ORIGINAL ARTICLE

Relation of total bilirubin and QT interval prolongation (from the Third National Health and Nutrition Examination Survey)

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Abstract

Objective: The association of bilirubin with cardiovascular disease (CVD) is controversial. We sought to explore the association of total bilirubin (TB) levels with QT interval in a multiracial cohort.

Methods: A total of 6,627 participants (59.0 ± 13.3 years; 52.6% women, 49.7% Non-Hispanic Whites) without CVD from the Third National Health and Nutrition Examination Survey were included in this analysis. QT was automatically measured from digital 12-lead electrocardiogram in a central reading center. A multivariable logistic regression model was used to examine the cross-sectional association between tertiles of TB and prolonged QT interval (≥ 450 ms in men and ≥ 460 ms in women).

Results: The prevalence of prolonged QT was higher among those with higher levels of TB (prolonged QT prevalence was 4.7%, 6.8%, and 7.0% across TB lower (0–0.4 mg/dl), middle (0.5–1.6 mg/dl), and higher (0.70–4.30 mg/dl) tertiles, respectively). In a model adjusted for potential confounders, participants within the highest TB tertile had significantly greater odds of the prolonged QT interval (Odds ratios [95% confidence interval] 1.53 [1.16–2.02]) compared to those with bilirubin levels in the first tertile. Each 0.29 mg/dl increase in TB levels was associated with a 12% (p -value $< .0001$) increase in the prevalence of prolonged QT interval. This association was stronger in men than in women (interaction p -value = .04).

Conclusion: Elevated bilirubin levels are associated with a prolonged QT interval. This finding extends our current knowledge on the relationship between serum bilirubin and CVD by demonstrating a link between higher TB and abnormal cardiac repolarization.

KEYWORDS

NHANES-III, QT interval, total bilirubin

1 | INTRODUCTION

Bilirubin is a byproduct of heme catabolism, and previous studies have shown an inverse association of total serum bilirubin (TB)

with incident cardiovascular disease (CVD) due to its anti-inflammatory, antithrombotic, and antioxidative properties (Djoussé et al., 2001; Kunutsor, Bakker, Gansevoort, Chowdhury, & Dullaart, 2015). TB levels were inversely associated with severity of coronary

atherosclerosis (Akboga et al., 2015), arterial stiffness (Huang et al., 2016), risk of hypertension (Wang & Bautista, 2015), and metabolic syndrome (Lin et al., 2009). However, this protective association is not consistent, with some studies showing an increased risk of mortality and major adverse cardiac events (MACE) with elevated serum total bilirubin (TB) (Baumann et al., 2016; Chung et al., 2016; Xu et al., 2019). Elevated TB levels were also associated with the severity of heart failure (HF) (van Deursen et al., 2010) and predicated increased risk of mortality among participants with pulmonary arterial hypertension (Takeda et al., 2010; Xu et al., 2017) and HF (Ambrosy et al., 2012).

Whether the association of TB with CVD is causal, or TB is a marker of the underlying disease is a matter of controversy and one approach to shed light on the controversial association of TB with CVD is to examine its association with well-defined pathophysiological markers that have established prognostic value in population studies. One such marker is QT interval, a commonly reported electrocardiographic interval on 12-lead electrocardiogram (ECG) that has been consistently associated with increased risk of CVD and all-cause mortality (Zhang et al., 2011). Therefore, in this analysis from the Third National Health and Nutritional Examination Survey (NHANES-III), we examined the association of TB with prolonged QT interval as a unique electrophysiological measure reflecting ventricular repolarization.

2 | METHODS

2.1 | Study participants

NHANES is a periodic survey of the noninstitutionalized civilian population in the United States. Its principal aim is to determine estimates of disease prevalence and health status of children and adults. The structure of the NHANES-III (1988 and 1994) is published somewhere else ("Plan and operation of the Third National Health and Nutrition Examination Survey, 1988-94. Series 1: programs and collection procedures," 1994). The NHANES-III study was approved by the National Center for Health Statistics (NCHS) Research Ethics Review Board, and documented consent was obtained from participants.

For this analysis, we only considered NHANES-III participants who underwent an ECG recording ($n = 8,561$). We excluded participants with prior CVD (coronary heart disease, HF, and stroke), those on antiarrhythmic medications and missing key covariates. We also excluded participants with poor quality ECGs or with major intraventricular conduction delay (i.e., complete bundle branch blocks and QRS duration ≥ 120 ms) since these conditions prohibit appropriate interpretation of QT. After all exclusions ($n = 1,934$), 6,627 participants were available for analysis.

2.2 | Total bilirubin

Serum TB concentrations were determined using 2,5-dichlorophenyl-diazonium tetrafluoroborate in a strongly acidic medium. The intensity

of the azobilirubin color was measured photometrically using a Hitachi 737 automated autoanalyzer (Boehringer Mannheim Diagnostics). Detailed descriptions of the blood sampling and handling procedures for laboratory procedures were published previously ("Plan and operation of the Third National Health and Nutrition Examination Survey, 1988-94. Series 1: programs and collection procedures," 1994).

2.3 | Electrocardiogram

Resting 12-lead ECGs were obtained with a Marquette MAC 12 system (Marquette Medical Systems) during the mobile examination visits by trained technicians. Analysis of ECGs was achieved through a computerized automated process and visual inspection by a trained technician located in a central core laboratory. Heart rate-corrected QT was calculated using the NHANES specific QT correction formula (Soliman, Shah, Boerkircher, Li, & Rautaharju, 2014). Prolonged QT was defined as QT ≥ 460 ms for women and ≥ 450 ms for men (Ahmad et al., 2019).

2.4 | Covariates

Age, sex, race/ethnicity, and smoking status were self-reported. Body mass index (BMI) was calculated from height and weight measurements. Blood pressure (mm Hg) was measured using a mercury sphygmomanometer according to the American Heart Association recommendations. Blood pressure was taken while seated, using a standard mercury sphygmomanometer and up to three measurements were averaged. Blood samples were collected via venipuncture by a phlebotomist. Samples were analyzed for total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG) glucose, etc., using laboratory procedures as reported by NCHS ("Plan and operation of the Third National Health and Nutrition Examination Survey, 1988-94. Series 1: programs and collection procedures," 1994). Hypertension was defined as systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 85 or the use of antihypertensive medications. Diabetes was defined as blood sugar level ≥ 126 mg/dl or use of antidiabetic medications. Hyperlipidemia was defined as serum TC ≥ 200 mg/dl or triglycerides ≥ 150 mg/dl or use of antihyperlipidemic medications. Obesity was defined as BMI ≥ 30 kg/m².

2.5 | Statistical analysis

Baseline characteristics were tabulated and compared by TB tertiles. Analysis of variance (ANOVA) was used to compare the continuous variables while the chi-square test was used to compare categorical variables.

Multivariable logistic regression analysis was used to examine the cross-sectional association between tertiles of TB and prolonged QT interval. Odds ratios (OR) and 95% confidence interval (95% CI) were calculated by comparing lower tertile of TB (reference) to higher tertiles of TB. Models were adjusted as follows: Model 1 was adjusted for age, sex, and race; Model 2 adjusted for model 1 plus current smoking, hypertension, diabetes, hyperlipidemia, and

TABLE 1 Baseline characteristics of 6,627 study participants from NHANES-III

Characteristics	Total bilirubin tertiles			p-value ^a
	1st (n = 2,511)	2nd (n = 2,265)	3rd (n = 1,851)	
Total bilirubin (mg/dl)	0.3 ± 0.1	0.5 ± 0.0	0.9 ± 0.3	<.0001
Age (years)	57.7 ± 12.7	59.3 ± 13.3	58.5 ± 12.3	<.0001
Men (%)	688 (27.4%)	1,120 (49.4%)	1,250 (67.5%)	<.0001
Race (%)				<.0001
Non-Hispanic Whites	1,091 (43.4%)	1,211 (53.4%)	961 (51.9%)	
Non-Hispanic Blacks	711 (28.3%)	460 (20.3%)	338 (18.2%)	
Mexican Americans	600 (23.8%)	509 (22.4%)	468 (25.2%)	
Others	109 (4.34)	85 (3.7%)	84 (4.5%)	
Systolic blood pressure (mm Hg)	132.1 ± 20.6	131.6 ± 18.4	131.5 ± 19.4	.57
Diastolic blood pressure (mm Hg)	75.7 ± 10.0	76.3 ± 10.2	77.4 ± 10.3	<.0001
Antihypertensive medications	521 (20.7%)	467 (20.6%)	356 (19.2%)	.41
Diabetes mellitus (%)	300 (11.9%)	258 (11.3%)	233 (12.5%)	.49
Anti diabetics (%)	193 (7.6%)	130 (5.7%)	123 (6.6%)	.02
Total cholesterol (mg/dl)	219.3 ± 43.3	219.5 ± 43.4	213 ± 43.9	<.0001
Serum triglycerides (mg/dl)	145.1 ± 91.0	158.2 ± 112.5	117.2 ± 174.2	<.0001
Aspartate aminotransferase (U/L)	20.4 ± 11.3	22.0 ± 11.6	25.4 ± 20.0	<.0001
Alanine aminotransferase (U/L)	14.9 ± 11.4	17.3 ± 13.4	19.8 ± 16.0	<.0001
C-reactive protein (mg/dl)	0.59 ± 0.94	0.43 ± 0.58	0.43 ± 0.75	<.0001
Anti hyperlipidemic (%)	74 (2.9%)	63 (2.7%)	51 (2.7%)	.91
Current smoker (%)	630 (25.0%)	510 (22.5%)	371 (20.0%)	.0004
Obesity (%)	756 (30.1%)	630 (27.8%)	464 (25.0%)	.001
QRS duration (ms)	94.6 ± 9.8	96.9 ± 9.7	97.0 ± 10.0	<.0001
QT interval (ms)	424.1 ± 19.7	423.3 ± 20.7	422.1 ± 20.6	.007
Prolonged QT interval (%)	120 (4.7%)	155 (6.8%)	130 (7.0%)	.001

Note: Obesity defined as body mass index ≥ 30 kg/m².

^ap-value calculated by ANOVA for continuous variables and chi-square for categorical variables.

obesity; and model 3 adjusted for model 2 plus serum alanine aminotransferase, serum aspartate transferase, and C-reactive protein.

Using a model adjusted similarly to model 3, we conducted a subgroup analysis stratified by age (using 60 years as a cut point), sex, and race (whites vs. non-whites). Test for interaction was performed between the main effect variable and the subgroups on its outcome that is prolonged QT interval.

In an additional analysis, we used QT as a continuous outcome variable in multivariable linear regression analysis adjusted in a similar fashion as the models described above.

All statistical analyses were performed using with SAS version 9.4 (SAS Institute Inc), and two-sided p-values were considered significant if less than .05.

3 | RESULTS

A total of 6,627 participants (59.0 ± 13.3 years; 52.6% women, 49.7% non-Hispanic whites) NHANES-III were included in the final analysis. Table 1 shows the baseline characteristics of the study participants stratified by serum TB tertiles. Participants in the highest TB tertile were more likely to be men, white, and had a lower prevalence of CVD risk factors such as obesity and diabetes and had lower levels of serum cholesterol, triglycerides, and C-reactive protein. The prevalence of prolonged QT was higher among those with higher levels of TB; prolonged QT prevalence was 4.7%, 6.8%, and 7.0% across TB lower (0–0.4 mg/dl), middle (0.5–1.6 mg/dl), and higher (0.70–4.30 mg/dl) tertiles, respectively.

TABLE 2 ORs and 95% CI of cross-sectional association of total bilirubin with QT interval

Total bilirubin	Model 1 OR (95% CI)	p-value	Model 2 OR (95% CI)	p-value	Model 3 OR (95% CI)	p-value
1st tertile	Ref	—	Ref	—	Ref	
2nd tertile	1.44 (1.12–1.86)	.004	1.50 (1.17–1.94)	.001	1.52 (1.18–1.96)	.001
3rd tertile	1.52 (1.16–2.00)	.002	1.61 (1.22–2.12)	.0006	1.53 (1.16–2.02)	.002
Per SD increase ^a	1.74 (1.28–2.35)	.0003	1.75 (1.30–2.36)	.0002	1.12 (1.03–1.23)	.007

Note: Model 1 adjusted for age, sex, and race.

Model 2 adjusted for model 1 plus hypertension, obesity, current smoker, diabetes, and hyperlipidemia.

Model 3 adjusted for model 2 plus alanine aminotransferase, aspartate aminotransferase, and C-reactive protein.

Abbreviations: CI, confidence interval; OR, odds ratio.

^aper 0.29 mg/dl increase in Total bilirubin levels.

TABLE 3 Association of total bilirubin with QT interval among subgroups

Subgroups	Bilirubin tertiles	Participants <i>n</i>	Events <i>n</i> (%)	OR (95% CI) ^a	Interaction <i>p</i> -value
White	2nd	1,211	76 (6.2%)	1.39 (0.95–2.04)	.86
	3rd	961	60 (6.2%)	1.49 (0.98–2.26)	
Non-white	2nd	1,054	79 (7.5%)	1.58 (1.12–2.22)	
	3rd	890	70 (7.8%)	1.70 (1.18–2.45)	
Men	2nd	1,120	70 (6.2%)	1.81 (1.14–2.88)	.04
	3rd	1,250	97 (7.7%)	2.16 (1.38–3.40)	
Women	2nd	1,145	85 (7.4%)	1.48 (1.09–2.02)	
	3rd	601	33 (5.4%)	1.09 (0.74–1.69)	
≤60 years	2nd	1,149	49 (4.2%)	1.32 (0.87–1.99)	.26
	3rd	983	47 (4.7%)	1.56 (1.01–2.41)	
>60 years	2nd	1,116	106 (9.5%)	1.67 (1.21–2.32)	
	3rd	868	83 (9.5%)	1.66 (1.16–2.36)	

Note: Model adjusted for age, sex, race, hypertension, diabetes, current smoking, obesity, hyperlipidemia, alanine aminotransferase, aspartate aminotransferase, and C-reactive protein.

^aAbbreviations: CI, confidence interval; OR, odds ratio.

In a model adjusted for potential confounders, participants in the highest TB tertile had significantly greater odds of the prolonged QT interval (OR [95% CI]: 1.53 [1.16–2.02]) compared to those with TB levels in the first tertile (Table 2). Each 0.29 mg/dl increase in TB levels was associated with a 12% (*p*-value .07) increase in the prevalence of prolonged QT interval (Table 2).

The association between serum TB tertiles and QT was consistent across subgroups stratified by age and race. However, the association was stronger in men than women (interaction *p*-value = .04) (Table 3).

Table 4 shows the association between serum TB and QT as a continuous variable using the linear regression analysis. As shown, increasing tertiles of TB were also associated with a statistically significant prolongation of the QT interval.

4 | DISCUSSION

In this analysis from a large racially diverse community-based sample of participants free of clinical CVD, we observed an association

of TB with prolonged QT interval after rigorous adjustment of potential confounders. This association was stronger among men compared with women. This finding extends our current knowledge on the relationship between serum bilirubin and CVD by demonstrating a link between higher TB and abnormal cardiac repolarization.

Prolongation of QT interval has been associated with incident CVD, stroke, SCD, CVD death, and all-cause death and is predictive of poor outcomes among those with CVD (Beinart et al., 2014; Soliman et al., 2012; Zhang et al., 2011). Prolonged QT is also a marker of subclinical atherosclerosis and viewed as a manifestation of subclinical myocardial ischemia, autonomic dysfunction, and left ventricular hypertrophy (Soliman et al., 2012). Therefore, finding of a strong association between TB and prolonged QT interval in our study may highlight the role of TB as a marker for risk stratification. To the best of our knowledge, no previous studies have examined the association between TB and prolonged QT interval.

Previous studies have shown that TB level is inversely associated with coronary artery disease (CAD). However, this role in the prevention of CVD controversial. TB reduces the oxidation of low-density lipoprotein, which is involved in the pathogenesis of atherosclerosis

TABLE 4 Beta-coefficient and 95% CI of cross-sectional association of total bilirubin with QT interval

Total bilirubin	Model 1 beta-coefficient (95% CI)	p-value	Model 2 beta-coefficient (95% CI)	p-value	Model 3 beta-coefficient (95% CI)	p-value
1st tertile	Ref	—	Ref	—	Ref	—
2nd tertile	1.32 (0.20–2.44)	.02	1.53 (0.42–2.65)	.007	1.53 (0.41–2.65)	.007
3rd tertile	2.30 (1.06–3.53)	.0003	2.63 (1.40–3.86)	<.0001	2.32 (1.09–3.56)	.0002
Per SD increase ^a	1.01 (0.53–1.49)	<.0001	1.06 (0.58–1.53)	<.0001	0.83 (0.34–1.31)	.0007

Note: Model 1 adjusted for age, sex, race.

Model 2 adjusted for model 1 plus hypertension, obesity, current smoker, diabetes, hyperlipidemia.

Model 3 adjusted for model 2 plus alanine aminotransferase, aspartate aminotransferase and C-reactive protein.

Abbreviations: CI, confidence interval; OR, odds ratio.

^aper 0.29 mg/dl increase in total bilirubin levels.

(Holvoet, Stassen, Van Cleemput, Collen, & Vanhaecke, 1998). It has been suggested that the prognostic significance of TB is different in stable CAD and acute myocardial infarction (AMI) (Huang et al., 2017). For stable CAD, elevated TB levels are associated with better prognosis through reduction of cardiac reperfusion injury and improvement of postischemic cardiac function (Bakrania et al., 2017; Clark et al., 2000), while in AMI patients, elevated TB levels correlated with high burden thrombus (Hamur et al., 2016), coronary atherosclerosis (Sahin et al., 2013), and angiographic no-flow (Celik et al., 2014). The activity of myocardial heme oxygenase-1 (HO-1) increased significantly in response to acute infarction, and therefore, elevated TB levels represent stress-induced HO-1 activation in AMI patients (Okuhara et al., 2010). It has been suggested that acute elevation of TB represents disease severity, and therefore, the higher the levels, the higher is the risk of MACE (Shen, Zeng, Wu, Liu, & Chen, 2019). As TB levels are elevated in oxidative stress, it is plausible that TB levels represent compensatory response or marker of underlying oxidative stress, and thus correlate with prolongation of QT interval, as previous studies have shown an increased risk of QT prolongation in participants with elevated levels of inflammation (Medenwald et al., 2014). Hepatic dysfunction or poor hepatic perfusion due to HF has been associated with elevated TB, representing a marker of poor hepatic/cardiac function (Ambrosy et al., 2012), a risk factor for prolonged QT interval. However, the exact mechanism underlying the association of TB with prolonged QT in participants free of CVD in our cohort is unclear. Future studies are needed to understand the pathophysiological basis of association of TB with QT interval.

In a study by Bauman et al. in participants with ST-elevation myocardial infarction, elevated TB was associated with MACE only in men (Baumann et al., 2016). The underlying mechanism of such gender differences in CVD outcomes with TB is unknown. Our findings of gender differences in the association of TB with QT add to accumulating evidence of sex/gender differences in the prevalence and outcomes of different CVD. Further studies are needed to confirm our findings and to explore underlying biologic mechanisms that could explain the gender differences.

Certain limitations of our study must be acknowledged when considering its results and implications. Due to the cross-sectional design of the study, temporality and residual confounding should

be considered as a limitation of the study. The NHANES-III survey recorded ECG only at one point of time, and hence, we could not examine the longitudinal changes of QT over time. Also, we are unable to differentiate indirect bilirubin from direct bilirubin as each may have different prognostic significance (Xu et al., 2019). The strength of our study includes large sample size, community-based multiracial population, and well-ascertained variables including ECG data evaluated at a central reading center.

5 | CONCLUSION

In this large cohort, we observed a strong association of elevated TB with prolonged QT interval especially in men. Future studies are needed to assess causality between elevated bilirubin and QT prolongation and how this association between bilirubin and QT interval could be used to improve CVD risk estimation.

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