Atherosclerosis 265 (2017) 155–161

Contents lists available at ScienceDirect

Atherosclerosis

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

Relationship between serum total bilirubin levels and mortality in uremia patients undergoing long-term hemodialysis: A nationwide cohort study

Hui-Hsien Su [a, 1], Chia-Man Kao [b, 1], Yi-Chun Lin [e, f], Yen-Chung Lin [b, c, d, **, 2], Chih-Chin Kao [c], Hsi-Hsien Chen [c], Chih-Cheng Hsu [g], Kuan-Chou Chen [b], Chiung-Chi Peng [b], Mai-Szu Wu [b, c, d, *, 2]

[a] Division of Gastroenterology, Department of Internal Medicine, Taipei Medical University Hospital, 252, Wu-xing St., Taipei, Taiwan, ROC
[b] Graduate Institute of Clinical Medicine, College of Medicine, Taipei Medical University, 250, Wu-xing St., Taipei, Taiwan, ROC
[c] Division of Nephrology, Department of Internal Medicine, Taipei Medical University Hospital, 252, Wu-xing St., Taipei, Taiwan, ROC
[d] Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, 252, Wu-xing St., Taipei, Taiwan, ROC
[e] Division of Endocrinology & Metabolism, Department of Medicine, Taipei Veterans General Hospital, 201, Sec.2, Shi-Pai Rd., Taipei, Taiwan, ROC
[f] Faculty of Medicine, National Yang-Ming University, 155, Sec.2, Linong St., Taipei, Taiwan, ROC
[g] Institute of Population Health Sciences, National Health Research Institutes, 35 Keyan Rd, Zhunan, Miaoli county, Taiwan, ROC

ARTICLE INFO

Article history:
Received 24 April 2017
Received in revised form
11 June 2017
Accepted 1 September 2017
Available online 4 September 2017

Keywords:
Atherosclerosis
Bilirubin
End stage renal disease
Hemodialysis
Unconjugated

ABSTRACT

Background and aims: Previous studies show that serum bilirubin has potent antioxidant effect and is associated with protection from kidney damage and reduce cardiovascular events. The aim of this study was to examine the association of serum total bilirubin level and mortality in uremia patients who underwent hemodialysis.

Methods: This is a nationwide retrospective long-term cohort study. Patients were registered in the Taiwan Renal Registry Data System (TWRDS) from 2005 to 2012. A total of 115,535 hemodialysis patients were surveyed and those with valid baseline total bilirubin (TB) data were enrolled. All-cause mortality was the primary outcome.

Results: A total of 47,650 hemodialysis patients followed for 27.6 ± 12 months, were divided into 3 groups according to different baseline serum total bilirubin levels (0.1–0.3, 0.3–0.7, 0.7–1.2 mg/dL). Mean age was 61.4 ± 13.6 years, 50% were male, 13% were hepatitis B carriers, and 20% were hepatitis C carriers. Primary outcome was the 3-year mortality. The TB level 0.7–1.2 mg/dL group had high mortality, statistically significant hazard ratio of mortality was 1.14 (crude HR, 95% 1.07–1.20, $p < 0.01$), and adjusted HR was 1.18 (model 1, 95% CI 1.11–1.25), 1.21 (model 2, 95% CI 1.14–1.29, $p < 0.01$), 1.44 (model 3, 95% CI 1.06–1.96, $p < 0.01$), respectively. Sensitivity test showed that after excluding 14,899 patients with hepatitis B or C, or abnormal liver function, the highest level of TB associated with higher significant mortality was still robust.

Conclusions: In our study, high TB level is associated with mortality in uremia patients undergoing long-term hemodialysis, but further studies of the different effects of unconjugated or conjugated bilirubin on hemodialysis patients are needed.

1. Introduction

Cardiovascular disease-related mortality risk increases about 30-fold in end-stage renal disease patients receiving hemodialysis. Lipid oxidation or oxidative stress is important in the pathogenesis of atherosclerosis [1], which may be attributed to bilirubin's antioxidant properties [2]. Thus, a low serum total bilirubin (TB) concentration is associated with accelerated progression of chronic

* Corresponding author. Present address: 110 No. 252, Wu-xing St., Taipei Medical University Hospital, Taiwan, ROC.
** Corresponding author. Present address: 110 No. 252, Wu-xing St., Taipei Medical University Hospital, Taiwan, ROC.
E-mail addresses: yclin0229@tmu.edu.tw (Y.-C. Lin), maiszuwu@gmail.com (M.-S. Wu).
[1] These authors contributed equally to this work as first authors.
[2] These authors contributed equally to this work as corresponding authors.

http://dx.doi.org/10.1016/j.atherosclerosis.2017.09.001
0021-9150/

kidney disease (CKD), is an independent predictor of CKD progression [3], and is associated with a high incidence of cardiovascular events [4].

In patients with uremia, unlike other anti-oxidative agent-uric acids [5], serum TB level is stable and not affected by hemodialysis therapy itself. There is only one study in which a graded, reverse association was observed between serum TB and adverse outcomes among chronic hemodialysis patients [6]. However, it was a small, single-center, observational study. A larger cohort study with 5900 Korean men showed that higher serum direct bilirubin was associated with a lower risk of new-onset non-alcoholic fatty liver disease. However, body mass index also showed an inverse trend with TB. There is a counterintuitive phenomenon present in hemodialysis patients: obese patients may have a better prognosis than non-obese patients [7]. Therefore, how TB affects clinical outcomes in dialysis patients remains controversial due to a paucity of data.

The aim of this study was to investigate the relationship between TB and mortality in patients undergoing long-term HD using the nationwide TWRDS database. TWRDS is a registered online system for the dialysis center to upload their annual biochemistries for reimbursement from the National Health Insurance bureau in Taiwan. The system was operated by specialized nurses, and repeated records of bilirubin, taken every 3 months in each hemodialysis (HD) patient, were used to predict its association with mortality.

2. Materials and methods

This study was approved by the ethics committee of the Taipei Medical University Institutional Review Board (No. N201610006) and was carried out in accordance with the Declaration of Helsinki of 1975, as revised in 2013. The Waiver of the Requirements for Obtaining Informed Consent was approved by the Taipei Medical University Institutional Review Board since the study met all applicable regulations.

2.1. Taiwan Renal Registry Data System

The TWRDS was initially established in 1987 for the accreditation of dialysis therapy. All dialysis units in Taiwan are obligated to upload relevant data to the website constructed by TWRDS in 2005. This provided only a very small portion of incentives (5%) for dialysis centers and did not correlate with the NHI's medical reimbursement for overall expenditures from the organization. A registered nurse from each dialysis unit submits a quarterly report. The data in the TWRDS form a solid foundation for continual dialysis quality control at the national level.

2.2. Patient enrollment

We included in the analysis patients registered with the TWRDS from 2005 to 2012 (n = 115,565). Patients who had received HD or peritoneal dialysis (PD) for >3 months were distributed to either the HD group or the PD group, respectively. There were 4661 patients who changed their dialysis modality, 9232 who used PD (categorical or continuous), 998 patients with extremely old or young age (>90 years or <20 years), 42,887 patients without a TB record (with the same sex distribution and a similar average age as the study population), and 2978 patients with higher (>1.2 mg/dL) or lower (<0.1 mg/dL) TB. These patients were excluded from the analysis and, finally, 47,650 HD patients with valid baseline TB data (average TB level in the first year) were followed for 3 years (Fig. 1).

2.3. Statistical analysis

All variables were analyzed with the Chi-squared test (categorical variables), analysis of variance (continuous variables normally distributed), or the Mann–Whitney *U* test (continuous variables with non-parametric distributions). After excluding 2978 patients with a TB value beyond the reference level (0.1–1.2 mg/dL), patients were divided into groups based on a clinically acceptable level of 0.3 and 0.7 mg/dL, and quartiles of TB levels were also used for grouping. Kaplan-Meier curves were used to determine the unadjusted survival curves, and a Cox regression analysis was used to test the association between predictors and primary outcomes, with adjustment for multiple confounders. A sensitivity test was performed by excluding from the population hepatitis B virus (HBV) and hepatitis C virus (HCV) carriers, and patients with liver function abnormalities. A two-tailed p-value <0.05 was used to indicate statistical significance.

3. Results

3.1. Demographic characteristics of the overall 47,650 uremia patients who underwent hemodialysis

Table 1 shows the baseline characteristics of the population, stratified by 3 different TB levels (0.1–0.3, 0.3–0.7, and 0.7–1.2 mg/dL). The average TB levels in these groups were 0.2 ± 0.1, 0.5 ± 0.1, and 0.8 ± 0.1 mg/dL, respectively; the mean age was 61.4 ± 13.6 years, 50% were men, 13% carried HBV, and 20% carried HCV. The groups had similar biochemistries, including with respect to uric acid, ferritin, cholesterol, triglycerides, albumin, hematocrit, and calcium or phosphate levels, except for total bilirubin and liver function (ALT). During the follow-up period, only 908 (1.9%) patients received kidney transplantation, the comparisons of basic characteristics between those who had kidney transplantation or not are listed in Supplementary Data 1, there were no significant differences in TB levels. The issue of selection bias could be avoided.

3.2. Unadjusted and adjusted survival analysis for total bilirubin as predictors (categorical or continuous)

Fig. 2 shows a Kaplan-Meier curve and reveals that those with TB levels <0.3 mg/dL had the best unadjusted survival rate, followed by those with TB levels between 0.3 and 0.7 and > 0.7 mg/dL. The average follow-up duration was 27.6 ± 12 months, similar across the different TB groups. Table 2 shows more detailed information for the groups with TB levels ranging from 0.3 to 1.2 mg/dL with an interval of 0.1 mg/dL. The group with the highest level of TB (between 0.7 and 1.2 mg/dL) had a statistically significant hazard ratio (HR) for mortality of 1.14 (crude HR; 95% confidence interval (CI), 1.07–1.20, $p < 0.01$), and adjusted HRs of 1.18 (model 1; 95% CI, 1.11–1.25), 1.21 (model 2; 95% CI, 1.14–1.29), and 1.44 (model 3; 95% CI, 1.06–1.96). For continuous predictors, TB showed similar trends: crude HR 1.03 (95% CI 1.03–1.04) and adjusted HRs 1.03 (95% CI, 1.03–1.04) in model 1, 1.04 (95% CI, 1.03–1.05) in model 2, and 1.05 (95% CI, 1.01–1.09) in model 3, for each 0.1-mg/dL increase in TB. The sensitivity test was also performed by including those with TB > 1.2 mg/dL, and <0.1 mg/dL (total N = 50,601), the results that higher TB was associated with high morality remained unaffected (Supplemental Data 2).

3.3. Survival analysis stratified by quartile of total bilirubin levels

Table 3 shows the crude and adjusted HRs for mortality for HD patients according to quartile (Q1 to Q4). It reveals that the Q4 group with the highest average TB (mean TB, 0.93 ± 0.78 mg/dL)