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Editorial

Bilirubin: From a Disease Predictor to a Potential Therapeutic in Stroke

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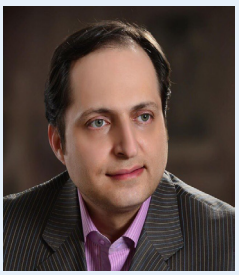
Stroke is one of the main reasons for death and the principal cause of longstanding incapability worldwide. The most common type of stroke is ischemic stroke, which arises after embolism, thrombolysis, or cryptogenic mechanisms in which blood flow to the brain is damaged.[1] Early prediction of the outcome in patients with ischemic stroke is significant. Reliable prognostic markers existing during the initial phase after acute stroke could help clinical decision-making. Many of the blood markers are related to poor outcomes after ischemic stroke.[2] Higher levels of serum bilirubin were common in acute ischemic stroke, which developed against oxidative stress (OS) and could indicate OS intensity. Acute stroke signifies a prospect to additional study the role of bilirubin in the cerebral injury pathophysiology for the reason that primary cerebral ischemia includes OS.[3,4]

Bilirubin as a heme oxygenase-1 metabolite, after being gathered in high concentrations in tissues, is a highly toxic substance. Currently, it is known as one of the most powerful anti-inflammatory, antioxidant, and neuroprotective mediators in the body. These attributes enable the anti-atherogenic effects of bilirubin to inhibit thrombus formation in ischemic stroke.[5]

Bilirubin levels in the serum are deliberated as an antioxidant that can influence stroke prognosis. According to various studies, an increase in bilirubin leads to an elevation in stroke intensity, longer hospitalization, and poor prognosis.[6] There is still a difference of opinion on this issue. Perlstein et al revealed that an increase in the total bilirubin (TBIL) of 1.71 μmol/L can decrease the ischemic stroke incidence to approximately 9%.[7] In contrast to the results of Kurzepa et al, indicating that there is a poor relationship between the risk of ischemic stroke and serum TBIL.[8] The findings of a meta-analysis study exhibited that serum bilirubin levels may be a useful biomarker for acute stroke prediction.[9] The results of a research study conducted in Korea represented that bilirubin levels in the serum were not a risk factor for stroke.[10] Likewise, the findings of a meta-analysis study in prospective studies by Kunutsor et al,[11] examining the circulating TBIL association with the risk of cardiovascular disease incidents, revealed no important evidence of a correlation among TBIL levels and the risk of stroke. Thus, the bilirubin role as a prognostic or risk factor for stroke is unclear due to possible confusing factors.

The results of a cross-sectional prospective study performed by Sagheb Asl et al showed that TBIL, direct bilirubin (DBIL), and indirect bilirubin (IBIL) levels were considerably related to mortality in the acute phase of patients with ischemic stroke.[12] The results of a recent meta-analysis in 11 observational studies demonstrated that serum bilirubin levels have a negative correlation with the risk for ischemic stroke. Further, the association between the serum TBIL level and the occurrence of ischemic stroke in men was statistically significant but not in women.[13] Furthermore, the findings of one study revealed that plasma bilirubin concentration may be a useful marker in patients who are suffering from hemorrhagic stroke. Based on the findings of another study, elevated TBIL serum levels on admission were independently related to a high risk of hemorrhagic transformation (HT) after acute ischemic stroke. The baseline TBIL level was considerably higher in HT patients than in non-HT patients. Additionally, the severity of HT elevates with increasing the TBIL level.[14] In acute ischemic stroke, a prevalent occurrence is early neurological

Author's Biosketch



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deterioration (END) which has been related to a decrease in neurological function and disability and mortality rate. The lower levels of TBIL were independently associated with END, indicating that TBIL is significant in acute ischemic stroke.[15] The elevated levels of TBIL and DBIL 48 hours after the beginning of symptoms can be an independent marker for stroke intensity at admission and discharge for all acute ischemic stroke patients. Elevated bilirubin levels following acute ischemic stroke recommend a good prognosis for patients with mild stroke.[16] In patients with type 2 diabetes mellitus, low TBIL levels were related to an enhancement in stroke risk. The bilirubin level is a significant biological marker for depression risk in patients who suffer from ischemic stroke. A high bilirubin level is related to the prediction of post-stroke depression.

The mechanisms in which bilirubin affects ischemic stroke differ before and after the stroke onset. Several studies confirmed that a high serum bilirubin level in the normal range is associated with a reduced risk of ischemic stroke by anti-oxidation defense mechanisms in pre-stroke situations. After the occurrence of stroke, the negative effect of high serum bilirubin levels on the outcome of patients probably reveals the strength of early OS. Ischemic stroke patients with high serum bilirubin levels had more brain infarcts, larger noticeable cerebral edema, and higher intense reperfusion injury with minor functional outcomes.[17]

Previous studies suggested that bilirubin acts via a direct antioxidation pathway and an indirect pathway complemented by the inhibition of the nicotinamide adenine dinucleotide phosphate oxidase activity with tetrapyrroles. The negative association between bilirubin levels in the serum and ischemic stroke incidence was clarified through the anti-oxidative capacity of the bilirubin, the prevention of oxidation of low-density lipoprotein by bilirubin, the vascular structure, and reactive pathways. The available evidence represents that bilirubin in the serum acts as a physiological lipid antagonist and can increase cholesterol transport from blood vessels to the plasma, motivating lipolysis and bile clearance.[18] The anti-peroxidative role of bilirubin is important in the deceleration and inhibition of atherogenesis in ischemic stroke patients.

In conclusion, bilirubin could be used as an efficacious marker of OS and is a potent scavenger of free radicals that can effectually inhibit ischemia-induced nerve damage and may be a potential treatment for ischemic stroke. It is commonly recognized to have neuroprotective effects on stroke, thus it could impact the incidence and prognosis of ischemic stroke. However, more research is required to provide evidence, supporting the existing studies in this regard.

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Conflict of interests

The author declares that he has no competing interests.

Consent for Publication

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All data generated or analyzed during this study are included in this published article.

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