

Bilirubin in Physiologic Concentration May be a Protective Factor for Ischaemic Stroke

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ABSTRACT

Keywords: Bilirubin; Ischaemic Stroke; Neuroprotection

Abbreviations: IS: Ischemic Stroke; AIS: Acute Ischaemic Stroke; DM: Diabetes Mellitus; BP: Blood Pressure; TBIL: Total Serum Bilirubin

Mini Review

Stroke is a multifactorial disease with high rate of morbidity, mortality and disability. It is categorized into two types: ischemic and hemorrhagic stroke (IS), and ischemic stroke (IS) accounts for about 80% of all strokes (AS). Although some certain factors, such as atrial thrombosis and hypertension, are closely related to the occurrence of IS, its mechanism is still unclear [1,2]. Once ischaemia occurs, excessive oxidative stress ensues and leads to structural and functional damage to the brain, which is an important pathophysiological process of ischaemic brain damage [3-5]. Recently, a number of biomarkers pertaining to vascular injury, metabolic changes, oxidative injury, and inflammation have shown encouraging results in occurrence and prognosis of acute ischaemic stroke (AIS) [6].

Bilirubin, an end-product of heme catabolism, long been seen as a potentially toxic agent at high levels in the human body [7], has been shown to harbour anti-inflammatory [8], antioxidant [7,9], neuroprotective [10], and platelet activation inhibiting [11] properties. These properties of bilirubin have

recently emerged as a feasible endogenous defense mechanism against diverse diseases associated with increased oxidative stress, such as IS [12]. Studies have demonstrated that the level of bilirubin may serve as a predictor of some vascular events, such as hypertension [13], coronary artery diseases [14], diabetes mellitus (DM) [15], diabetic kidney disease [16], metabolic syndrome [17], peripheral artery disease [18] and carotid atherosclerosis [19], which are vascular risk factors of IS. Some other studies found that a low level of total serum bilirubin (TBIL) was associated with an increased risk of stroke in patients with bilirubin metabolism-related diseases, such as type 2 DM [20] and overweight/obese [21]. Multifaceted interventions achieving the blood pressure (BP), lipid and glycaemia control targets may reduce the risk of developing stroke associated with low levels of bilirubin. Nowadays, several studies have shown the neuroprotective effects of bilirubin in the occurrence and prognosis of IS; however, there is still controversy on this issue. Here, we will propose our ideas about the relationship between bilirubin and IS based on previous work.

In 2017, our study group performed a systemic review and meta-analysis of 11 population-based observational studies involving 5,060 stroke cases among 131,450 subjects investigating the relationship between total serum bilirubin and risk for stroke, supporting an inverse association between serum total bilirubin and risk for IS and AS in males [12]. A large number of studies showed that bilirubin is involved in antioxidation defense mechanisms and a higher level of serum bilirubin in the normal range was associated with a decreased risk of IS [22]. In order to make this issue more accurate, we conducted a dose-response meta-analyses to quantify the relationship between TBIL levels within physiologic range and risk of stroke in 2020, and it has been accepted by Chinese Circulation Journal and will soon be published online in April 2021. Eleven observational studies involving 202,641 participants and 4,904 stroke cases from China, Japan, Korea, Sweden, the United States, and other countries were included for this analysis. The results showed that 1 $\mu\text{mol/L}$ increment of serum TBIL level was associated with a 1.2% decreased risk of IS (OR=0.988, 95%CI: 0.981-0.996, P=0.002) and a 1.5% decreased risk of AS (OR=0.985, 95% CI: 0.979-0.992, P<0.001). These results are consistent with previous observational studies [23-25] and support the protective effects of bilirubin on stroke occurrence. Choi et al conducted a two-sample Mendelian Randomization study to examine whether elevated serum bilirubin levels were causally associated with decreased stroke risk and found genetically increased bilirubin levels are causally associated with decreased total stroke risk and when limiting the outcome to IS, the magnitude of relevance became stronger [26]. However, a small number of studies showed only moderately positive or null relationship [27,28]. In addition, as described in our previous published review, the relationship between bilirubin and stroke risk may be influenced by gender and stroke types [22]. In this article, we also reviewed the relationship between bilirubin and stroke prognosis. Though the prognostic value of serum bilirubin in AIS seems controversial, the majority of them appear to support that an elevated level of serum bilirubin is an independent predictor of greater stroke severity and poorer functional outcome after AIS. The level of serum bilirubin might be a marker of oxidative stress after AIS. Higher bilirubin level is associated with greater IS severity, and the latter in turn results in poorer functional outcomes and increased mortality in AIS patients.

In summary, most of these studies show a protective effect of bilirubin within physiologic range in the occurrence of IS. However, majority of them only studied the effect of total bilirubin on IS. Bilirubin levels are reported as total bilirubin (direct and indirect) and direct bilirubin (conjugated bilirubin) in clinical, and indirect bilirubin (unconjugated bilirubin) can be calculated separately. In addition, bilirubin also flows in the plasma in the unbound (free) form [29]. All types of bilirubin share some of the same antioxidant

properties, yet during an IS, only unbound, bioactive bilirubin is effective in treatment, as it can cross the blood-brain barrier [9]. To compare the relationship between different types of bilirubin and stroke prevalence should be a future endeavor to better understand bilirubin's protective effects. Also, majority of published studies only looked at one type of stroke, IS. It would be beneficial to expand the current research to HS and traumatic brain injury to see the potential benefits of bilirubin in these pathological states.

Bilirubin is not only one of the most potent endogenous antioxidants [30] but also an excellent marker of oxidative stress [31]. Studies have shown the beneficial effects of bilirubin in cardiovascular disease; however, the same extent of research has not yet been replicated in stroke. Can we increase neuroprotection or reduce neurotoxicity of bilirubin by modulate bilirubin concentration? Can multifaceted intervention achieving the BP, lipid and glycaemia control targets attenuate the increased risk of IS associated with low bilirubin level? Rigorous research is needed to provide evidence supporting the existing studies, expand on these studies.

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