



PROTECTIVE ROLE OF BILIRUBIN AGAINST THE ATHEROSCLEROSIS IN METABOLIC SYNDROME

Niraj Khatri Sapkota*, Deepak Sharma, Dev Kumar Shah

Department of physiology, Chitwan medical college, Kailashnagar, Chitwan.

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*Correspondence for

Author

Niraj khatri sapkota

Department of physiology,
Chitwan medical college,
Kailashnagar, Chitwan.

ABSTRACT

Atherosclerotic cardiovascular disease characterized by a chronic inflammation of the arterial wall, which also involves deposition and peroxidation of lipids is the leading cause of morbidity and mortality both in industrialized and developing countries. Bilirubin, an endogenous antioxidant, may limit lipid peroxidation and retard the

progression of atherosclerosis. However, in presence of multiple risk factors, similar concentrations of serum bilirubin may not confer the same level of protection against coronary artery disease. This review explores detailed information on the relation between the bilirubin and atherosclerosis in different disease like cardio-vascular disease (CVD), and the related diseases such as diabetes, metabolic syndrome, and obesity. All of these pathological conditions represent an important threat to human civilization, being the major killers in developed countries, with a steadily increasing prevalence. Thus, it is extremely important to search for novel markers of these diseases, along with therapeutic modalities to reverse this unfavorable situation.

KEYWORDS: Bilirubin, peroxidation, atherosclerosis, coronary artery disease(CAD).

INTRODUCTION

The complex metabolic disorder of insulin resistance (hyper-insulinemia), lipid metabolism (dyslipidemia), blood pressure (hypertension), and body waist to hip ratio (obesity) has been described as a "metabolic syndrome". Development of metabolic syndrome(Mets) is associated with chronic inflammation and oxidative stress.^[1,2] Bilirubin, the by-product of hemoglobin metabolism from haemo-oxygenase pathway by reticulo-endothelial cell is an antioxidant that can prevent low-density lipoprotein (LDL) oxidation and has a protective

effect against cardiovascular disease (CVD). Thus the level of bilirubin is inversely associated with metabolic syndrome.^[3] Persons linked with expressing Gilbert syndrome (i.e., unconjugated hyperbilirubinemia) and healthy individual with high total bilirubin (TB) presented lower circulating levels of oxidized-LDL (Ox-LDL),^[4,5] expressing a protective association between serum bilirubin level and cardiovascular disease (CVD).^[6]

Intervention of bilirubin in development of atherosclerosis

Bilirubin, has now emerged as an important endogenous anti-inflammatory and antioxidant molecule in all its form whether it is free or albumin bound^[7] and unconjugated or conjugated.^[8,9] Accumulating evidence suggests that bilirubin may be a part of a cell defense strategy in response to oxidative stress. Previous studies also indicated that bilirubin serves as a physiological antioxidant in ischemia-reperfusion.^[10] Serum bilirubin may prevent experimental atherosclerosis possibly by scavenging of oxygen radicals which prevents low-density lipoprotein (LDL) oxidation.^[11,12] The metabolic syndrome is the one of the pro-inflammatory condition in which several cell types synthesize and secrete phospholipase A2 that catalyses oxidation of LDL. Myeloperoxidase, a haeme protein secreted by activated phagocytes, oxidizes L-tyrosine to a tyrosyl radical that is a physiological catalyst for the initiation of lipid oxidation in LDL. Lipid oxidation results in the generation of aldehydes that substitute lysine residues in the apolipoprotein B-100 moiety. Lipid together with protein oxidation in LDL results in the generation of oxidized LDL, a metabolic syndrome component.^[13]

Important Functions of bilirubin

Bilirubin is a tetrapyrrolic compounds formed during heme catabolism and has been considered a toxic waste product since decade but recent epidemiologic studies supported by in vitro and in vivo experimental data revealed its inverse association with cardiovascular disease (CVD). Bilirubin not mere scavenge overproduced reactive oxygen species but also inhibit vascular smooth muscle cell proliferation, has anti-inflammatory effect by attenuating chemo-tactic activity of monocytes and strongly inhibits adhesion of leukocytes to venule ceasing the production of pro-inflammatory cytokines. Moreover, animal and human studies have proven the involvement of bilirubin to suppress oxidation of cholesterol, an important step that initiate atherosclerosis. Thus, bilirubin protects against oxidative stress-mediated diseases especially against atherosclerosis.^[14, 15]

Biomarker of coronary artery atherosclerosis

High serum bilirubin with metabolic and cardiovascular disease is inversely correlated.^[16] A study showed bilirubin level lower in patients with critical stenosis compared to non-critical stenosis of blood vessels. Primarily noncalcified plaque (NCP) and mixed plaque (MP) have lower bilirubin levels compared to calcified plaque (CP) and normal subjects demonstrating that serum bilirubin level was significantly associated with the presence of atherosclerotic plaque and its severity and morphology. Several prospective clinical studies are needed to clarify the exact physiopathology and prognostic role of bilirubin in CAD.^[17] Plasma level of inflammatory mediator are also effective biomarker of CAD that includes and measured are high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), plasminogen activator inhibitor-1, and vascular endothelial growth factor. IL-6 level was found elevated in patients with predominantly calcified plaque. However, number of stenotic vessels was not significantly related to inflammatory markers.^[18, 19] Low serum bilirubin concentration would be a potential risk factor for CAC (coronary artery calcification) in males.^[20]

Bilirubin as a possible therapeutic approach of atherosclerosis

The beneficial effect of antioxidant properties of bilirubin and cost-effective strategies to increase bilirubin levels can be one of the important solution in the prevention of the CVD. The main potential modifiable behaviour to increase bilirubin levels is physical activity. Regular participation in physical activity has been shown to increase antioxidant enzyme and coenzyme in the body.^[21, 22]

Heme oxygenase-1 (HO-1), is the rate-limiting enzyme that can degrade heme into equimolar quantities of carbon monoxide (CO), biliverdin, and free iron. The fate of Biliverdin is rapid conversion to bilirubin by the enzyme biliverdin reductase, and free iron. HO-1 is a ubiquitous stress protein and is induced in many cell types by various stimuli that modulate anti-inflammatory, antiapoptotic, antiproliferative, and antioxidant properties, as well as its effects on the immune response.^[22, 23]

Enzyme heme oxygenase-1 anticipate to form bilirubin and its precursor biliverdin, that act to suppress the components of atherosclerosis, vascular smooth muscle cell proliferation that leads to intimal proliferation and causes narrowing of the vessels. Therefore, the antiproliferative effects of the bile pigments in vitro system has protective role in atherosclerotic type disease.^[24, 25]

Bilirubin and Ox-LDL levels

High density lipoprotein is known as an atheroprotective protein and is capable to protect LDL from oxidative modification *in vitro*. The increase in the number of LDL particles, and high levels of TG lead to the formation of smaller, denser LDL species, which are known to be more prone to undergo oxidative modification.^[16,27] On the other hand,^[28,29] previous study previously demonstrated that bilirubin is also capable to prevent LDL (low density lipoprotein) from oxidation *in vitro* and two recent studies involving young males and patients under hemodialysis^[30] reported a similar association *in vivo* between bilirubin and Ox-LDL, suggesting a potential cardiovascular risk protection of bilirubin. Obesity and insulin resistance (IR) are main independent predictors of higher Ox-LDL, when whole-body insulin sensitivity but these relationships disappeared after adjustment for BMI. BMI and markers of glucose metabolism were positively and significantly correlated with Ox-LDL levels in recent study.^[29]

A previous work demonstrated that young obese patients with higher body fat percentage present lower circulating levels of bilirubin and a higher degree of inflammation. Indeed, the correlation between waist circumference and Ox-LDL was far from being statistically significant. In addition, waist circumference presented well known correlations with other variables, such as insulin, TG and HDLc.^[30, 31, 32]

Physical activity, bilirubin and chronic disease

Physical and mental health is the function of various physiological parameters, such as cholesterol, blood pressure, and glycemic control. In addition to these serum bilirubin is considered to be a new biomarker for various chronic diseases^[32]; metabolic syndrome,^[33] type 2 diabetes,^[34] stroke severity,^[35] certain cancers^[36], autoimmune disease.^[37] For every 30 minute increase of Moderate to vigorous physical activity (MVPA), there occurred 0.08 mg/dL increase in bilirubin among insulin resistant adults. As reported^[36] bilirubin changes of this magnitude (i.e., < 0.1 mg/dL) have been shown to associate with an approximate 3% decreased risk of peripheral vascular disease, 4% reduced risk of stroke, and a 5% reduced risk of cardiovascular disease. Various study documented independent influence of physical activity on bilirubin levels whereas some literatures reported no association between cycling training and bilirubin levels in lean or obese adults. Other study however, demonstrate a positive association between 6 months of aerobic exercise training and bilirubin levels among insulin resistant adults, with no association found for insulin sensitive adults.^[36,37] A possible explanation of this finding is that insulin resistant

individuals had lower bilirubin levels when compared to insulin sensitive individuals, which may allow for greater change in bilirubin from physical activity. Most recently, in 2013, Tanaka *et al.*^[38] reported no association between self-reported physical activity and bilirubin levels.^[39, 40]

Bilirubin may modulate risk of these diseases by, for example, reducing lipid peroxidation and mitigating inflammation. The null findings by Devries *et al.*^[36] may also have been a result of the mode of exercise (i.e., cycling). Increased heel-strike, weight bearing physical activity may facilitate increased hemoxygenase-1 activity (HO-1)^[34], which is the enzyme responsible for the conversion of biliverin to bilirubin. In addition to increases in HO-1 activity, other potential mechanisms include weight-bearing physical activity-induced hemolysis (due to increased heel strike). Speculatively, cycling training may not be sufficient enough to increase the activity of the HO-1 system or induce haemolysis.^[23, 41]

CONCLUSION

Bilirubin, a byproduct of hemoglobin catabolism, although for decades was believed to be only a waste product of the heme catabolic pathway at best, and a potentially toxic compound at worst has multiple biological functions. Recent data has convincingly demonstrated that mildly elevated serum bilirubin levels are strongly associated with a lower prevalence of oxidative stress-mediated diseases and therefore is one of the protective endogenous agents. Thus, the patients presenting lower bilirubin level may tend to have increased atherogenic risk and strategies to reduce Ox-LDL levels should include regular foot heel exercise.

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