Atherosclerosis 234 (2014) 421–425

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Low serum bilirubin concentration is a predictor of chronic kidney disease

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ARTICLE INFO

Article history:
Received 18 November 2013
Received in revised form
13 March 2014
Accepted 17 March 2014
Available online 13 April 2014

Keywords:
Chronic kidney disease
Bilirubin
Antioxidant

ABSTRACT

Objective: Chronic kidney disease (CKD) is a worldwide public health problem. It is very important to identify the factors that affect CKD. Previous studies have reported that serum bilirubin concentration was positively correlated with renal function in a cross-sectional study. The aim of this study was to investigate the relationship between serum bilirubin concentration and the progression of CKD.
Methods: A cohort study was performed on a consecutive series of 2784 subjects without CKD, defined as estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2, at baseline. We analyzed the relationship between serum total bilirubin concentration at baseline and new-onset CKD in the general population.
Results: We followed the subjects for a median period of 7.7 years. There were 1157 females and 1627 males, and 231 females and 370 males developed CKD during this period. Multiple Cox regression analyses revealed that serum total bilirubin concentration (hazard ratio (HR) per 1.0 μmol/L increase 0.97 (95% CI 0.95–0.99), $P = 0.0084$) in addition to age, gamma-glutamyl transpeptidase (GGT), uric acid (UA), creatinine and medication for hypertension in men and serum total bilirubin concentration (HR per 1.0 μmol/L increase 0.96 (95% CI 0.93–1.00), $P = 0.0309$) in addition to age, GGT, alanine aminotransferase, UA, creatinine and medication for dyslipidemia in women were independent predictors of new-onset CKD, after adjusting for confounders.
Conclusion: Our study demonstrated that serum total bilirubin concentration could be a novel risk factor for the progression of CKD, defined as eGFR <60 ml/min/1.73 m^2, in the general population.

1. Introduction

Chronic kidney disease (CKD) is a worldwide public health problem, and especially the rising prevalence and associated morbidity of CKD have resulted in a significant disease burden for our limited health care resources [1]. Besides, recent study demonstrated that reduced estimated glomerular filtration rate (GFR) < 60 ml/min per 1.73 m^2 independently predicts the risk for death, hospitalization and cardiovascular events [2]. Because renal disease often progresses to end stage renal disease (ESRD), the identification of risk factors for kidney disease progression is essential.

Bilirubin is not merely an end product of heme degradation but is also a potent antioxidant that acts via inhibitions of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, a key source of oxidants in phagocytic and non-phagocytic cells [3–5]. In addition, previous studies have reported that low serum bilirubin concentrations are associated with an increased risk of cardiovascular disease (CVD) [6,7]. Although previous studies have reported that serum bilirubin concentration was positively correlated with renal function in a cross-sectional study [8,9], the relationship between serum bilirubin concentration and development of CKD remains to be elucidated. To determine whether low serum bilirubin concentration could be a predictor of CKD, we examined the data of a large community-based cohort of adults.

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http://dx.doi.org/10.1016/j.atherosclerosis.2014.03.015
0021-9150/

2. Methods

2.1. Subjects and study design

The Oike Health Survey is an ongoing cohort investigation of risk factors for chronic diseases including hypertension, diabetes and CKD. Oike Clinic (Kyoto, Japan) provides regular health check-up for the employees of various companies. In Japan, yearly routine examination for employees is legally mandated, and all or most of the costs for the health check-up are usually paid by their employers. Between 1998 and 2003, 3531 Japanese subjects were enrolled in this study. Subjects with malignant disease, liver cirrhosis or hematologic disease were excluded from this study. We excluded 673 subjects who had CKD at baseline. Furthermore, we excluded the subjects with missing data of covariates ($n = 74$). We followed up 2784 subjects and evaluated the risk factors for CKD and assessed whether low serum total bilirubin concentration could predict CKD. Approval for this study was obtained from the Ethical Committee of Oike Clinic, and the study was conducted in accordance with Declaration of Helsinki. Informed consent was obtained from each subject.

2.2. Data collection and measurements

All subjects provided details of their demographics. Smoking was defined as current tobacco usage. History of alcohol was defined as daily alcohol consumption. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. After an overnight fast, venous blood was collected for the measurement of the levels of various factors, including fasting plasma glucose (FPG), low-density lipoprotein (LDL) cholesterol, triglycerides, gamma-glutamyl transpeptidase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), uric acid (UA), creatinine, total bilirubin and total leukocyte count. GFR was estimated using the equation of Japanese Society of Nephrology: $eGFR = 194 \times Cre^{-1.094} \times age^{-0.287}$ (ml/min/1.73 m^2) [10]. For women, eGFR was multiplied by a correction factor of 0.739. CKD was defined as eGFR <60 ml/min/1.73 m^2.

2.3. Statistical analysis

The statistical analyses were performed using the JMP version 8.0 software (SAS Institute Inc., Cary, North Carolina). A P value <0.05 was considered statistically significant. Continuous variables are presented as the mean value ±1 SD and categorical variables are presented as number (percentage). Categorical and continuous variables were compared between the groups by chi-square analyses and unpaired Student's t-tests, respectively. We evaluated the predictor for CKD by univariate and multiple Cox regression analyses to adjust for covariates including age, history of smoking or alcohol intake, BMI, systolic blood pressure (SBP), FPG, LDL

Table 1
Baseline characteristics of subjects.

	All	Non-CKD	CKD	*P* Value
(A) Men				
n	1627	1257	370	
Age (y)	47.7 ± 9.7	46.5 ± 9.5	51.6 ± 9.3	<0.0001
Smoking (%)	358 (22.0)	287 (22.8)	71 (19.2)	0.1326
Alcohol (%)	746 (45.9)	580 (46.1)	166 (44.9)	0.6647
Body mass index (kg/m^2)	23.3 ± 2.9	23.2 ± 2.9	23.6 ± 2.7	0.0163
Systolic blood pressure (mmHg)	121.1 ± 16.5	120.2 ± 16.3	124.1 ± 17.1	<0.0001
Fasting plasma glucose (mmol/L)	5.32 ± 1.11	5.28 ± 1.07	5.47 ± 1.24	0.0029
Low-density lipoprotein cholesterol (mmol/L)	3.34 ± 0.81	3.31 ± 0.81	3.42 ± 0.82	0.0251
Triglycerides (mmol/L)	1.42 ± 0.79	1.38 ± 0.77	1.55 ± 0.82	0.0004
Gamma-glutamyl transpeptidase (μkat/L)	0.87 ± 0.82	0.89 ± 0.85	0.80 ± 0.74	0.0780
Aspartate aminotransferase (μkat/L)	0.40 ± 0.42	0.41 ± 0.47	038 ± 0.13	0.3028
Alanine aminotransferase (μkat/L)	0.47 ± 0.42	0.47 ± 0.46	0.44 ± 0.24	0.1194
Uric acid (μmol/L)	352.7 ± 71.3	348.3 ± 68.9	367.6 ± 77.1	<0.0001
Creatinine (μmol/L)	78.6 ± 9.0	77.3 ± 9.0	83.2 ± 7.1	<0.0001
Total leukocyte count (10^9/L)	6.0 ± 1.7	6.0 ± 1.7	5.9 ± 1.6	0.5652
Medication for hypertension (%)	337 (20.7)	214 (17.0)	123 (33.2)	<0.0001
Medication for diabetes (%)	99 (6.1)	70 (5.6)	29 (7.8)	0.1187
Medication for dyslipidemia (%)	197 (12.1)	127 (10.1)	70 (18.9)	<0.0001
Total bilirubin (μmol/L)	13.1 ± 5.3	13.4 ± 5.5	12.2 ± 4.7	0.0003
(B) Women				
n	1157	926	231	
Age (y)	46.3 ± 9.7	45.2 ± 9.6	50.4 ± 9.0	<0.0001
Smoking (%)	87 (7.5)	72 (7.8)	15 (6.5)	0.5015
Alcohol (%)	219 (18.9)	181 (19.6)	38 (16.5)	0.2761
Body mass index (kg/m^2)	21.4 ± 2.9	21.3 ± 2.9	21.8 ± 2.7	0.0099
Systolic blood pressure (mmHg)	113.6 ± 17.4	112.3 ± 16.5	118.6 ± 20.0	<0.0001
Fasting plasma glucose (mmol/L)	4.90 ± 0.69	4.89 ± 0.68	4.95 ± 0.71	0.2434
Low-density lipoprotein cholesterol (mmol/L)	3.19 ± 0.88	3.14 ± 0.86	3.40 ± 0.90	<0.0001
Triglycerides (mmol/L)	0.91 ± 0.48	0.90 ± 0.49	0.94 ± 0.44	0.3023
Gamma-glutamyl transpeptidase (μkat/L)	0.39 ± 0.40	0.40 ± 0.41	0.36 ± 0.33	0.1240
Aspartate aminotransferase (μkat/L)	0.33 ± 0.12	0.32 ± 0.12	0.35 ± 0.13	0.0071
Alanine aminotransferase (μkat/L)	0.28 ± 0.18	0.27 ± 0.18	0.31 ± 0.20	0.0057
Uric acid (μmol/L)	252.2 ± 52.2	249.2 ± 51.4	264.5 ± 53.5	<0.0001
Creatinine (μmol/L)	58.8 ± 7.5	58.0 ± 7.6	62.1 ± 6.4	<0.0001
Total leukocyte count (10^9/L)	5.3 ± 1.4	5.3 ± 1.4	5.1 ± 1.4	0.0509
Medication for hypertension (%)	142 (12.2)	90 (9.7)	52 (22.5)	<0.0001
Medication for diabetes (%)	17 (1.5)	12 (1.3)	5 (2.2)	0.3499
Medication for dyslipidemia (%)	119 (10.3)	75 (8.1)	44 (19.1)	<0.0001
Total bilirubin (μmol/L)	11.6 ± 4.5	11.7 ± 4.6	11.0 ± 4.0	0.0355

CKD, chronic kidney disease. Data are expressed as mean ± SD or number (percentage).