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

Gilbert sendromlu hastalarda artmış bilirubin düzeyinin
kardiyovasküler hastalıklardan koruyucu etkisi

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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]

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.

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

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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. 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. 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.

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. Superoxide anion and H$_2$O$_2$ 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. 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.

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. 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. 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. 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. 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.

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REFERENCES

2. Neuzil J, Stocker R. Free and albumin-bound bilirubin are efficient co-antioxidants for alpha-tocopherol, inhibiting


