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LDL cholesterol as a novel risk factor for contrast-induced acute kidney injury in patients undergoing percutaneous coronary intervention

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ABSTRACT

Background: Low density lipoprotein cholesterol (LDL-C) is associated with endothelial dysfunction, inflammation and increased vasoconstriction, which are involved in the development of contrast-induced acute kidney injury (CI-AKI). However, whether LDL-C is an independent risk factor of CI-AKI in patients undergoing percutaneous coronary intervention (PCI) is unknown. **Methods**: We prospectively enrolled 3236 consecutive patients undergoing PCI between January 2010 and September 2012. Multivariate logistic regression analysis was used to determine whether LDL-C is an independent risk factor of CI-AKI. CI-AKI was defined as an absolute increase in serum creatinine of $\geq$0.5 mg/dL or $\geq$25% over the baseline value within 48–72 h after contrast exposure. **Results**: CI-AKI was observed in 338 patients (10.4%). Patients with CI-AKI had a significantly higher rate of in hospital mortality (4.4% vs. 0.5%, $p < 0.001$), and significantly higher rates of other in hospital complications compared with those without CI-AKI. The LDL-C quartiles were as follows: Q1 (<2.04 mmol/L), Q2 (2.04–2.61 mmol/L), Q3 (2.61–3.21 mmol/L) and Q4 (>3.21 mmol/L). Patients with high baseline LDL-C levels were more likely to develop CI-AKI and composite end points including all-cause mortality, renal replacement therapy, non-fatal myocardial infarction, acute heart failure, target vessel revascularization or cerebrovascular accident during the observation period of hospitalization (8.9%, 9.9%, 10.5%, 12.6%, $p = 0.001$, and 5.0%, 5.2%, 6.1%, 8.1%, respectively; $p = 0.007$). Univariate logistic analysis showed that LDL-C levels (increment 1 mmol/L) were significantly associated with CI-AKI (odds ratio = 1.25, 95% confidence interval (CI), 1.11–1.39, $p < 0.001$). Furthermore, LDL-C remained a significant risk factor of CI-AKI (odds ratio = 1.23, 95% CI, 1.04–1.45, $p = 0.014$), even after adjusting for potential confounding risk factors. **Conclusions**: Measurement of plasma LDL-C concentrations in patients undergoing PCI may be helpful to identify those who are at risk of CI-AKI and poor in hospital outcomes.

1. Introduction

Contrast-induced acute kidney injury (CI-AKI) after a percutaneous coronary intervention (PCI) is a common and serious complication of this procedure. CI-AKI is strongly associated with prolonged hospitalization, additional healthcare expenses, late renal and cardiovascular adverse events, and death [1,2]. Great efforts have been devoted to the prevention and medical treatment of CI-AKI. However, very few therapeutic options of CI-AKI have consistently shown benefit, except for periprocedural hydration and use of a small amount of low-osmolality contrast media (LOCM) [3]. Accordingly, an essential part of reducing CI-AKI is the ability to identify patients who are at great risk of CI-AKI, so that closer monitoring and swift intervention might be implemented.

Although some risk factors such as chronic kidney disease, and diabetic mellitus, are strongly associated with CI-AKI, the search for new risk factors that can be used to improve the identification of CI-AKI remains an active area of great interest. Low density lipoprotein

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cholesterol (LDL-C) is the most common and strong cardiovascular risk factor associated with incident myocardial infarction and ischemic coronary heart disease [4]. LDL-C induces dysfunction of the endothelium, causes vascular wall inflammation and induces up-regulation of vaso-constrictive endothelin type B receptor expression with increased vasoconstriction [5–9], which play major role in the development of CI-AKI [10]. Moreover, statins, as a class of medications that improves the lipid profile of patients, exhibit pleiotropic effects, including: improving endothelial function, increasing nitric oxide production, and having a rapid onset of anti-oxidant efficacy after the initiation of treatment [11,12], which are considered as the most important contributing factors to CI-AKI progression, although the patho-physiological mechanisms of CI-AKI are still unclear [10,13,14]. Recent studies have shown that rosuvastatin, as a potent LDL-C-lowering statins and anti-inflammatory, significantly reduces the risk of CI-AKI [15,16]. However, few studies have been conducted to evaluate the relationship between LDL-C and CI-AKI. Therefore, we hypothesized that LDL-C may be associated with CI-AKI through above mechanisms involved in CI-AKI development. Then, we conducted the present study to evaluate whether LDL-C is an independent risk factor of CI-AKI in patients undergoing PCI.

2. Materials and methods

2.1. Study population

This prospective observational study was conducted at Guangdong Cardiovascular Institute, Guangdong General Hospital in China. All of the 3236 consecutive patients who were undergoing PCI were reviewed according to the institutional protocol between January 2010 and September 2012. Exclusion criteria were a history of cardiogenic shock, pregnancy, allergy to CM, use of CM within prior 7 days, treatment with statins in previous more than 14 days, or treatment with nephro-protective drugs (e.g. *N*-acetylcysteine, theophylline, prostaglandin E1, and sodium bicarbonate) or nephro-toxic drugs (e.g. steroids or non-steroidal anti-inflammatory drugs, aminoglycosides, amphotericin B, and cisplatin). Patients were also excluded if they had renal transplantation, dialysis or severe hepatic insufficiency.

The study protocol was approved by Guangdong General Hospital ethics committee and the study was performed according to the declaration of Helsinki. Written informed consent was obtained from almost all of the patients before the procedure, and some of next of kin were involved in the process of getting informed consent in patients undergoing primary PCI, who could not signed informed consent themselves.

2.2. Laboratory investigations

Serum creatinine (SCr) levels were measured at admission and within 48–72 h after CM exposure. Serum levels of glucose and lipid profiles including LDL-C, triglycerides, total cholesterol, and high density lipoprotein cholesterol were measured at fasting state on the morning of the day before the procedure. We also measured blood urea nitrogen, high-sensitivity C reactive protein (hs-CRP), and albumin levels, as well as other standard clinical parameters at fasting state. Left ventricular function was evaluated in patients with echocardiography within 24–48 h before the elective procedure, and within 24 h after primary procedure. We evaluated estimated glomerular filtration rate (eGFR) using the four-variable Modification of Diet in Renal Disease equation based on Chinese patients [17].

2.3. Percutaneous coronary intervention and medications

PCI was performed by experienced interventional cardiologists according to standard clinical practice using a standard technique. Elective PCI was performed for patients with stable coronary artery disease. Primary PCI was performed for patients with ST-segment elevation acute myocardial infarction (STEMI) if they presented within 12 h from the onset of symptoms. We used nonionic, LOCM in all of the patients (either Iopamiron or Ultravist, both 370 mg I/mL). 0.9% Normal saline at a rate of 1 mL/kg/h was administered intravenously 6–12 h before and after exposure to CM (during the procedure and for 12 h after the procedure in patients with STEMI undergoing primary PCI). In patients with left ventricular dysfunction (left ventricular ejection fraction: LVEF < 40%) or overt heart failure, the hydration rate was reduced to 0.5 mL/kg/h. The use of anti-platelet agents (aspirin/clopidogrel), beta-adrenergic blocking agents, statins, diuretics, angiotensin-converting enzyme inhibitors and inotropic drugs in-hospital or after discharge was at the cardiologist's discretion according to clinical protocols based on interventional guidelines.

2.4. Clinical outcomes

The primary end-point of the study was the incidence of CI-AKI, defined as an absolute increase in SCr of $\geq$0.5 mg/dL or $\geq$25% over baseline values within 48–72 h after CM exposure [3]. The secondary end-points included: all-cause mortality and composite end points, including all-cause mortality, renal replacement therapy, non-fatal myocardial infarction, acute heart failure, target vessel revascularization or cerebrovascular accident during the observation period of hospitalization (Median follow-up time was 4 days, Minimum and max duration were 2 and 25 days).

2.5. Statistical analysis

Continuous variables are described as the mean ± SD or as median (interquartile range). Demographics and traditional risk factors were compared between patients with and without CI-AKI. Patients were categorized into four groups for the comparison of clinical outcomes, according to the quartiles of baseline LDL-C concentrations. The Student's *t*-test, Wilcoxon rank sum test or one way-analysis of variance was performed to determine differences between groups. Categorical variables are reported as absolute values and percentages, and analyzed by the Chi-square test or Fisher's exact test. The value of hs-CRP was expressed as geometric means. Univariate and multivariate logistic regression analyses were performed to identify independent risk factors of CI-AKI. Univariate analysis included variables such as LDL-C, diabetes, hemoglobin, renal failure, CM volume, Mehran risk score and intra-aortic balloon pump. Variables with p values <0.15 in the univariate analysis were entered into multivariate logistic regression analysis by forward stepwise selection. The adjusted odds ratio (OR) and 95% confidence interval (CI) were calculated. All analyses were performed with SPSS software (version 16.0; SPSS Inc, Chicago, IL, USA). All probability values are two-tailed and statistical significance was defined as $P < 0.05$.

3. Results

3.1. Baseline clinical characteristics

A total of 3236 consecutive patients undergoing PCI were analyzed (mean age 63.3 ± 11.0 years; mean LDL-C level, 2.7 ± 0.9 mmol/L; mean eGFR 81.4 ± 25.3 mL/min/1.73 m^2 and mean Mehran score 4.5 ± 3.8). Based on the baseline LDL-C levels,