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Association of serum bilirubin with renal outcomes in Han Chinese patients with chronic kidney disease

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ABSTRACT

Background: Oxidative stress and inflammation play pivotal roles in chronic kidney disease (CKD). Bilirubin is an endogenous anti-inflammatory antioxidant. However, the relationship between serum bilirubin and renal outcomes in CKD is controversial. We explored the association of serum bilirubin levels with renal outcomes in Han Chinese patients with CKD.

Methods: Clinical and laboratory data were collected from 316 patients with CKD. The primary clinical endpoint was renal replacement therapy or death. The association between serum bilirubin and clinical parameters was assessed by correlation analysis. Multiple Cox regression analysis was used to explore the relationship between serum bilirubin and renal outcomes in patients with CKD.

Results: Serum total and indirect bilirubin were positively correlated with estimated glomerular filtration rate, but negatively correlated with 24-h urine protein in patients with CKD. Serum total and indirect bilirubin were inversely associated with CKD stages in patients with CKD stages 1–5. Multiple Cox regression analysis demonstrated that the higher concentration of serum total bilirubin was independently associated with better renal outcomes in CKD.

Conclusions: Our results suggest that serum total bilirubin may have protective effects on kidneys.

1. Introduction

The prevalence of chronic kidney disease (CKD) has increased in recent decades, and clinicians have sought to improve prevention and treatment strategies for CKD [1]. Oxidative stress and inflammation play pivotal roles in the development of CKD [2–6]. Bilirubin, a metabolic product of heme catabolism, is an antioxidant and cytoprotective molecule [7–11]; direct bilirubin has an anti-complement role in vitro and prevents tissues from inflammatory damage in animal models [12]. Yamaguchi et al. revealed that oxidative stress can further induce bilirubin synthesis in vitro [13]. Furthermore, supplemental exogenous bilirubin has antioxidant and cytoprotective effects on immune tolerance and organ transplantation [14]. However, the relationship between serum bilirubin and renal outcomes in patients with CKD is unclear based on data from different populations [15,16]. In addition, the association between serum bilirubin subtypes and renal outcomes in patients with different stages of CKD remains largely unknown.

Therefore, in this study, we aimed to elucidate the relationship between serum bilirubin subtypes and renal outcomes in Han Chinese patients with different stages of CKD.

2. Materials and methods

2.1. Patients and study design

As a retrospective cohort study, clinical and laboratory data were collected from 316 hospitalized Han Chinese patients (between January 1, 2002 and September 1, 2016) at the Department of Nephrology and Rheumatology, Shanghai Tenth People's Hospital. The diagnosis of CKD was based on Kidney Disease Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for Evaluation and Management of Chronic Kidney Disease. The primary clinical endpoint was renal

Abbreviations: CKD, chronic kidney disease; ESRD, end-stage renal disease; CVD, cardiovascular disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; 24-h-P, 24-h urine protein

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Table 1
Baseline characteristics of subjects according to renal endpoints.

	Total	Endpoints		*p*-Value
		Yes	No	
Number (*n*)	316	117	199	–
Age (y)	61.7 ± 10.9	61.72 ± 10.40	61.89 ± 11.21	NS
Male (%)	56.0	59.8	53.8	NS
History of hypertension (%)	85.1	88.9	82.9	NS
NS	61.7	64.1	60.3	NS
History of CVD (%)	63.0	65.9	61.8	NS
History of smoking (%)	20.6	22.2	19.6	NS
History of drinking (%)	10.4	11.1	10.1	NS
Follow-up time (months)	29.09 (14.12–53.43)	25.03 (6.44–50.57)	31.50 (17.03–56.00)	0.028
SBP (mm Hg)	152 ± 24	155 ± 26	150 ± 23	NS
DBP (mm Hg)	85 ± 15	84 ± 14	84 ± 15	NS
FBG (mmol/l)	6.5 ± 3.0	6.4 ± 3.5	6.5 ± 3.7	NS
Hemoglobin (g/l)	115.9 ± 24.7	105.1 ± 26.5	122.1 ± 21.2	< 0.0001
ALT (U/l)	18.1 ± 11.6	15.6 ± 8.5	19.5 ± 12.8	0.004
Serum albumin (g/l)	37.8 ± 6.4	36.2 ± 6.6	38.7 ± 6.1	0.001
DBIL (mg/dl)	0.17 ± 0.09	0.15 ± 0.08	0.18 ± 0.09	< 0.0001
TBIL (mg/dl)	0.53 ± 0.30	0.46 ± 0.27	0.57 ± 0.31	< 0.0001
IBIL (mg/dl)	0.36 ± 0.23	0.31 ± 0.21	0.38 ± 0.23	< 0.0001
AST (U/l)	19.9 ± 13.2	17.8 ± 7.6	21.1 ± 15.5	0.003
TC (mmol/l)	5.06 ± 1.33	5.14 ± 1.34	5.01 ± 3.12	NS
TG (mmol/l)	2.06 ± 1.85	1.84 ± 1.42	2.19 ± 2.06	NS
LDL (mmol/l)	2.91 ± 1.08	2.98 ± 1.03	2.92 ± 1.09	NS
Serum uric acid (μmol/l)	419 ± 120	419 ± 124	420 ± 119	NS
Serum phosphorus (mmol/l)	1.31 ± 0.35	1.45 ± 0.45	1.24 ± 0.28	< 0.0001
eGFR (ml/min/1.73 m^2)	43.89 (24.28–65.51)	21.77 (9.54–46.61)	52.57 (37.81–70.30)	< 0.0001
24-h-P (g/24 h)	1.07 (0.33–2.94)	2.12 (0.86-4.46)	0.67 (0.21–1.90)	< 0.0001

Values are expressed as means ± SD, medians (interquartile ranges) and percentages (%).
SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; IBIL, indirect bilirubin; 24-h-P, 24-hour urine protein.

replacement therapy or death. Patients who received renal replacement therapy (hemodialysis, peritoneal dialysis, or renal transplantation) were excluded. Patients who met the following criteria were also excluded: (1) patients with polycystic kidney, solitary kidney, acute kidney injury, history of malignant disease, chronic liver or biliary tract disease, hemolytic disease, or acute infection; and (2) patients whose serum total bilirubin, alanine aminotransferase (ALT), or aspartate aminotransferase (AST) levels were > 1.5 times the upper limit of normal value. The clinical diagnosis and exclusion criteria were confirmed by three senior physicians on the basis of medical history and laboratory parameters. We followed up all patients until they reached the endpoint or until the end of the study. This study was approved by the research ethics committee of the Shanghai Tenth People's Hospital, and written informed consent was obtained from all patients.

2.2. Clinical and biochemical assessment

Cardiovascular disease (CVD) was defined as coronary atherosclerosis, coronary atherosclerotic heart disease, or heart failure. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation corrected for Asians [17]. Biochemical parameters included hemoglobin, serum albumin, serum creatinine, serum uric acid, serum phosphorus, total cholesterol (TC), triglycerides (TGs), low-density lipoprotein (LDL), high-density lipoprotein (HDL), ALT, AST, and 24-h urine protein (24-h-P). Serum total bilirubin was measured by the colorimetric diazo-method using Bilirubin Total Gen.3 reagent (Roche Diagnostics GmbH). Direct bilirubin was measured by the diazo-method (Roche) and serum creatinine was measured by the enzymatic method (Roche). A Cobas c 701/702 analyzer (Roche) was used to measure these biomedical parameters. Two patients' data were collected before the serum creatinine reference measurement was standardized to isotope-dilution mass spectrometry, and the 2 serum creatinine values were corrected to calculate eGFR according to a previous study [18]. Serum indirect bilirubin levels were calculated by the serum total bilirubin concentration minus the direct bilirubin concentration. The remaining clinical variables were also measured in the same central laboratory according to standard procedures.

2.3. Statistical analysis

The patients were stratified into four groups according to quartiles of baseline serum bilirubin concentrations. Baseline data were presented as means ± SD or medians (interquartile ranges) for continuous variables depending on the data distribution and as percentages (%) for categorical variables. Analysis of variance, Student's *t*-tests, or Kruskal-Wallis tests were used to detect the statistical differences in baseline variables in different groups. The relationships among serum bilirubin, eGFR, and 24-h-P were assessed by Spearman correlation analysis. Multivariable Cox proportional hazards regression models were used to investigate the relationship between baseline serum bilirubin concentrations and renal outcomes in patients with CKD. A 2-tail $p < 0.05$ indicated statistical significance. Data analysis was performed by SPSS (ver 19.0) and SAS (ver 9.4).

3. Results

3.1. Baseline characteristics of patients

Among 316 patients with CKD, 124 (39.24%) were diagnosed with diabetic nephropathy, which was the most common cause of CKD in this cohort. Moreover, 119 patients (37.66%) were diagnosed with chronic nephritis, and the remaining causes of CKD were uric acid-related nephropathy (13.92%), benign renal arterioles sclerosis (6.96%), chronic pyelonephritis (1.58%), lupus nephritis (0.32%), and purpura nephritis (0.32%).

The median follow-up period for the 316 patients was 29.09 months. A total of 117 (37.0%) patients met the clinical endpoint, of which five (1.6%) died, and 112 patients required renal replacement therapy. In contrast, 119 patients (37.7%) reached the end of the study.