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Original Paper

Hypobilirubinemia Might be a Possible Risk Factor of End-Stage Kidney Disease Independently of Estimated Glomerular Filtration Rate

Eiji Oda[1] Ryuzi Aoyagi[2] Yoshifusa Aizawa[3]

[1] Tachikawa Medical Check-up Center, Tachikawa Medical Center, Nagaoka, Japan, [2] Chuetsu Kidney Center, Tachikawa Medical Center, Nagaoka, Japan, [3] Department of Research and Development, Tachikawa Medical Center, Nagaoka, Japan

Key Words
Bilirubin • Chronic kidney disease • Estimated GFR • End-Stage kidney disease

Abstract
Background/Aims: The relationship between serum total bilirubin (TB) and estimated glomerular filtration rate (eGFR) is controversial and there is no report on the association between TB and end-stage kidney disease (ESKD). ***Methods:*** We examined the cross-sectional association between TB and eGFR and investigated whether TB can predict ESKD with multivariable logistic regression adjusted for age, sex, and baseline eGFR using hospital-based data. ***Results:*** The geometric mean TB of patients with eGFR ≥ 90 mL/min/1.73 m^2 (S1), 89-60 mL/min/1.73 m^2 (S2), 59-30 mL/min/1.73 m^2 (S3), 29-15 mL/min/1.73 m^2 (S4), and < 15 mL/min/1.73 m^2 (S5 = ESKD) was 0.55 mg/dL, 0.59 mg/dL, 0.56 mg/dL, 0.47 mg/dL, and 0.36 mg/dL (all p<0.0001 except for S1 vs. S3 where p=0.3726), respectively excluding patients with hyperbilirubinemia (TB > 1.24 mg/dL). The odds ratio (95% confidence interval) of incident ESKD for each 0.1 mg/dL increase in TB and hypobilirubinemia defined as TB ≤ 0.34 mg/dL were 0.92 (0.80-1.07) (p=0.2804) and 3.51 (1.56-7.88) (p=0.0023), respectively in patients with baseline eGFR ≥ 15 mL/min/1.73m^2 and 0.59 (0.37-0.95) (p=0.0283) and 6.03 (1.63-22.30) (p=0.0071), respectively in patients with baseline eGFR 29-15 mL/min/1.73m^2. ***Conclusions:*** Hypobilirubinemia might be a possible risk factor of ESKD.

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Eiji Oda

Tachikawa Medical Check-up Center, Tachikawa Medical Center
Nagachou 2-2-16, Nagaoka, Niigata, 940-0053 (Japan)
Tel. +81-258-36-6221, Fax +81-258-34-1113
E-Mail ijie@venus.sannet.ne.jp

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Introduction

The prevalence of chronic kidney disease (CKD) is increasing worldwide [1]. Reduced estimated glomerular filtration rate (eGFR) and increased urinary albumin excretion are established risk factors of end-stage renal disease (ESKD) [2, 3], cardiovascular disease (CVD), and all-cause mortality [3-7]. The identification of additional risk factors of ESKD other than known risk factors such as reduced eGFR and increased urinary excretion of albumin may be helpful for patients with CKD to predict future ESKD and to prevent from the disease progression to ESKD. Bilirubin is a potent antioxidant [8] and some epidemiological studies suggest that low levels of serum total bilirubin (TB) may be a risk factor of CVD [9-11]. Information on the association between TB and eGFR is limited and controversial. Fukui et al. found that TB was positively associated with eGFR and negatively associated with albuminuria in Japanese diabetic patients [12]. Shin et al. reported similar results in Korean diabetic and non-diabetic adults [13], indicating that bilirubin has a potential renoprotective effect. In contrast, Targher et al. found that a higher TB was significantly associated with lower eGFR both in hospital-based unselected outpatients [14] and in the US general population [15], suggesting fatty liver disease as a link between increased TB and decreased eGFR. However, these reports are all cross-sectional studies while whether TB can predict future ESKD has not been studied yet. Therefore, we examined the cross-sectional association between TB and eGFR using data from 14 508 unselected patients whose TB and eGFR were simultaneously measured and investigated whether TB can predict incident ESKD defined as eGFR < 15 mL/min/1.73 m^2 using data of unselected 6 251 patients with baseline eGFR ≥ 15 mL/min/1.73m^2 whose TB and eGFR were simultaneously measured in the next year. This study was approved by the ethics committee in Tachikawa Medical Center.

Subjects and Methods

Simultaneously measured TB and creatinine data at the biochemical laboratory of our Medical Center in 2009 and 2010 were all collected. The data of the first time measurements were used for each patient who underwent multiple measurements in the same year. The numbers (male/female) of the patients were 14 508 (8 177/6 331) in 2009 and 14 552 (8 199/6 353) in 2010. The data in 2009 were used in the cross-sectional study. The data in 2009 and 2010 of the same patients were paired excluding patients with baseline eGFR < 15 mL/min/1.73m^2 in 2009, resulting in 6 251 pairs which were used for the longitudinal study. Hospital records of 28 patients who developed new ESRD were reviewed.

Biochemical measurements and calculations of eGFR

TB and serum creatinine were measured by enzymatic methods on an automatic analyzer TBA-c16000 (Toshiba, Tokyo, Japan). In this assay system, the physiological range of TB was 0.3-1.2 mg/dL and that of creatinine was 0.65-1.09 mg/dL in men and 0.46-0.82 mg/dL in women. eGFR was calculated from serum creatinine with the gender-specific equations for Japanese recommended by the Japanese Society of Nephrology [16].

Statistical analysis

Stages of renal dysfunction were defined according to the CKD staging [17]; namely, eGFR ≥ 90 mL/min/1.73 m^2 (S1), 89-60 mL/min/1.73 m^2 (S2), 59-30 mL/min/1.73 m^2 (S3), 29-15 mL/min/1.73 m2 (S4), and < 15 mL/min/1.73 m^2 (S5 = ESKD). TB < 0.25 mg/dL was found in 1.8% and TB < 0.35 mg/dL was found in 9.7% of patients. In this study, we conveniently called TB ≤ 0.34 mg/dL as hypobilirubinemia. TB > 1.24 mg/dL was considered hyperbilirubinemia indicating possible liver diseases because TB > 1.24 mg/dL was found in 4.5% of patients. Geometric mean TB was calculated for each stage of renal dysfunction using 2009 data including and excluding patients with hyperbilirubinemia because TB was not distributed normally. Odds ratios (ORs) of eGFR < 15 mL/min/1.73 m^2, < 30 mL/min/1.73 m^2, and < 60 mL/min/1.73 m^2 were calculated for each 0.1 mg/dL increase in TB and hypobilirubinemia adjusting for age and sex including and excluding patients with hyperbilirubunemia using 2009 data. ORs of incident ESKD in 2010 were calculated for each 0.1 mg/dL increase in TB (mg/dL) and hypobilirubinemia adjusting for age, sex, and baseline eGFR

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Table 1. Geometric mean total bilirubin (TB) in each category of estimated glomerular filtration rate (eGFR) including and excluding patients with hyperbilirubinemia (TB >1.24 mg/dL)

	S1	S2	S3	S4	S5
eGFR (mL/min/1.73m^2)	90 ≤	60-89	30-59	15-29	< 15
including patients with hyperbilirubinemia (n = 14 508)					
n	1 983	7 889	4 031	390	215
female (%)	48.9	41.6	44.7	51.3	38.6
age (years)	49.1 ± 19.6	63.8 ± 14.7	74.4 ± 10.9	77.7 ± 12.3	70.1 ± 13.8
TB (mg/dL)	0.59 ± 1.65 [a]	0.63 ± 1.56 [a]	0.60 ± 1.61 [a]	0.54 ± 1.82 [a]	0.37 ± 1.76 [a]
excluding patients with hyperbilirubinemia (n = 13 647)					
n	1 868	7 426	3 789	354	210
female (%)	50.2	42.4	45.4	53.1	38.1
age (years)	49.0 ± 19.7	63.9 ± 14.7	74.5 ± 10.8	77.7 ± 12.3	70.2 ± 13.9
TB (mg/dL)	0.55 ± 1.49 [b]	0.59 ± 1.44 [b]	0.56 ± 1.47 [b]	0.47 ± 1.54 [b]	0.36 ± 1.69 [b]

[a] p = 0.7393 (S1 vs. S3), = 0.0132 (S1 vs. S4), = 0.0006 (S3 vs. S4), < 0.0001 (all other comparisons); [b] p < 0.0001 for all comparisons other than (S1 vs. S3) where p = 0.3726

including and excluding patients with hyperbilirubunemia and by baseline renal function. Means were compared with Scheffe's tests after ANOVA. Statistical analysis was performed using Dr SPSS-2 (IBM Japan, Tokyo, Japan). P values of lower than 0.05 were considered significant.

Results

Cross-sectional associations between TB and eGFR

The geometric mean TB of patients whose TB and eGFR were simultaneously measured in 2009 are presented by eGFR categories in Table 1. The geometric mean TB was 0.59 mg/dL, 0.63 mg/dL, 0.60 mg/dL, 0.54 mg/dL, and 0.47 mg/dL, respectively in S1, S2, S3, S4, and S5 including patients with hyperbilirubinemia. The p values were = 0.7393 for S1 vs. S3, = 0.0132 for S1 vs. S4, = 0.0006 for S3 vs. S4, and < 0.0001 for all other comparisons. The geometric mean TB was 0.55 mg/dL, 0.59 mg/dL, 0.56 mg/dL, 0.47 mg/dL, and 0.36 mg/dL, respectively in S1, S2, S3, S4, and S5 excluding patients with hyperbilirubinemia. The p values were < 0.0001 for all comparisons other than (S1 vs. S3) where the p value was 0.3726. Table 2 shows the age- and sex-adjusted OR of renal dysfunction for each 0.1 mg/dL increase in TB and hypobilirubinemia including and excluding patients with hyperbilirubinemia. The OR was adjusted for age and sex because renal function is affected by age and sex. The OR (95% confidence interval (CI)) of eGFR < 15 mL/min/1.73m^2, eGFR < 30 mL/min/1.73m^2, and eGFR < 60 mL/min/1.73m^2 for each 0.1 mg/dL increase in TB and hypobilirubinemia was 0.59 (0.54-0.64) (p < 0.0001) and 8.81 (6.68-11.60) (p < 0.0001), 0.91 (0.88-0.94) (p < 0.0001) and 4.48 (3.72-5.41) (p < 0.0001), and 0.993 (0.986-0.999) (p = 0.0316) and 1.77 (1.56-2.00) (p < 0.0001), respectively including patients with hyperbilirubinemia and 0.52 (0.47-0.57) (p < 0.0001) and 8.60 (6.51-11.36) (p < 0.0001), 0.70 (0.67-0.74) (p < 0.0001) and 4.65 (3.84-5.62) (p < 0.0001), and 0.94 (0.92-0.95) (p < 0.0001) and 1.78 (1.57-2.02) (p < 0.0001), respectively excluding patients with hyperbilirubinemia.

Longitudinal associations between baseline TB and incident ESKD in the next year

Among 6 251 patients whose TB and eGFR were simultaneously measured both in 2009 and in 2010 and whose baseline eGFR were ≥ 15 mL/min/1.73m^2, 28 patients newly developed ESKD in 2010, of which 24 cases were from 2 165 patients with baseline eGFR of 15-59 mL/min/1.73m^2 and 18 cases were from 164 patients with baseline eGFR of 15-29 mL/min/1.73m^2. Baseline clinical backgrounds of patients who developed new ESKD are presented in Table 3. The mean follow-up period, age, eGFR, and TB were 10.3 ± 5.0 months, 76.2 ± 11.9 years, 33.3 ± 23.7 mL/min/1.73m^2, and 0.53 ± 0.36 mg/dL, respectively and the baseline complication of diabetes, hypertension, and CVD were 42.9%, 75.0%, and 64.3%, respectively. Age-, sex-, and baseline eGFR-adjusted OR of ESKD for each 0.1 mg/dL increase

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Table 2. Odds ratios of renal dysfunction for each 0.1 mg/dL increase in total bilirubin (TB) and hypobilirubinemia (TB ≤0.34 mg/dL) adjusted for age and sex including and excluding patients with hyperbilirubinemia (TB >1.24 mg/dL). (95%) = 95% confidence interval)

	odds ratio (95%)	p
including patients with hyperbilirubinemia (n = 14 508)		
for eGFR[a] <15 mL/min/1.73m² (n=215)		
TB (0.1 mg/dL increase)	0.59 (0.54-0.64)	<0.0001
hypobilirubinemia	8.81 (6.68-11.60)	<0.0001
for eGFR[a] <30 mL/min/1.73m² (n=605)		
TB (0.1 mg/dL increase)	0.91 (0.88-0.94)	<0.0001
hypobilirubinemia	4.48 (3.72-5.41)	<0.0001
for eGFR[a] <60 mL/min/1.73m² (n=4 636)		
TB (0.1 mg/dL increase)	0.993 (0.986-0.999)	0.0316
hypobilirubinemia	1.77 (1.56-2.00)	<0.0001
excluding patients with hyperbilirubinemia (n = 13 647)		
for eGFR[a] <15 mL/min/1.73m² (n=210)		
TB (0.1 mg/dL increase)	0.52 (0.47-0.57)	<0.0001
hypobilirubinemia	8.60 (6.51-11.36)	<0.0001
for eGFR[a] <30 mL/min/1.73m² (n=564)		
TB (0.1 mg/dL increase)	0.70 (0.67-0.74)	<0.0001
hypobilirubinemia	4.65 (3.84-5.62)	<0.0001
for eGFR[a] <60 mL/min/1.73m² (n=4 353)		
TB (0.1 mg/dL increase)	0.94 (0.92-0.95)	<0.0001
hypobilirubinemia	1.78 (1.57-2.02)	<0.0001

[a] estimated glomerular filtration rate

Table 3.

Baseline clinical backgrounds of patients who developed new end-stage kidney disease	
n (male/female)	28 (15/13)
follow-up months	10.3 ± 5.0
baseline age (years)	76.2 ± 11.9
baseline eGFR[a] (mL/min/1.73m²)	33.2 ± 23.7
baseline total bilirubin (mg/dL)	0.53 ± 0.36
baseline complications	
diabetes (%)	42.9
hypertension (%)	75.0
cardiovascular disease (%)	64.3

[a] estimated glomerular filtration rate

in TB and hypobilirubinemia are presented in Table 4. The adjusted OR (95% CI) of ESKD for each 0.1 mg/dL increase in TB and hypobilirubinemia were 0.92 (0.80-1.07) (p = 0.2804) and 3.51 (1.56-7.88) (p = 0.0023), respectively including patients with hyperbilirubinemia and 0.87 (0.71-1.07) (p = 0.1901) and 3.46 (1.53-7.85) (p = 0.0029), respectively excluding patients with hyperbilirubinemia among patients with baseline eGFR ≥ 15 mL/min/1.73m². The adjusted OR (95% CI) of ESKD for each 0.1 mg/dL increase in TB and hypobilirubinemia were 0.92 (0.78-1.09) (p = 0.3560) and 3.21 (1.31-7.80) (p = 0.0102), respectively including patients with hyperbilirubinemia and 0.84 (0.65-1.08) (p = 0.1700) and 3.24 (1.30-8.09) (p = 0.0115), respectively excluding patients with hyperbilirubinemia among patients with baseline eGFR of 15-59 mL/min/1.73m². The adjusted OR (95% CI) of ESKD for each 0.1 mg/dL increase in TB and hypobilirubinemia were 0.59 (0.37-0.95) (p = 0.0283) and 6.03 (1.63-22.30) (p = 0.0071), respectively including patients with hyperbilirubinemia and 0.59 (0.37-0.95) (p = 0.0287) and 5.78 (1.56-21.41) (p = 0.0086), respectively excluding patients with hyperbilirubinemia among patients with baseline eGFR of 15-29 mL/min/1.73m².

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Table 4. Odds ratios of end-stage kidney disease for each 0.1 mg/dL increase in total bilirubin (TB) and hypobilirubinemia (TB ≤0.34 mg/dL) adjusted for age, sex, and baseline estimated glomerular filtration rate (eGFR) stratified by baseline eGFR categories including and excluding patients with hyperbilirubinemia (TB >1.24 mg/dL). (95%) = 95% confidence interval)

	odds ratio (95%)	p
including patients with hyperbilirubinemia		
in patients with eGFR ≥15 mL/min/1.73m^2 (n=6 251)		
TB (0.1 mg/dL increase)	0.92 (0.80-1.07)	0.2804
hypobilirubinemia	3.51 (1.56-7.88)	0.0023
in patients with eGFR 15-59 mL/min/1.73m^2 (n=2 165)		
TB (0.1 mg/dL increase)	0.92 (0.78-1.09)	0.3560
hypobilirubinemia	3.21 (1.31-7.80)	0.0102
in patients with eGFR 15-29 mL/min/1.73m^2 (n=164)		
TB (0.1 mg/dL increase)	0.59 (0.37-0.95)	0.0283
hypobilirubinemia	6.03 (1.63-22.30)	0.0071
excluding patients with hyperbilirubinemia		
in patients with eGFR ≥15 mL/min/1.73m^2 (n=5 890)		
TB (0.1 mg/dL increase)	0.87 (0.71-1.07)	0.1901
hypobilirubinemia	3.46 (1.53-7.85)	0.0029
in patients with eGFR 15-59 mL/min/1.73m^2 (n=2 054)		
TB (0.1 mg/dL increase)	0.84 (0.65-1.08)	0.1700
hypobilirubinemia	3.24 (1.30-8.09)	0.0115
in patients with eGFR 15-29 mL/min/1.73m^2 (n=155)		
TB (0.1 mg/dL increase)	0.59 (0.37-0.95)	0.0287
hypobilirubinemia	5.78 (1.56-21.41)	0.0086

Discussion

In the present study, we demonstrated that TB was significantly lower in subjects with advanced renal dysfunction than in those with normal renal function and suggested that hypobilirubinemia may be a possible risk factor of ESKD independently of age, sex, and baseline eGFR.

The definition and classification for CKD was proposed by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) in 2002 and endorsed by the Kidney Disease: Improving Global Outcomes (KDIGO) in 2004 [17]. CKD is the primary cause of ESKD and is one of the major risk factors of CVD and all-cause mortality [3-7]. Not only ESKD but also less severe renal dysfunction increases the risk of death, CVD, and hospitalization [6]. Apart from CKD which consists of decreased eGFR and/or increased albuminuria, age, anemia, cigarette smoking, blood pressure, low HDL cholesterol, and fasting glucose independently predict ESKD [2]. However, to date, decreased TB has not been reported as an independent risk factor of ESKD.

As for cross-sectional associations between TB and eGFR, Fukui et al. found that TB was positively associated with eGFR in Japanese diabetic patients [12] and Shin et al. reported similar results in Korean diabetic and non-diabetic adults [13], while Targher et al. reported an opposite finding in both hospital-based unselected outpatients [14] and in the US general population [15]. In the present study, TB was significantly lower in S1 than in S2, in S3 than in S2, in S4 than in S3, and in S5 than in S4. We speculate that decrease in TB may reflect increased oxidative stress which is associated with renal dysfunction and that hyperbilirubinemia indicates possible liver disease which confounds the relationship between TB and eGFR. We think that TB was lower in S1 than in S2 because S1 includes glomerular hyper-filtration which is one of the early stages of renal dysfunction and may be associated with slightly increased oxidative stress.

Bilirubin is a potent antioxidant [8] and low serum TB levels may reflect increased oxidative stress. Some epidemiological studies suggest that low TB levels may be a risk factor

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of CVD [9-11]. The flow-mediated dilatation of brachial artery [18] and coronary flow reserve [19] were significantly lower in subjects with lower TB and carotid intima-media thickness [18] and coronary artery calcification [20] were associated with lower TB. Balloon injury-induced neointima formation is less in genetically hyperbilirubinemic rats and in wild-type rats treated with biliverdin, the precursor of bilirubin, than in controls and bilirubin inhibits the proliferation of vascular smooth muscle cells [21]. Oxidative stress and renal dysfunction may form a vicious cycle. Oxidative stress is one of the causal mechanisms of renal dysfunction and increases as renal dysfunction progresses as a result of increased oxidant activity and reduced antioxidant capacity [22]. Antioxidants may prevent the progression of renal dysfunction. Hyperbilirubinemia, acting as an antioxidant, can improve glomerular filtration rate and renal blood flow in a mouse model of angiotensin-induced hypertension [23]. An induction of heme oxigenase-1, which increases the bilirubin/biliverdin system, interrupts and counteracts the influence of the renin-angiotensin system to increase in blood pressure in renovascular hypertension rats [24]. In patients with mild to moderate CKD, a treatment strategy with antioxidants consisting of pravastatin, vitamin E, and homocysteine reduced carotid intima-media thickness and urinary albumin excretion and increased flow-mediated dilatation of brachial artery [25].

Clinical Implications

The results of the present study suggest that hypobilirubinemia which may indicate increased oxidative stress may be a possible risk factor of ESKD independently of baseline eGFR. The present results suggest that strategies aimed to increase TB such as cessation of smoking [9] and administration of TB increasing agents [26] may possibly prevent the progression of renal dysfunction to ESKD. CKD patients with hypobilirubinemia may be promising candidates for an antioxidant therapy and TB may be a useful marker of oxidative stress under antioxidant therapy in CKD patients.

Limitations

This study was not based on the general population but on unselected laboratory data in our Medical Center and the follow-up period was only more or less than one year. Other important outcomes of renal dysfunction than ESKD such as CVD and all-cause mortality were not examined and the OR was not adjusted for albuminura and other confounding factors because information about other laboratory data including albuminuria, hemoglobin, fasting glucose, or cholesterol and clinical backgrounds of the patients was not included in the present study. The longitudinal association was examined with logistic regression using only two time points because the exact follow-up period of each subject was not included in the study. Nevertheless, the present results suggested that hypobilirubinemia may be a possible risk factor of ESKD independently of baseline eGFR.

Conflict of Interest Statement

All authors have no conflict of interest to declare. The results presented in this paper have not been published previously in whole or part. The authors received no financial support.

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