c, GA remained an independent risk factor for CI-AKI. GA≥21% was associated with increased rates of dialysis and MACE during one-year follow-up in patients with or without CI-AKI.

Conclusions: Increased GA level serves as a valuable risk factor for CI-AKI and indicates poor one-year clinical outcome in patients with T2DM and moderate to severe RI.

1. Introduction

Contrast-induced acute kidney injury (CI-AKI) denotes an acute decline in renal function after administration of iodinated contrast media (CM) in the absence of an alternative cause [1], and is the third common cause of hospital acquired acute renal failure, associated with increased in-hospital and one-year mortality [2–4]. Despite low occurrence in general population without risk factors (<5%), CI-AKI increases dramatically among those with advanced age, diabetes, chronic renal insufficiency (RI), congestive heart failure, hypovolemia, and use of nephrotoxic drugs or excessive CM volume [5–10].

Several studies demonstrated a close relationship between the pre-procedural blood glucose and the occurrence of CI-AKI [11,12], and patients with increased glycosylated hemoglobin A1c (HbA1c) levels being at high risk for renal dysfunction after CM exposure [13]. Recently, glycated albumin (GA), one of the amadori-type early glycation proteins, has been considered as an alternative marker for reflecting glycemic control over a retrospective period [14,15]. It correlates closely with and is approximately three times greater than HbA1c [15,16]. Furthermore, GA was proved to be a better indicator than HbA1c in terms of severity of coronary artery disease and renal impairment in patients with type 2 diabetes mellitus (T2DM) [17–20]. Inhibition of GA formation could reduce structural, functional and cell biological abnormalities in the kidney microvasculature [21,22]. These observations suggest that GA may be an independent and potent mediator contributory to renal damage in diabetes. However, it is not clear whether GA is related to the occurrence of acute kidney injury and prognosis in diabetic patients with renal impairment after CM exposure.

In this study, we sought to examine the association between serum GA levels and the risk of subsequent CI-AKI among patients with T2DM and moderate to severe RI. Major adverse cardiac events (MACE) during one-year follow-up were also recorded to evaluate

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the impact of GA on clinical outcome in these patients with or without CI-AKI.

2. Methods

2.1. Study population

A total of 1571 patients with T2DM and moderate to severe RI undergoing coronary angiography/intervention recruited from the database of Shanghai Rui Jin Hospital Percutaneous Coronary Intervention (PCI) Outcomes Program between July 2007 and February 2010 were screened. This program utilizes clinical and angiographic information for various cardiovascular diseases to estimate risk-adjusted outcomes. Data on demographics, clinical and angiographic features, and in-hospital management were collected retrospectively, whereas clinical outcomes during follow-up were identified prospectively. The diagnosis of T2DM was made according to the criteria of American Diabetes Association (FBG level ≥ 7.0 mmol/L [126 mg/dL] and/or 2 h postprandial glucose level ≥ 11.1 mmol/L [200 mg/dL], or receiving anti-diabetic medications or parenteral insulin treatment) [23]. Moderate to severe RI was defined as an estimated glomerular filtration rate (eGFR) between 15 and 59 mL/min/1.73 m^2 calculated by Modification of Diet in Renal Disease (MDRD) equation [24]. Hypertension was defined as a blood pressure of at least 140/90 mm Hg or the use of antihypertensive drugs. Dyslipidemia was diagnosed according to the National Cholesterol Education Program (ATP III) [25]. Exclusion criteria were the history of allergy to iodinated CM ($n = 7$), NYHA class IV ($n = 12$), use of CM within prior 7 days ($n = 3$), serum creatinine (SCr) > 3.0 mg/dL (265.2 μmol/L) ($n = 5$), acute coronary syndrome within 7 days ($n = 124$), administration of theophylline or fenoldopam ($n = 8$) and severe renal artery stenosis (angiographic unilateral stenosis > 70% or bilateral stenosis > 50%) ($n = 126$). Taking into account the impact of hemoglobin and serum albumin on HbA1c and GA [26,27], we further excluded patients with anemia (hemoglobin < 120 g/L for male and < 110 g/L for female) ($n = 221$) and disorders of albumin metabolism including nephrotic syndrome ($n = 13$), thyroid dysfunction (hyperthyroidism or hypothyroidism) ($n = 20$) and liver cirrhosis ($n = 2$). The remaining 1030 eligible patients were enrolled for analysis.

The study protocol was approved by the hospital Ethics Committee, and written informed consent was obtained from all participants.

2.2. Angiography and medications

Coronary angiographic procedures were performed through femoral or radial approach by experienced interventional cardiologists as described previously [19,28]. Patients were assigned to intra-arterial administration of Iodixanol-320 (Visipaque, GE Healthcare, Munich, Germany) or Iopamidol-370 (Iopamiro, Bracco Diagnostics Inc., Milan, Italy) using a computer-generated random-allocation system. Hydration with intravenous normal saline (1.0–1.5 mL/kg/h) was commenced 2–4 h before the procedure until 6 h afterwards. Intravenous diuretics and nephrotoxic drugs such as metformin were withdrawn 72 h before the procedure. According to the clinical standards of care, all eligible patients received aspirin (100 mg/d) and clopidogrel (150 mg/d) for at least 3 days before angiography, and dual antiplatelet therapy continued for at least 12 months after implantation of drug-eluting stents. The use of anticoagulant agents (unfractionated or low-molecular-weight heparin) and glycoprotein IIb/IIIa inhibitors during PCI was at physician's discretion.

2.3. Biochemical investigations

SCr was measured 2 h after saline infusion on the day of procedure before CM exposure, and 48 h and 72 h after the procedure. Serum levels of fasting blood glucose (FBG), HbA1c and GA were determined on the morning of the day before procedure. High-sensitivity C-reactive protein (hs-CRP) and fasting lipid profiles including triglyceride, total cholesterol, low-density lipoprotein, and high-density lipoprotein were measured 24 h before angiographic procedure.

Serum HbA1c level was assessed by an ion-exchange high-performance liquid chromatography with Bio-Rad Variant Hemoglobin Testing System (Bio-Rad Laboratories, USA). Serum GA level was determined with bromocresolpurple method using a Lucica™ glycated albumin-L assay kit (Asahi Kasei Pharma, Japan) with an interassay coefficient of variance less than 3.0% [17–19]. Serum levels of SCr, FBG, and lipid profiles were measured with standard laboratory techniques on a Hitachi 912 Analyzer (Roche Diagnostics, Germany), and hs-CRP was assessed with a high-sensitivity ELISA kit (Biocheck Laboratories, USA).

2.4. Assessment of renal function

The change of renal function was expressed as a maximal difference (ΔSCr) and percentage change (%SCr) of SCr between post-procedural and baseline measurements, respectively: ΔSCr = (maximal post-procedural SCr) − (baseline SCr); %SCr = ([maximal post-procedural SCr] − [baseline SCr])/(baseline SCr) * 100%. CI-AKI was defined as ≥25% increase in SCr within 72 h after the procedure [1,29].

2.5. Follow-up

Clinical follow-up was completed by an outpatient clinic visit or through telephone contact with patients or their relatives at 1, 3, 6 and 12 months after discharge. To determine the impact of different serum GA levels on renal failure requiring dialysis and MACE including cardiac death, non-fatal myocardial infarction and target vessel revascularization, patients were further divided into high-GA (GA ≥ 21%, $n = 418$) and low-GA (GA < 21%, $n = 612$) groups, which was equivalent to HbA1c ≥ 7% and < 7% groups [16]. In order to guarantee data quality, all MACE were reviewed by two experienced cardiologists who were blinded to angiographic and biochemical data.

2.6. Statistical analysis

Continuous variables are presented as mean ± SD or median (25th–75th percentiles). Categorical data are presented as absolute values (percentages). Baseline characteristics, changes of renal function and clinical events in patients with and without CI-AKI were compared using t test or Wilcoxon rank sum test (if not normally distributed) for continuous variables and χ^2 and Fisher's exact test (when there were < 5 values in a given cell) for categorical variables. The association of changes in renal function (ΔSCr and %SCr) with GA, HbA1c and FBG was assessed via partial correlation analysis. Receiver-operating characteristic curve (ROC) analysis was used to calculate area under the curve for detecting CI-AKI. Multivariate logistic regression model was created to evaluate whether the association between pre-procedural GA values and CI-AKI persisted after adjustment for other patient characteristics and potential confounders. Cumulative event curves were constructed using Kaplan–Meier survival method and were compared with log-rank statistics in patients with or without CI-AKI. All statistical analyses were done using IBM SPSS software (version 19.0), and a value of $P < 0.05$ was considered statistically significant.

3. Results

3.1. Baseline characteristics

Among overall 1030 patients, 114 developed CI-AKI (11.1%). Patients with CI-AKI were older, more female in gender and lower body mass index (BMI), and had worse glycemic control (FBG, HbA1c and GA), higher baseline SCr, and reduced eGFR and left ventricular ejection fraction (LVEF). Multi-vessel disease was more common and amount of CM during the procedure was larger in patients with CI-AKI (Table 1). When patients were stratified according to median CM volume used (100 mL), the rate of CI-AKI was higher in patients with GA ≥ 21% than in those with GA < 21% for both groups with small (≤100 mL) or large (>100 mL) CM volume used (Fig. 1).

3.2. GA, HbA1c, FBG and CI-AKI

Serum levels of GA, HbA1c and FBG were higher in patients with CI-AKI than in those without (Table 1). GA correlated significantly with ΔSCr (Peason's $r = 0.15$), and %SCr (Peason's $r = 0.14$) (both $P < 0.001$) after controlling for age, gender, BMI, baseline SCr, hypertension, hyperlipidemia, preexisting chronic kidney disease, multivessel disease, type and volume of CM, LVEF, and HbA1c. However, no significant relation between HbA1c and changes in renal function existed if GA served as one of the confounders. Likewise, FBG did not correlate with renal function changes.

ROC analysis showed that area under the curve of GA (0.82, 95% CI 0.78–0.86, $P < 0.001$) was significantly greater than that of HbA1c (0.67, 95% CI 0.61–0.73, $P < 0.001$) and FBG (0.56, 95% CI 0.50–0.62, $P = 0.044$) (Fig. 2).

At multivariate logistic regression analysis, apart from female gender, age ≥ 65 years, LVEF < 40%, BMI < 18.5 kg/m^2, preexisting chronic kidney disease, and high contrast volume (>100 mL), serum GA was an independent risk factor for CI-AKI (adjusted OR = 1.26 per 1% increment, 95% CI 1.19–1.32, $P < 0.001$) (Table 2). However, HbA1c (≥7%) and FBG (≥7 mmol/L) were not independent variables in the model.

3.3. Clinical outcome

Clinical outcome during one-year follow-up was available in 943 patients (91.6%). Renal failure requiring dialysis and MACE occurred in 28 (3.0%) and 113 (12.0%) patients, respectively. The rates of