JACC: ASIA VOL. 3, NO. 2, 2023

EDITORIAL COMMENT

Prognostic Potential of Total Bilirubin in Secondary CVD Prevention*

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Bilirubin is the end product of heme degradation.[1-4] In circulation, it is present in an insoluble (unconjugated) form that is solubilized by binding to albumin, and a soluble (conjugated) form representing a minor part of total bilirubin.[4] In micromolar concentrations in vitro[1,2] and in vivo,[3,4] bilirubin possesses antioxidant activity, protecting from lipid and protein oxidation,[2,3] and promotes nitric oxide bioavailability in cardiac tissue.[3,4] Recently, it was discovered that unconjugated bilirubin possesses hormonal activity by binding to peroxisome proliferator-activated receptor (PPAR)-α, which controls target genes involved in β-oxidation, improving insulin resistance and obesity.[4] Total bilirubin (TBil) as a prognostic marker is documented in both primary and secondary cardiovascular disease (CVD) prevention.

In this issue of *JACC: Asia*, Cao et al[5] have performed a prospective, observational study of long-term prognosis of circulating TBil within physiological levels and above, in 3,809 patients with a previous myocardial infarction and angiography-proven CVD. The reference range of TBil was defined as 5.1 to 17.1 μmol/L. Patients with medical conditions that may affect bilirubin were excluded before inclusion. Follow-up was performed every 6 months, up to 4 years, during which a major adverse cardiac event (nonfatal myocardial infarction [MI], ischemic stroke, ischemia-driven revascularizations, or cardiovascular death) occurred in 11.6% of patients. Study subjects were divided into tertiles (low-normal 5.1-10.9 μmol/L, middle-normal 11.0-14.3 μmol/L, high-normal 14.4-17.1 μmol/L). The 2 lower tertiles served as reference and were classified as group 1 (n = 1,973). Patients in tertile 3 (group 2, n = 987) were compared with the reference population, so also was an additional group (group 3) with TBil >17.1 μmol/L (n = 849). Mean age was 61.7 years. After adjusting for confounders, the authors found a J-shaped association between total bilirubin and the incidence of a major adverse cardiac event. Similar results were recorded for separate hard endpoints and all-cause mortality, respectively. Results have been discussed in the context of previous reports.

In general populations, several reports show a U-shaped association between TBil levels and ischemic heart disease.[6-8]

A U-shaped relationship was challenged by a US National Health and Nutrition Examination Survey 1999-2014,[9] in which 37,234 participants, irrespective of age, were studied, showing a linear relationship between TBil and all-cause mortality.

From a primary database in the United Kingdom, with a median follow-up of 43 months and measurements of serum TBil levels recorded 3 months before initiation of statin treatment, an L-shaped nonlinearity association between physiological levels of TBil and the occurrence of CVD events and total mortality, respectively, was obtained from 130,052 men and women with no history of liver disease or CVD.[10]

Another research group[11] investigated potential improvements in risk through increasing quintiles of TBil in 2,936 asymptomatic diabetic subjects with a mean age of 62.7 years and a mean follow-up time of 5.4 years. After adjusting for traditional risk factors for CVD, the addition of TBil was negatively associated with cardiovascular death and all-cause death. The addition of TBil for cardiovascular death improved the C-statistic from 0.713 to 0.729, $P = 0.008$, with 8.57% improvement in net reclassification analysis ($P = 0.022$).

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The author attests they are in compliance with human studies committees and animal welfare regulations of the author's institution and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2772-3747 https://doi.org/10.1016/j.jacasi.2022.12.001

In a meta-analysis of 20 published studies[12] involving 323,891 subjects with arteriosclerotic CVD, TBil was positively related to in-hospital cardiovascular mortality and negatively associated with the prognosis of acute MI. In the general analysis, higher TBil concentrations significantly improved the prognosis of patients with established arteriosclerotic cardiovascular disease.

Stender et al[13] did not observe an association between genetically elevated bilirubin levels and ischemic heart disease or MI, focusing on the UDP-glucuronosyltransferase (UGT1A1) gene in 3 independent Danish studies, corroborated by adding 8 studies in a meta-analysis, including 14,711 cases and 60,324 controls. Their results suggest that raised plasma bilirubin is not causally associated with ischemic cardiovascular disease.

The literature contains substantial evidence of an association between physiologically higher TBil levels and reduced all-cause and cardiovascular mortality, respectively. The current report by Cao et al[5] demonstrates similar findings in secondary CVD prevention. Moreover, these authors also observed increasing risk above the upper reference level, by which a J-shaped risk curve was generated. To differentiate between a J- or a U-shaped curve, patient numbers and events might have been sufficient to perform the statistical analysis based on quintiles, rather than tertiles, and to define the group with the lowest hypothesized event rate as reference. However, the chosen approach will identify a broader population at risk of CVD, which may be practical in a clinical perspective. Based on C-statistic models, the authors claim that TBil provides prognostic information and might help the clinician to further risk stratify post-MI patients, but they did not present a net risk reclassification analysis, as previously reported for asymptomatic diabetic individuals.[11]

Higher compared with lower reference levels of TBil are negatively associated with the proportion of large very low density lipoprotein and small low density lipoprotein particles in patients with type 2 diabetes,[14] supporting an antiatherogenic effect, which may partly explain its association with fewer cardiovascular events.[11] This may also apply to nondiabetic individuals with CVD.[15]

Bilirubin is a powerful antioxidant.[15] Recently, attention has been focused on both direct and indirect antioxidant properties of bilirubin, also engaging components of the heme catabolic pathway upfront of glucuronidation by UGT1A1.[4,15] Hence, heme oxygenase-1 (HMOX1) is the rate-controlling enzyme of heme degradation. Together with biliverdin reductase A (BLVRA1), which rapidly converts biliverdin to bilirubin, HMOX1 exerts potent cytoprotective and anti-inflammatory actions, by which heme-mediated oxidative stress in endothelial cells are counteracted, affecting CVD risk, diabetes, metabolic syndrome, arterial hypertension, and obesity.[15,16] Furthermore, in a meta-analysis, HMOX1 gene promotor polymorphisms were associated with susceptibility to type 2 diabetes.[17]

Consequently, less antioxidative effects of lower TBil concentrations, combined with reduced enzymatic activity in the heme catabolic pathway, might explain the risk profile of subjects with TBil in the lower physiological range, whereas TBil levels above the reference range may essentially reflect underlying pathological disorders. Hypothetically, in this perspective, nanocarrier-mediated delivery of bilirubin may have the potential to improve metabolic derangements in subjects with «hypobilirubinemia,»[4] and may be an area of future research.

The authors of the current paper[5] should be applauded for providing a broader insight into this interesting subject.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The author has reported that he has no relationships relevant to the contents of this paper to disclose.

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KEY WORDS myocardial infarction, prognosis, total bilirubin