Editorial / *Editöryal Yorum*

Protective effect of elevated bilirubin levels on cardiovascular disease in patients with Gilbert syndrome

Gilbert sendromlu hastalarda artmış bilirubin düzeyinin kardiyovasküler hastalıklardan koruyucu etkisi

Emre Gürel, M.D., Mustafa Kürşat Tigen, M.D.[#]

Department of Cardiology, Pendik State Hospital, Istanbul
[#]Department of Cardiology, Marmara University Faculty of Medicine, Istanbul

Gilbert's syndrome (GS), a condition of mild and benign hyperbilirubinemia, has recently become a topic of great interest due to its clear association with reduced cardiovascular disease (CVD). It affects 3-10% of the general population and is caused by a genetic mutation of the uridine diphosphate glucuronosyl transferase (UGT1A1) gene. This mutation inhibits hepatic UGT1A1 enzyme synthesis, bilirubin conjugation and excretion, and is associated with mildly elevated serum unconjugated bilirubin (UCB) concentration in GS (>17 µmol/L).[1] The mechanisms of decreased CVD rate in GS are not entirely known, but probably multifactorial.

Several *in vitro* studies have shown that different forms of bilirubin (conjugated, unconjugated or free) are powerful antioxidants, effective scavengers of peroxyl radicals and protective against low density lipoprotein (LDL) peroxidation.[2] A growing number of studies have also demonstrated the impact of increased serum bilirubin levels on reduction of oxidation products *in vivo*.[3] Additionally, studies have shown that individuals with GS have decreased susceptibility to serum oxidation and that bilirubin level is significantly related to serum oxidizability.[4] Considering the role of oxidized LDL in the development of atherosclerosis, it has been suggested that increased concentration of plasma bilirubin may reduce atherogenic risk.[1]

Abbreviations:

CAC	*Coronary artery calcification*
CAD	*coronary artery disease*
CRP	*C-reactive protein*
CVD	*Cardiovascular disease*
GS	*Gilbert's syndrome*
LDL	*Low density lipoprotein*
PWV	*Pulse wave velocity*
UCB	*Unconjugated bilirubin*
UGT1A1	*Uridine diphosphate glucuronosyl transferase*

Elevation of serum LDL is well established as a major risk factor for coronary artery disease (CAD). Oxidative modification of LDL is a key step in the development of atherosclerosis, and its circulating concentration correlates with impaired endothelial function and the prevalence of CAD.[5] Negative relationships between circulating UCB and serum lipid concentrations exist in multiple cross-sectional studies as recently reviewed by Bulmer and colleagues.[6] Decreased LDL, triglycerides and total cholesterol are reported in patients with GS.[7] Tapan and colleagues reported reduced small dense LDL and oxidized LDL concentrations in GS.[8] Additionally, positive association of serum bilirubin with high density lipoprotein (HDL) concentrations and elevated HDL/LDL ratios have been documented in individuals with GS.[3] With respect to this clinical data, bilirubin's favourable effects on cholesterol homeostasis may be protective against CVD.

Correspondence: Dr. Emre Gürel. Petroliş Mahallesi, Ulaş Sokak, Birlik Apartmanı, No: 2/13, Kartal, İstanbul.
Tel: +90533 423 21 51 e-mail: emregurelctf@yahoo.com

Free radical induced oxidation of LDL can induce inflammation, endothelial dysfunction and platelet activation. Oxidized LDL also induces inflammatory responses in macrophages, which act as a trigger for the development of atherosclerosis. A significant reduction in C-reactive protein (CRP; a chronic inflammatory marker) was reported in subjects with GS when compared to healthy controls, and CRP levels were found to be correlated negatively with plasma bilirubin levels.[7] Endothelial dysfunction, increased carotid intima-media thickness and reduced flow mediated dilation are reported in individuals with reduced levels of serum bilirubin. These measurements indicate reduced vascular reactivity and therefore are important predictors of atherosclerosis in GS.[9] Coronary artery calcification (CAC) score is also an established quantitative measure of atherosclerosis, and reduced bilirubin concentrations are also associated with increased risk of CAC and CAD.[10]

Platelet adhesion under physiological conditions disaggregates naturally via the actions of nitric oxide (NO). However, under conditions of oxidative stress, activated platelets aggregate and initiate the formation of thrombi and encourage atherogenesis by promoting inflammation at the site of activation.[11] Superoxide anion and H_2O_2 interact with NO forming peroxynitrite and mobilizing arachidonic acid respectively, thus creating a positive feedback loop of platelet activation. It is therefore possible that the antioxidant potential of bilirubin contributes to cardiovascular protection by influencing platelet function. However this effect of bilirubin is an unexplored area of great interest with particular relevance to CVD prevention.

Several other studies have reported a negative relationship between increased bilirubin concentration (in GS) and incidence of metabolic disorders.[12] Diabetes and metabolic syndrome induce oxidative stress and contribute to increased CVD risk. While the mechanism of protection in GS in not yet fully understood, mildly elevated levels of UCB might increase insulin sensitivity, insulin signaling and glucose tolerance. Administration of bilirubin improved insulin sensitivity in leptin-receptor deficient mice in an experimental study.[13]

Atherosclerosis is a chronic and multifactorial disease affecting the whole arterial system. Therefore, atherosclerotic changes in any part of the arterial system provide a clue to the other parts. Aortic stiffness occurs normally with aging and it is an independent predictor of cardiovascular mortality and morbidity.[14] The most obvious consequences of aortic stiffness are increased pulsatile blood pressure due to higher systolic blood pressure (SBP) and lower diastolic blood pressure (DBP), thereby causing increased left ventricular afterload and altering coronary perfusion. Thus, large pulse pressure relative to mean pressure is the characteristic wave form of stiffened arteries. Aortic stiffness has also been shown to be correlated with the prevalence of CAD confirmed by routine coronary angiography.[15] Aortic pulse wave velocity (PWV) measurements in the detection of aortic stiffness have been performed in previous studies, and PWV's relationship with CAD has been clearly demonstrated.[14] It offers a simple, reproducible, and noninvasive evaluation of regional arterial stiffness.

In the current issue of the Archives of the Turkish Society of Cardiology, Yüce et al.[16] performed a prospective observational study in which an analysis was made of biochemical tests and aortic stiffness measurements in 58 GS patients and 58 healthy subjects. Aortic stiffness was calculated, measuring PWV from the right carotid artery and the right femoral artery. They concluded that individuals with GS had reduced PWV when compared to the age-matched healthy controls. They also found decreased serum CRP, LDL, diastolic and systolic blood pressure in GS patients in comparison to the controls.

Several limitations arise in this study. The limited study population and the inclusion of subjects only younger than 45 years prevent robust conclusions. Calculation of aortic stiffness with other parameters such as aortic strain and aortic distensibility in addition to PWV might provide for more accurate evaluation. Clinical follow-up studies assessing cardiovascular mortality and morbidity for detection of the protective role of bilirubin against atherosclerosis in GS patients might clarify controversies in this field.

Conflict-of-interest issues regarding the authorship or article: None declared.

REFERENCES

1. Novotný L, Vítek L. Inverse relationship between serum bilirubin and atherosclerosis in men: a meta-analysis of published studies. Exp Biol Med (Maywood) 2003;228:568–71.
2. 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;269:16712–9.

3. Vítek L, Kráslová I, Muchová L, Novotný L, Yamaguchi T. Urinary excretion of oxidative metabolites of bilirubin in subjects with Gilbert syndrome. J Gastroenterol Hepatol 2007;22:841–5. CrossRef
4. Yesilova Z, Serdar M, Ercin CN, Gunay A, Kilciler G, Hasimi A, et al. Decreased oxidation susceptibility of plasma low density lipoproteins in patients with Gilbert's syndrome. J Gastroenterol Hepatol 2008;23:1556–60. CrossRef
5. Yoshida H, Sasaki K, Namiki Y, Sato N, Tada N. Edaravone, a novel radical scavenger, inhibits oxidative modification of low-density lipoprotein (LDL) and reverses oxidized LDL-mediated reduction in the expression of endothelial nitric oxide synthase. Atherosclerosis 2005;179:97–102. CrossRef
6. Bulmer AC, Verkade HJ, Wagner KH. Bilirubin and beyond: a review of lipid status in Gilbert's syndrome and its relevance to cardiovascular disease protection. Prog Lipid Res 2013;52:193–205. CrossRef
7. Wallner M, Marculescu R, Doberer D, Wolzt M, Wagner O, Vitek L, et al. Protection from age-related increase in lipid biomarkers and inflammation contributes to cardiovascular protection in Gilbert's syndrome. Clin Sci (Lond) 2013;125:257–64. CrossRef
8. Tapan S, Karadurmus N, Dogru T, Ercin CN, Tasci I, Bilgi C, et al. Decreased small dense LDL levels in Gilbert's syndrome. Clin Biochem 2011;44:300–3. CrossRef
9. Erdogan D, Gullu H, Yildirim E, Tok D, Kirbas I, Ciftci O, et al. Low serum bilirubin levels are independently and inversely related to impaired flow-mediated vasodilation and increased carotid intima-media thickness in both men and women. Atherosclerosis 2006;184:431–7. CrossRef
10. Tanaka M, Fukui M, Tomiyasu K, Akabame S, Nakano K, Hasegawa G, et al. Low serum bilirubin concentration is associated with coronary artery calcification (CAC). Atherosclerosis 2009;206:287–91. CrossRef
11. Gawaz M, Langer H, May AE. Platelets in inflammation and atherogenesis. J Clin Invest 2005;115:3378–84. CrossRef
12. Vítek L. The role of bilirubin in diabetes, metabolic syndrome, and cardiovascular diseases. Front Pharmacol 2012;3:55. CrossRef
13. Dong H, Huang H, Yun X, Kim DS, Yue Y, Wu H, et al. Bilirubin increases insulin sensitivity in leptin-receptor deficient and diet-induced obese mice through suppression of ER stress and chronic inflammation. Endocrinology 2014;155:818–28.
14. Fukuda D, Yoshiyama M, Shimada K, Yamashita H, Ehara S, Nakamura Y, et al. Relation between aortic stiffness and coronary flow reserve in patients with coronary artery disease. Heart 2006;92:759–62. CrossRef
15. Hirai T, Sasayama S, Kawasaki T, Yagi S. Stiffness of systemic arteries in patients with myocardial infarction. A noninvasive method to predict severity of coronary atherosclerosis. Circulation 1989;80:78–86. CrossRef
16. Yüce S, Cüre E, Çiçek Y, Cumhur Cüre M, Yılmaz A, Kızılkaya B. Evaluation of aortic stiffness in Gilbert syndrome patients: a protective effect of elevated bilirubin levels. Turk Kardiyol Dern Ars 2015;43:599-606.