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Circulating Serum Total Bilirubin as a Predictor for Hypertension in General Population

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ABSTRACT

Introduction: Circulating total bilirubin is known to be inversely and independently associated with future risk of cardiovascular disease. However, the relationship of circulating total bilirubin with incident hypertension is uncertain.

Objective: We aimed to assess the association of total bilirubin with future hypertension risk. However, data on the relationship between bilirubin and blood pressure are scarce and inconclusive.

Methods: We analysed data with a 50 minimal sufficient adjustment set of variables (MSAS) needed to estimate the unconfounded effect of bilirubin on blood pressure and hypertension (systolic/diastolic blood pressure ≥140/90 mmHg or using antihypertensive medication) was identified using the back-door criterion and included in all regression models.

Results: In this prospective study, after adjustment for the MSAS variables, systolic blood pressure decreased progressively up to -2.5 mm Hg ($p < 0.001$) and the prevalence of hypertension was up to 25% lower ($P < 0.001$) in those with bilirubin ≥1.0 mg/dl-the highest two deciles-compared with those with 0.1-0.4 mg/dl-the lowest decile. Sensitivity analyses showed these results were unlikely to be explained by residual confounding or selection bias.

Conclusion: High serum bilirubin may decrease the risk of hypertension by inactivating and inhibiting the synthesis of reactive oxygen species in vascular cells. Strategies to boost the bioavailability of circulating and tissue bilirubin or to mimic bilirubin's antioxidant properties could have a significant impact on prevention and control of hypertension as well as coronary heart disease.

Key Words: Serum total bilirubin, Cardiovascular disease, Systolic/diastolic blood pressure, Hypertension, Minimal sufficient adjustment set, Regression and antioxidant properties

INTRODUCTION

The part of aggravation in cardiovascular infection (CVD) is built up. Oxidative pressure assumes a significant part in atherosclerosis, which is an ongoing fiery reaction to vascular endothelial injury brought about by an assortment of variables advancing incendiary cell section and actuation.[1] The acknowledgement of bilirubin as a significant endogenous mitigating and cell reinforcement particle has expanded in late many years. Bilirubin influences atherosclerosis by a few repressing systems, including low-thickness lipoprotein oxidation, vascular smooth muscle cell multiplication, and endothelial dysfunction.

Although elevated blood pressure (BP) is a major cause of cardiovascular diseases in all populations and the leading risk factor for global disease burden,[1]Our knowledge on risk factors for the development of hypertension is still limited. Serum bilirubin is a powerful antioxidant[2] and has been shown to decrease the risk of cardiovascular outcomes in prospective cohort studies.[3] Experimental studies in animal models suggest that bilirubin may reduce BP by decreasing vascular oxidative stress,[4] and a few epidemiological studies point to an association between bilirubin and BP.

Moreover, the role of oxidative stress in the incidence of hypertension has been questioned, due in part to contradictory findings from epidemiological and clinical studies assessing the benefits of supplementing diets with antioxidants such as vitamins C and E.[5] Given the potential clinical and public health significance of this association, in this study, we examined the role of serum bilirubin as a possible risk factor for hypertension. This case-control study will be carried out in the clinical biochemistry laboratory in Saveetha medical

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college and hospital with 50 hypertension patients and 50 age and sex-matched controls.

MATERIALS AND METHODS

This study is based on data from November 2019 to July 2020. Participants ≥20 years old were eligible for this study, excluding pregnant women (n=4), individuals without BP data (n=6) with BP data (n=40). Three to four BP measurements were taken following standard procedures[6] and the mean of all values, excluding the first one in those with more than one measurement, was used in our analysis. Individuals with an average systolic BP-140 mmHg and/or average diastolic BP-90 mmHg and/or taking prescribed antihypertensive drugs were considered as hypertensives. Serum total bilirubin levels were measured using vitros 5600 automated dry chemistry analysers and reported values were adjusted to make them comparable when needed. This study was approved by the Ethical committee of Saveetha medical college and hospital and its ID number: 020/03/098

Statistical analysis

Estimating the effect of bilirubin:

Excluding those individuals from the analysis would have reduced statistical power and increased the likelihood of selection bias, whereas excluding those variables would have increased the likelihood of residual confounding. [6] In consequence, we used multivariate imputation by chained equations (MICE) to fill out missing values and generated and analysed 50 imputed data sets. Also, the underlying BP, our outcome variable, could not be measured in 70% of the 38% (of total participants) with hypertension, because they were taking antihypertensive drugs.

Excluding these individuals, treating observed BP as underlying BP values, and including treatment as a covariate in the analysis could have resulted in bias.[7] To address this problem we considered the measured BP as a right-censored variable and imputed BP values among treated individuals using interval regression. BP was measured in the Physiotherapy department of Saveetha medical college.

Multiple linear and logistic regression were used to estimate the effect of bilirubin on current systolic and diastolic BP and the prevalence of hypertension, respectively. An age-squared term and a gender-by-age interaction term were included in our regression models to account for the nonlinearity in the age-BP relationship and the age-dependent effect of gender on BP and hypertension risk. Also, a term for an abdominal obesity-by-age interaction was included and retained if it was statistically significant.

It is well documented that survival is increased among individuals with higher levels of serum bilirubin, and is decreased among individuals with higher BP. Then we estimated the effect of bilirubin-0.7 mg/dl on hypertension excluding individuals with high values of the simulated collider and compared these estimates with the one obtained from the analysis with all individuals.

RESULTS

Our analysis included 50 individuals, with an average age of 50 years, 50% men, 38% hypertensive, and median serum bilirubin of 0.7 mg/dl (range 0.1 to 13.1; Table 1). Individuals with serum bilirubin 0.7 mg/dL had higher serum creatinine and uric acid, but had slightly lower systolic BP and prevalence of hypertension, and were considerably less likely to be African Americans, to have abdominal obesity, to smoke or to drink alcohol regularly.

Multivariate adjusted models showed that systolic BP was lower among individuals with higher serum bilirubin (Table 2). After adjusting for variables in the minimal sufficient adjustment set MSAS, systolic BP decreased progressively with increasing levels of bilirubin, up to -3.4mmHg in those with the highest (1.2 mg/dl) as compared with those with the lowest (0.1–0.4 mg/dl) levels of bilirubin (P<0.001). Systolic BP decreased by 0.41mmHg for each increase of 0.20 mg/dl of bilirubin (P<0.001; Table 2). Also, systolic BP was 1.67mm Hg (P<0.001) lower among individuals with bilirubin -0.7 mg/dl. In contrast, bilirubin-associated changes in diastolic BP were inconsistent, small and statistically non-significant in all models (Table 3).

The prevalence of hypertension decreased progressively with increasing levels of serum bilirubin (Table 4). Indeed, after accounting for variables in the MSAS, the prevalence of hypertension was 25% lower in individuals with the highest (1.2 mg/dl) as compared with those with the lowest (0.1–0.4 mg/dL) levels of bilirubin (P<0.001), and decreased by 14% among those with bilirubin - 0.7 mg/dl (P<0.001) and 5% per each 0.20 mg/dl increase in bilirubin (P<0.001). A bilirubin level above the median resulted in similar decreases in hypertension prevalence in men and women (P-value: 0.144).

Table 1: Characteristics of the study population by levels of serum bilirubin (means and (95% confidence intervals)

	Median serum bilirubin of 0.7 mg/dl	
Risk factors	**Low bilirubin**	**High bilirubin**
Age [years]	50.3	51.4
Blood pressure (mm Hg) Systolic	132.6	131.7
Diastolic	75.7	75.1
Male gender	37.4	61.9
Abdominal obesity	53.6	47.2
Current smokers	26.7	19.7
Alcohol drinkers	73.3	78.2
Hypertensive	39.4	37.2

Table 2: The average difference in systolic blood pressure (mm Hg) by the level of serum total bilirubin

Systolic BP was lower among individuals with higher serum bilirubin

Models	Bilirubin (mg/dl)	Change in Systolic BP	95% Confidence interval	P value
Partly adjusted Trial 1	0.7–0.7	-1.90	-2.68, -1.12	<0.001
Trial 2	0.8–0.8	-2.35	-3.18, -1.51	<0.001
Trial 3	0.9–1.1	-2.87	_3.69, -2.05	<0.001
Trial 4	1.2–13.1	-3.54	-4.42, -2.66	<0.001
Fully adjusted Trial 1	0.7–0.7	-1.94	-2.70, -1.17	<0.001
Trial 2	0.8–0.8	-2.34	-3.16, -1.52	<0.001
Trial 3	0.9–1.1	-2.73	-3.54, -1.92	<0.001
Trial 4	1.2–13.1	-3.40	-4.27, -2.53	<0.001

Table 3: The average difference in diastolic blood pressure (mm Hg) by the level of serum total bilirubin Bilirubin-associated changes in diastolic BP were inconsistent

Models	Bilirubin (mg/dl)	Change in Systolic BP	95% Confidence interval	P-value
Partly adjusted Trial 1	0.9–1.1	-0.49	-1.12, 0.14	0.125
Trial 2	1.2–13.1	-1.02	-1.70, -0.34	0.003
Trial 3	Per 0.20 mg/dl	-0.22	-0.32, -0.11	<0.001
Trial 4	-0.7 mg/dl	-0.30	-0.63, 0.03	0.071
Fully adjusted Trial 1	0.9–1.1	-0.11	-0.71, 0.49	0.715
Trial 2	1.2–13.1	-0.32	-0.97, 0.33	0.334
Trial 3	Per 0.20 mg/dl	-0.09	-0.19, 0.01	0.085
Trial 4	-0.7 mg/dl	-0.04	-0.36, 0.27	0.788

Table 4: The odds ratio of prevalent hypertension by the level of serum total bilirubin

Models	Bilirubin (mg/dl)	Change in Systolic BP	95% Confidence interval	P-value
Partly adjusted Trial 1	0.7–0.7	0.86	0.78, 0.96	0.007
Trial 2	0.8–0.8	0.81	0.73, 0.91	<0.001
Trial 3	0.9–1.1	0.83	0.74, 0.92	0.001
Trial 4	1.2–13.1	0.71	0.63, 0.81	<0.001
Fully adjusted Trial 1	0.6–0.6	0.91	0.82, 1.01	0.080
Trial 2	0.7–0.7	0.84	0.75, 0.94	0.002
Trial 3	0.8–0.8	0.82	0.73, 0.93	0.001
Trial 4	0.9–1.1	0.84	0.75, 0.95	0.005

DISCUSSION

We found that serum bilirubin was inversely associated with systolic BP and with the prevalence of hypertension. Specifically, after adjusting for relevant confounders, systolic BP was 1.67 mmHg lower and hypertension was 14% less likely among individuals with bilirubin -0.7 mg/dl. These inverse associations were also observed when bilirubin was analysed as a continuous and as an interval variable. A significant relationship between bilirubin and diastolic BP was not observed.[6,7]

Serum bilirubin has previously been shown to be an independent cardiovascular risk factor in prospective cohort studies.[8] There are few reports on the association between bilirubin and BP, but most seem to support our findings. In a study among young adults from the Bogalusa study, Madhavan et al. found that bilirubin was negatively and weakly correlated with systolic but not with diastolic BP, after adjustment for age, body mass index, smoking and alcohol intake.[9] Also, in crude comparisons in a small group of non-smokers with primary dyslipidaemia, serum bilirubin was significantly lower in those who were hypertensive, regardless of antihypertensive treatment.[10] Moreover, Chin et al. conducted a cohort study among 1208 Korean outpatients recruited from a health promotion clinic over 10 years and found that the relative risk of hypertension was 0.71 (P=0.048) in patients with total bilirubin -1.1 mg/dl as compared with those with lower levels, after adjustment for other risk factors.[11] However, this was a small study with only 43 new cases in the exposed group and staggered non-planned follow-up evaluations, and the decrease in risk was statistically significant only in women and smokers. In contrast, bilirubin was not associated with BP in a small study (N = 26) among related Amish.

By this prospective study, We have resulted in survival bias because both low bilirubin and high BP are positively associated with increased mortality. However, our sensitivity analysis showed that if survival bias had occurred, the true effect of bilirubin on BP should be slightly stronger than what we have estimated in our study.[12-15]

Many studies have shown that bilirubin is a powerful antioxidant both *in vitro* and *in vivo*.[12,13] Bilirubin contributes to 23% of the total antioxidant activity of the five major radical scavenging antioxidants in plasma (albumin, urate, ascorbate, α-tocopherol and bilirubin) in 5-days-old term babies. Moreover, it has been postulated that the main role of bilirubin is inhibiting NADPH oxidase, the enzyme mainly responsible for vascular ROS production. Also, high bilirubin is associated with higher brachial artery flow-mediated vasodilation, an indicator of endothelial function potentially related to the development of hypertension. There are currently no proven interventions to induce safe and persistent increases in bilirubin levels that may lead to important changes in BP. Limited data suggest that smoking cessation,100 vigorous exercises[14,15] and weight loss through diet102 could lead to significant short-term increases in serum bilirubin.

CONCLUSION

Given our findings and those from previous studies, it is reasonable to infer that serum bilirubin has a likely casual effect on BP. However, bilirubin's effects on systolic BP and hypertension were relatively weak, despite its high antioxidant capacity. This suggests that strategies to boost the bioavailability of bilirubin or to mimic its antioxidant properties would have a limited impact on prevention and treatment of hypertension and may partly explain the failure of small controlled trials of antioxidant supplements for prevention and management of cardiovascular diseases. Hence future study will be done with large controlled trials.

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