ejpmr, 2015,2(4), 129-136

SJIF Impact Factor 2.026

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 3294-3211

EJPMR

PROTECTIVE ROLE OF BILIRUBIN AGAINST THE ATHEROSCLEROSIS IN METABOLIC SYNDROME

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Article Received on 18/04/2015 **Article Revised on 09/05/2015** **Article Accepted on 31/05/2015**

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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 catabolismn 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 supress 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 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 hemooxygnase-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 tends to have increased atherogenic risk and strategies to reduce Ox-LDL levels should include regular foot heel exercise.

REFERENCES

1. Hanson RL, Imperatore G, Bennett PH, Knowler WC. Components of the "metabolic syndrome" and incidence of type 2 diabetes. Diabetes, 2002; 51(10): 3120-7.
2. David E, Laaksonen, Hanna-Maaria Lakka, Leo K. Niskanen.etal. Metabolic Syndrome and Development of Diabetes Mellitus: Application and Validation of Recently Suggested Definitions of the Metabolic Syndrome in a Prospective Cohort Study Am. J. Epidemiol, 2002; 156 (11): 1070-1077.
3. Kwon KM, Kam JH, Kim MY, Kim MY, Chung CH, etal. Inverse association between total bilirubin and metabolic syndrome in rural Korean women, 2011; 20(6): 963-9.
4. Boon AC, Hawkins CL, Bisht K, Coombes JS, Bakrania B, Wagner KH, *et al*.: Reduced circulating oxidized LDL is associated with hypocholesterolemia and enhanced thiol status in Gilbert syndrome. Free Radic Biol Med, 2012; 52: 2120-212.

5. Horsfall LJ, Nazareth I, Petersen I: Cardiovascular events as a function of serum bilirubin levels in a large, statin-treated cohort. Circulation, 2012; 126: 2556-256.
6. McArdle PF, Whitcomb BW, Tanner K, Mitchell BD, Shuldiner AR, Parsa A: Association between bilirubin and cardiovascular disease risk factors: using Mendelian randomization to assess causal inference. BMC Cardiovasc Disord, 2012; 12:16.
7. Stocker R, Yamamoto Y, McDonagh AF, Glazer AN, Ames BN Bilirubin is an antioxidant of possible physiological importance. Science, 1987; 235: 1043–1046.
8. Stocker R, Glazer AN, Ames BN Antioxidant activity of albumin-bound bilirubin. Proc Natl Acad Sci, 1987; 84: 5918–5922
9. Stocker R, Peterhans E Antioxidant properties of conjugated bilirubin and biliverdin: biologically relevant scavenging of hypochlorous acid. Free Radic Res Commun, 1989;6: 57–66.
10. Wu TW, Fung KP, Wu J, Yang CC, Weisel RD Antioxidation of human low density lipoprotein by unconjugated and conjugated bilirubins. Biochem Pharmacol, 1996; 51: 859–862 .
11. Yamaguchi T, Terakado M, Horio F, Aoki K, Tanaka M, et al. Role of bilirubin as an antioxidant in an ischemia-reperfusion of rat liver and induction of heme oxygenase. Biochem Biophys Res Commun, 1996; 223: 129–135.
12. Neuzil J, Stocker R Free and albumin-bound bilirubin are efficient co-antioxidants for alpha-tocopherol, inhibiting plasma and low density lipoprotein lipid peroxidation. J Biol Chem, 1994; 269: 16712–16719.
13. Holvoet P.Oxidized LDL and coronary heart disease.Acta Cardiol, 2004; 59(5): 479-84.
14. Novotný L, Vítek L.Inverse relationship between serum bilirubin and atherosclerosis in men: a meta-analysis of published studies.Exp Biol Med (Maywood), 2003; 228(5): 568-71.
15. Kang SJ, Lee C, Kruzliak P.Effects of serum bilirubin on atherosclerotic processes.Ann Med, 2014; 46(3): 138-47.
16. Kang SJ, Kim D, Park HE, Chung GE, Choi SH, Choi SY, Lee W, Kim JS, Cho SH.Elevated serum bilirubin levels are inversely associated with coronary artery atherosclerosis. Atherosclerosis, 2013; 230(2): 242-8.
17. Canpolat U, Aytemir K, Yorgun H, Hazırolan T, Kaya EB, etal.Association of serum total bilirubin levels with the severity, extent and subtypes of coronary atherosclerotic plaques detected by coronary CT angiography.Int J Cardiovasc Imaging, 2013; 29(6): 1371-9.

18. Harada K, Amano T, Uetani T, Yoshida T, Kato B, Kato M, Marui N, Kumagai S, Ando H, Ishii H, Matsubara T, Murohara T.Association of inflammatory markers with the morphology and extent of coronary plaque as evaluated by 64-slice multidetector computed tomography in patients with stable coronary artery disease.Int J Cardiovasc Imaging, 2013; 29(5): 1149-58.
19. Fischer C, Hulten E, Belur P, Smith R, Voros S, Villines TC.Coronary CT angiography versus intravascular ultrasound for estimation of coronary stenosis and atherosclerotic plaque burden: a meta-analysis.J Cardiovasc Comput Tomogr, 2013; 7(4): 256-66.
20. Zhang ZY, Bian LQ, Kim SJ, Zhou CC, Choi YH.Inverse relation of total serum bilirubin to coronary artery calcification score detected by multidetector computed tomography in males.Clin Cardiol, 2012; 35(5): 301-6.
21. Ollinger R, Yamashita K, Bilban M, Erat A, Kogler P, etal.Bilirubin and biliverdin treatment of atherosclerotic diseases.Cell Cycle, 2007; 6(1): 39-43.
22. Ollinger R, Wang H, Yamashita K, Wegiel B, Thomas M, etal.Therapeutic applications of bilirubin and biliverdin in transplantation.Antioxid Redox Signalm, 2007; 9(12): 2175-85.
23. Vítek L The role of bilirubin in diabetes, metabolic syndrome, and cardiovascular diseases. Front Pharmacol, 2012; 3: 55.
24. Chait A, Brazg RL, Tribble DL, Krauss RM: Susceptibility of small, dense, low-density lipoproteins to oxidative modification in subjects with the atherogenic lipoprotein phenotype, pattern B. Am J Med, 1993; 94: 350-356.
25. de Graaf J, Hak-Lemmers HL, Hectors MP, Demacker PN, Hendriks JC, Stalenhoef AF: Enhanced susceptibility to in vitro oxidation of the dense low density lipoprotein subfraction in healthy subjects. Arterioscler Thromb, 1991; 11(2): 298-306.
26. Arterioscler Thromb 1991, 11: 298-306. 15. Kontush A: HDL-mediated mechanisms of protection in cardiovascular disease. Cardiovasc Res, 2014; 103: 341-349.
27. Mertens A, Holvoet P: Oxidized LDL and HDL: antagonists in atherothrombosis. Faseb J, 2001; 15: 2073-2084.
28. do Sameiro-Faria M, Kohlova M, Ribeiro S, Rocha-Pereira P, Teixeira L, Nascimento H, et al.: Potential cardiovascular risk protection of bilirubin in end-stage renal disease patients under hemodialysis. Biomed Res Int, 2014; 2014: 175286
29. Kelly AS, Jacobs DR Jr, Sinaiko AR, Moran A, Steffen LM, Steinberger J: Relation of circulating oxidized LDL to obesity and insulin resistance in children. Pediatr Diabetes, 2010; 11: 552-555.

30. Belo L, Nascimento H, Kohlova M, Bronze-da-Rocha E, Fernandes J, Costa E, et al.: Body fat percentage is a major determinant of total bilirubin independently of UGT1A1*28 polymorphism in young obese. PLoS One, 2014; 9: e98467.
31. Nascimento H, Silva L, Lourenco P, Weinfurterova R, Castro E, Rego C, *et al*.: Lipid profile in Portuguese obese children and adolescents: interaction of apolipoprotein E polymorphism with adiponectin levels. Arch Pediatr Adolesc Med, 2009; 163: 1030-1036
32. de Sauvage Nolting PR, Kusters DM, Hutten BA, Kastelein JJ: Serum bilirubin levels in familial hypercholesterolemia: a new risk marker for cardiovascular disease? J Lipid Res, 2011; 52: 1755-1759.
33. Djousse L, Levy D, Cupples LA, Evans JC, D'Agostino RB, Ellison RC: Total serum bilirubin and risk of cardiovascular disease in the Framingham offspring study. Am J Cardiol, 2001; 87: 1196-1200.
34. Giral P, Ratziu V, Couvert P, Carrie A, Kontush A, Girerd X, Chapman MJ: Plasma bilirubin and gamma-glutamyltransferase activity are inversely related in dyslipidemic patients with metabolic syndrome: relevance to oxidative stress. Atherosclerosis, 2010; 210: 607-613.
35. Han SS, Na KY, Chae D-W, Kim YS, Kim S, Chin HJ: High serum bilirubin is associated with the reduced risk of diabetes mellitus and diabetic nephropathy. Tohoku J Exp Med, 2010; 221: 133-140
36. Xu T, Zhang J, Liu W, Kong Y, Zhang Y: Association of serum bilirubin with stroke severity and clinical outcomes. Can J Neurol Sci, 2013; 40: 80-84.
37. Zucker SD, Horn PS, Sherman KE: Serum bilirubin levels in the U.S. population: gender effect and inverse correlation with colorectal cancer. Hepatology, 2004; 40: 827-835.
38. Yang Z, Liang Y, Li C, Xi W, Zhong R: Bilirubin levels in patients with systemic lupus erythematosus: increased or decreased?Rheumatol Int, 2012; 32: 2423-2430.
39. Radhakrishnan R, Kanigere M, Menon J, Calvin S, Janish A, Srinivasan K: Association between unconjugated bilirubin and schizophrenia. Psychiatry Res, 2011; 189: 480-482.
40. Franchini M, Targher G, Lippi G: Serum bilirubin levels and cardiovascular disease risk: a Janus Bifrons? Adv Clin Chem, 2010; 50: 47-63.
41. Senturk UK, Gunduz F, Kuru O, Kocer G, Ozkaya YG,etal. Exercise-induced oxidative stress leads hemolysis in sedentary but not trained humans. J Appl Physiol, 2005, 99: 1434-1441.