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Vascular cell adhesion molecule-1, but not intercellular adhesion molecule-1, is associated with diabetic kidney disease in Asians with type 2 diabetes

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ABSTRACT

Background and Aims: The association of adhesion molecules ICAM-1 and VCAM-1 with cardiovascular diseases has been well-studied. However, their roles in diabetic kidney disease (DKD) are incompletely understood. We aim to study the association of plasma ICAM-1 and VCAM-1 with DKD in Asians with type 2 diabetes (T2DM).

Subjects and Methods: A total of 1950 Asians with T2DM were included in this cross-sectional study. Plasma ICAM-1 and VCAM-1 were measured by immunoassays.

Results: Renal filtration function (eGFR) declined and urinary albumin-to-creatinine ratio (ACR) levels increased progressively with the increase in plasma VCAM-1 levels. In contrast, no significant changes in eGFR and ACR were observed in subjects across different plasma ICAM-1 levels. Both ICAM-1 and VCAM-1 were correlated with ACR (rho = 0.153, $p < 0.001$ for VCAM-1 and ACR; rho = 0.053, $p = 0.020$ for ICAM-1 and ACR) in bivariate correlation analysis. However, only VCAM-1 was correlated with eGFR (rho = −0.228, $p < 0.001$). Multivariable linear regression models revealed that VCAM-1, but not ICAM-1, was independently associated with eGFR and albuminuria. Backward linear regression suggested that plasma VCAM-1 variability was mainly determined by eGFR whereas plasma ICAM-1 level was mainly determined by C-reactive protein in patients with T2DM.

Conclusions: Plasma VCAM-1 level, but not ICAM-1 level, was independently associated with prevalent DKD in Asians with T2DM. High level of ICAM-1 may be indicative of systemic inflammation and portends increase risk of incipient DKD.

1. Introduction

Diabetic kidney disease (DKD) is a common microvascular complication in patients with diabetes. It is not only the leading cause of end stage renal disease but also an important risk factor for cardiovascular mortality (Macisaac, Ekinci, & Jerums, 2014). With the prevalence of type 2 diabetes (T2DM) in Western countries reaching an epidemic level and the rapid increase of T2DM in Asian countries in the past decade, DKD is becoming a serious public health threat worldwide (Kong et al., 2013). Notably, Asians with T2DM are especially vulnerable to renal injury when compared to Caucasians (Kong et al., 2013). Epidemiological data suggest that DKD affects 25% to 40% Caucasians with diabetes. However, the prevalence of DKD is estimated to be 40% to 60% among Asians with T2DM (Kong et al., 2013; Macisaac et al., 2014).

Endothelial dysfunction and chronic inflammation play important roles in the pathogenesis of DKD (Karalliedde & Gnudi, 2011; Macisaac et al., 2014; Tousoulis et al., 2013). Adhesion molecules including vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) are expressed on plasma membrane of activated endothelial cells in response to risk factors such as advanced glycation end-products (AGE) and pro-inflammatory cytokines. ICAM-1 and VCAM-1 participate and perpetuate inflammatory process by mediating firm attachment and transmigration of leucocytes. Therefore, adhesion molecules have been considered as mediators between dysmetabolism, chronic inflammation, endothelial dysfunction and macro- and microvascular complications in patients with diabetes (Navarro-Gonzalez, Mora-Fernandez, Muros de Fuentes, & Garcia-Perez, 2011; Tousoulis et al.,

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2013; Zhang et al., 2003). In animal models with diabetes, intrarenal expression of adhesion molecules was up-regulated and in concordance, ICAM-1-deficiency in db/db mice (T2DM model) reduced intrarenal leukocyte infiltration accompanied by attenuated glomerular and tubular damage (Chow, Nikolic-Paterson, Ozols, Atkins, & Tesch, 2005).

Early clinical studies suggest that adhesion molecules may play a role in pathogenesis and progression of DKD in human (Blankenberg, Barbaux, & Tiret, 2003; Clausen et al., 2000; Fotis, Giannakopoulos, Stamogiannou, & Xatzipsalti, 2012; Tousoulis et al., 2013). In patients with T1DM, both circulating lCAM-1 and VCAM-1 levels were elevated in patients with DKD. An accelerated increase in urinary albumin excretion has been observed longitudinally in those with higher ICAM-1 levels at baseline (Clausen et al., 2000; Lin et al., 2008). In patients with T2DM, an early study showed that circulating VCAM-1 levels were correlated with urinary albumin excretion and glomerular filtration rate (GFR). The findings, though interesting, are still awaiting validation by other independent studies (Jager et al., 2000; Stehouwer et al., 2002). The relationship between circulating ICAM-1 and indicators of DKD has not been well-studied in patients with T2DM.

It is also interesting to note that the association of circulating ICAM-1 and VCAM-1 with clinical phenotypes may differ among ethnic groups. The whites have higher circulating ICAM-1 and VCAM-1 levels as compared to the black (Lee, Gungor, Bacha, & Arslanian, 2007; Miller et al., 2003). Intriguingly, a meta-analysis showed that the association of ICAM-1 gene polymorphism with diabetic microvascular complications was significant in Asians but not in Caucasians (Su et al., 2013). To the best of our knowledge, the association of circulating ICAM1- and VCAM-1 with DKD among Asians with T2DM has not been systematically studied.

2. Subjects and methods

2.1. Subjects

SMART2D (Singapore Study of MAcro-angiopathy and Micro-Vascular Reactivity in Type 2 Diabetes) aims to study traditional and novel risk factors associated with vascular complications among multi-ethnic Asians with T2DM. Diagnosis of T2DM was based on American Diabetes Association criteria (ADA, 2012). Subjects were recruited consecutively from a community polyclinic and a secondary hospital in Singapore. All subjects with T2DM were enrolled in the study after excluding (1) those with age less than 21 or more than 90 years old; (2) pregnant subjects; (3) those who cannot fulfill informed consent process; (4) subjects with active inflammation (e.g., systemic lupus erythromatosis) and cancer; (5) subjects with point-of-care test (POCT) fasting glucose level < 4.5 mM or >15.0 mM or POCT HbA1c >12%; (6) subjects who took NSAIDS within the same day of phlebotomy and (7) current user of oral steroids equivalent to prednisolone >5 mg/day. Demographic, clinical and biochemical data as well as history of medication usage were recorded in a standardized form and entered into a data management server. Retinopathy was ascertained by medical records. By the cut-off time of this study (end of January 2014), 1950 T2DM subjects have been recruited. SMART2D study complies with Helsinki Declaration, has been approved by our domain specific ethical review board and written informed consent has been obtained from all participants.

2.2. Clinical and biochemical measurements

Blood pressure was taken in a sitting position by an automated blood pressure monitor after letting the subjects rest for 5 minutes (Dinamap Pro 100V2, Freiburg, Germany). HbA1c was quantified by point-of-care immunoassay analyzer which had met NGSP (National Glycohemoglobin Standardization Program) performance standard (DCA Vantage Analyzer; Siemens AG, Erlangen, Germany). Total cholesterol, HDL cholesterol and LDL cholesterol were measured by enzymatic methods using Kodak Ektachem chemistry slides. Triglycerides and creatinine were quantified by enzymatic methods (Roche/Hitachi Cobas C System; Roche Diagnostic GmbH, Mannheim, Germany). Urinary albumin was measured by solid-phase competitive chemiluminescent enzymatic immunoassay (Immulite, DPC, Gwynedd, UK). Estimated glomerular filtration rate (eGFR) was calculated based on the Modified Diet in Renal Disease (MDRD) formula, which performed well in subjects with diabetes (Rognant, Lemoine, Laville, Hadj-Aissa, & Dubourg, 2011). High sensitivity c-reactive protein (hsCRP) concentration was quantified by solid phase sandwich ELISA with a minimum detection limit of 0.022 ng/ml and intra- and inter-assay coefficients of 5.5% and 6.5%, respectively (R&D Systems, Minneapolis, MN, USA). Depending on hsCRP concentration in each sample, samples were diluted between 50 to 10,000 times to ensure that the measurements fell within the range of the standard curve. Plasma ICAM-1 and VCAM-1 levels were measured by multiplex immunoassays on a Luminex 200 platform according to protocol provided by the manufacture (Affymetrix, Santa Clara, CA, USA). Plasma samples were diluted 200 times before multiplex assay. The minimum detection limit for VCAM-1 and ICAM-1 was 1.13 pg/ml and 2.92 pg/ml, respectively. The intra-assay coefficients were 3.1% and 5.6% and the inter-assay coefficients were 5.2% and 7.8% for VCAM-1 and ICAM-1, respectively.

2.3. Statistical analysis

Continuous data were presented as mean ± standard deviation (SD) and categorical data were expressed as proportions. Total triglycerides, urinary albumin-to-creatinine ratio (uACR), VCAM-1, ICAM-1 and hsCRP were reported as median (interquartile range, IQR) and log-transformed before statistical analyses because of skewed frequency distribution. Subjects were divided into quartiles based on either plasma VCAM-1 or ICAM-1 levels to visualize clinical and biochemical characteristics. One way analysis of variance (ANOVA) or χ^2 test was used to analyze the differences in continuous or categorical variables across quartiles where appropriate (Table 1 and Supplementary Table 1). Bivariate correlations between clinical, biochemical variables and plasma VCAM-1 or ICAM-1 levels were examined with Spearman rank correlation test. General linear regression models were employed to study which variables were independently associated with plasma VCAM-1 or ICAM-1 levels. Plasma VCAM-1 or ICAM-1 level was entered as dependent variable in the model and age, gender and ethnicities (Chinese, Malay and Chinese) were entered as main confounders (model 1). Selection of covariates was informed by pathophysiology of DKD and also based on suggestions from literature. Duration of diabetes, indicators of glycemic control (HbA1c and fasting plasma glucose), waist circumference (indicator of central obesity), systolic blood pressure and lipids profile (HDL, LDL cholesterol and triglycerides) were entered as covariates (model 2). BMI was not included with waist circumferences in the same model due to concerns of multi-collinearity. Renal filtration function (eGFR), uACR and plasma hsCRP were further adjusted in models 3 and 4. In the fully adjusted model, we also included medication usage as suggested by univariate analysis in Table 1 and Supplementary Table 1 (model 5). Finally, we employed backward linear regression on the basis of model 5 to identify the most parsimonious explanatory variables which determine plasma ICAM-1 or VCAM-1 variability. Data analysis was performed by SPSS version 21 and two-sided $p < 0.05$ was considered statistically significant.

3. Results

The baseline clinical and biochemical characteristics of the study participants were shown in Table 1. Individuals with VCAM-1 in the higher quartiles were older, had longer duration of diabetes, had poorer glycemic control and had higher systolic blood pressure (SBP) as compared to subjects with VCAM-1 in the lower quartiles. There