Perspective

Does serum bilirubin prevent cardiovascular disease?

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Abstract: Bilirubin possesses potent antioxidant, anti-inflammatory, anti-platelet, anti-hypercholesterolemic and anti-adiposity properties. Cross-sectional studies have demonstrated negative associations between serum bilirubin and metabolic syndrome (MetS), diabetes and atherosclerotic cardiovascular diseases (CVDs). However, longitudinal studies show conflicting results. Serum bilirubin levels are determined both genetically and environmentally, and fluctuate throughout one's life. Longitudinal data suggest that some genetically hyperbilirubinemic individuals may have a lower CVD risk than the general population. However, the reverse may be also true; that is, postnatal metabolic or atherosclerotic diseases may cause oxidative stress and reduce serum bilirubin levels. Therefore, baseline serum bilirubin levels may not always be associated with future metabolic or atherosclerotic diseases. This situation resembles a phenomenon called antioxidant paradox; that is, randomized controlled trials have failed to confirm a role for antioxidant supplementation in CVD prevention, although oxidative stress is involved in the pathogenesis of CVD. Further prospective studies are required to confirm whether serum bilirubin prevents metabolic and atherosclerotic diseases.

Keywords: Bilirubin; oxidative stress; diabetes; cardiovascular disease (CVD); metabolic syndrome (MetS)

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Introduction

Oxidative stress has been implicated in the pathogenic mechanisms of most non-communicable diseases, including metabolic syndrome (MetS) (1), atherosclerosis and cancer. LDL cholesterol is rendered more atherogenic by oxidative modification (2) and many carcinogens create free oxygen radicals that damage DNA and other cellular structures, initiating and promoting tumor development (3). Therefore, antioxidant agents have been extensively evaluated in the prevention of cardiovascular disease (CVDs) and cancer. Vitamin E has been shown to reduce atherosclerotic lesions in animals (4), smooth muscle cell proliferation (5), platelet adherence and aggregation (6). Epidemiological data indicate a negative association between cardiovascular or cancer risk and vitamin E intake from dietary sources and/or supplements (7). However, most randomized controlled trials have failed to confirm a role for vitamin E supplementation in cardiovascular prevention (8-12). Indeed, vitamin E has been reported to have no significant effect on myocardial infarction, stroke, cardiovascular death, unstable angina, revascularization, total mortality (13) or diabetes (14,15). The findings from trials of cancer chemoprevention have also been disappointing (16-18). This situation is called the antioxidant paradox. Bilirubin has been recognized as a potent antioxidant, so does serum bilirubin prevent metabolic or atherosclerotic CVD?

Bilirubin as an antioxidant

The catabolism of heme by heme oxygenase generates carbon monoxide, free iron, and biliverdin, which is rapidly converted to bilirubin by ubiquitously expressed biliverdin reductase. Bilirubin efficiently scavenges a wide range of physiological oxidants by electron donation. In this process, it is often reconverted to biliverdin, but biliverdin reductase quickly regenerates bilirubin, thereby greatly boosting its antioxidant potential. Bilirubin suppresses the oxidation of lipids in liposomes more than vitamin E, which is regarded as the best antioxidant of lipid peroxidation (19,20). The

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water-soluble glutathione primarily protects water soluble proteins, whereas the lipophilic bilirubin protects lipids from oxidation (21). Serum bilirubin has been demonstrated to be a major contributor to the total antioxidant capacity in blood plasma (22) and is proven to have anti-inflammatory (23) and anti-platelet (24) properties. However, serum bilirubin is not an ideal marker of oxidative stress because serum levels of bilirubin are influenced by various factors related to hemoglobin metabolism as well as conjugation and excretion of bilirubin apart from oxidative stress.

Bilirubin as an anti-hypercholesterolemic agent

Apart from its antioxidant and anti-inflammatory properties, bilirubin is suggested to have a hypocholesterolemic property (25-27). The profound hypocholesterolemia and hypotriglyceridemia found in a murine model of hyperbilirubinemia (Gunn rat) suggests that an increase in serum bilirubin levels may decrease serum levels of cholesterol and triglycerides (25,26). Gilbert's Syndrome is associated with a mutation in the hepatic Uridine Glucuronosyl Transferase 1A1 (UGT1A1) gene promoter, reducing UGT1A1 activity, which normally conjugates bilirubin, allowing its elimination from the blood. Individuals with Gilbert's syndrome demonstrate mildly elevated plasma antioxidant capacity due to the elevated levels of unconjugated bilirubin. In a case-control study, when subdivided into younger and older cohorts, older patients with Gilbert's syndrome demonstrated reduced levels of total cholesterol and LDL cholesterol compared with controls (26). The author observed that serum bilirubin was significantly negatively associated with incident hyper-LDL cholesterolemia in a health screening population (27). The exact mechanisms underlying this negative association between baseline serum bilirubin and incident hyper-LDL cholesterolemia are unknown. However, it has been suggested that increased bilirubin levels affect lipid homeostasis through increased intestinal cholesterol secretion, reduced hepatic cholesterol synthesis and increased biliary cholesterol excretion (28). Recently, a direct effect of bilirubin on cholesterol efflux was demonstrated and is associated with decreased ABCA1 protein expression (29).

Bilirubin as an anti-adiposity agent

Bilirubin has a new function as a ligand for PPARα. Stec *et al.* demonstrated that bilirubin can bind directly to PPARα and increase transcriptional activity (30). When they compared the PPARα transcriptional activation of biliverdin with that of a known PPARα ligand, fenofibrate, fenofibrate and biliverdin have similar activation properties. Treatment of 3T3-L1 adipocytes with biliverdin suppressed lipid accumulation and upregulated PPARα target genes. They treated wild-type and PPARα KO mice on a high fat diet with fenofibrate or bilirubin and found that both signal through PPARα dependent mechanisms. Furthermore, the effect of bilirubin on lowering glucose and reducing body fat percentage was blunted in PPARα KO mice (30). These data suggest a new function for bilirubin as an agonist of PPARα, which mediates the protection from adiposity. Involvement of AMPK pathway was also suggested for the protection of Gilbert's syndrome from adiposity (31).

Cross-sectional negative associations between serum bilirubin and metabolic and atherosclerotic CVD as well as CVD risk factors

Serum bilirubin has been shown to be negatively associated with MetS in Chinese children, adolescents and adults (32,33): Korean men and women (34,35) and nonsmoking Japanese men and women (36) in cross-sectional studies. Serum bilirubin levels are negatively associated with impaired flow-mediated vasodilation and carotid intima-media thickness in men and women (37). Patients with Gilbert's syndrome had low levels of oxidative stress associated with enhancement of endothelium-dependent vasodilation (38). A low serum bilirubin concentration is associated with coronary artery calcification (39). Serum bilirubin has been demonstrated to be negatively associated with coronary heart disease (40-42), stroke (42,43) and peripheral artery disease (44) in cross-sectional studies. One author reported that serum bilirubin is negatively associated with hemoglobin A1c, independently of other cardiovascular risk factors, in healthy men and women in a cross-sectional study suggesting an negative inverse association between bilirubin and diabetes (45). Fukui *et al.* observed a significant cross-sectional negative association between serum bilirubin and albuminuria in patients with diabetes (46). The presence of silent cerebral infarction increases the risk of transient ischemia attack, symptomatic stroke, CVD and dementia. A cross-sectional study demonstrated that a higher serum bilirubin was associated with a lower risk of silent cerebral infarction (47). These cross-sectional studies are summarized in *Table 1*.

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Table 1 Cross-sectional associations between serum bilirubin and metabolic and atherosclerotic diseases or risk factors

Studies (reference)	Subjects	Risk factors or diseases	Relationships
Lin *et al.* (32)	4,723 children and adolescents	Metabolic syndrome	Negative association
Wu *et al.* (33)	1,423 adults	Metabolic syndrome	Negative association
Choi *et al.* (34)	12,342 adults	Metabolic syndrome	Negative association
Kwon *et al.* (35)	5,266 women	Metabolic syndrome	Negative association
Oda *et al.* (48)	3,681 adults	Metabolic syndrome	Negative association
Erdogan *et al.* (37)	91 middle-aged subjects	Endothelial dysfunction	Negative association
		Carotid intima-media thickness	Negative association
Maruhashi *et al.* (38)	108 men with Gilbert's syndrome *vs.* controls	Endothelial dysfunction	Negative association
		Oxidative stress markers	Negative association
Tanaka *et al.* (39)	637 patients	Coronary artery calcification	Negative association
Schwertner *et al.* (40)	877 men	Coronary heart disease	Negative association
Hopkins *et al.* (41)	161 subjects with EFCHD and 155 controls	Coronary heart disease	Negative association
Oda *et al.* (42)	3,375 men and 2,069 women	Coronary heart disease	Negative association
		Stroke	Negative association
Perlstein *et al.* (43)	13,214 adults	Stroke	Negative association
Perlstein *et al.* (44)	7,075 adults	Peripheral artery disease	Negative association
Oda *et al.* (45)	2,500 men and 1,680 women	Hemoglobin a1c	Negative association
Fukui *et al.* (46)	633 diabetics	Albuminuria	Negative association
		Pulse wave velocity	Negative association
Li *et al.* (47)	1,831 men and 1,034 women	Silent cerebral infarction	Negative association
		Pulse wave velocity	Negative association

EFCHD, early familial coronary heart disease.

Conflicting results in longitudinal studies on the association between serum bilirubin and metabolic and atherosclerotic CVD as well as CVD risk factors

A U-shaped relationship was observed between serum bilirubin and risk of coronary heart disease in middle-aged British men in a large, long-term prospective study (49). Another nested case-control study also observed a U-shaped relationship between bilirubin concentration and coronary heart disease risk in middle-aged men (50). Serum bilirubin levels are determined both genetically and environmentally. Linkage studies have identified a major locus at the chromosome 2q telomere that affects bilirubin concentrations and a candidate gene in the linkage region encodes UGT1A1 (51). The insertion of a TA in the TATAA box of the gene promotor region, an allele designated UGT1A1*28, decreases gene transcription. Individuals homozygous for UGT1A1*28 (genotype 7/7) have increased serum bilirubin levels compared with carriers of the 6 allele (52). In the Rotterdam Study, homozygote or heterozygote UGT1A1*28 allele carriers were not associated with myocardial infarction (53). However, homozygote UGT1A1*28 allele carriers with elevated serum bilirubin concentrations exhibited a strong negative association with a reduced risk of CVD in the Framingham heart study offspring cohort (54). McArdle *et al.* reported that the UGT1A1*28 genotype was not significantly associated with any of the traditional CVD risk factors, and they suggested that the CVD benefits associated with increased serum bilirubin may in part be mediated by the early regulation of vascular structure and reactivity (55). A genome-wide association meta-analysis for total serum

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bilirubin levels showed a strong association between the UGT1A1 rs6742078 genotype and serum bilirubin (56). To test the hypothesis that elevated serum bilirubin is causally related to decreased risk of CVD, Stender *et al.* genotyped rs6742078 in the UGT1A1 gene in 67,068 individuals, 11,686 of whom had coronary heart disease (57). UGT1A1 rs6742078 TT versus GG genotype was not significantly associated with CVD risk; the TT versus GG genotype was associated with odds ratios (ORs) [95% confidence intervals (CIs)] of 1.03 (0.96–1.11) (P=0.73) for coronary heart disease and 1.01 (0.92–1.12) (P=0.68) for myocardial infarction (57). In their meta-analysis of 14,711 cases and 60,324 controls, the random effects OR (95% CI) of coronary heart disease for genotypes with approximately 100% increased bilirubin levels versus reference genotypes was 1.01 (0.88–1.16), and they concluded that serum bilirubin is not causally associated with the risk of coronary heart disease (57).

A study from Korea reported that the lowest serum bilirubin level category (bilirubin ≤0.32 mg/dL) was an independent risk factor for coronary heart disease (58). Another study from Germany observed that a 1-SD higher bilirubin level was associated with a 19% lower frequency of incident cardiovascular events in an age- and gender-adjusted Cox regression analysis [hazard ratio 95% CI: 0.81 (0.68; 0.96), P=0.014]; however, this hazard ratio became insignificant after adjustment for traditional cardiovascular risk factors [0.87 (0.73; 1.04), P=0.13] (59). A study suggested that serum bilirubin might have some protective function against ischemic stroke risk in Korean men, excluding subjects with Gilbert's syndrome (60). We suggested that serum bilirubin might be a negative predictor of end-stage kidney disease in Japanese using hospital-based data (61). Sakoh *et al.* reported that a lower serum bilirubin concentration was independently associated with adverse renal outcomes in Japanese patients with moderate-to-severe chronic kidney disease (62). Riphagen *et al.* observed a protective effect of bilirubin against progression of diabetic nephropathy in patients with type 2 diabetes in a post hoc analysis using Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial and Irbesartan Diabetic Nephropathy Trial (IDNT) data (63). Okada *et al.* suggested that low serum bilirubin levels could be a risk factor for the development of albuminuria in Japanese patients with type 2 diabetes (64). Mashitani *et al.* reported that serum bilirubin levels were associated with the progression of diabetic nephropathy in Japanese type 2 diabetic patients, independent of possible confounders and suggested that serum bilirubin levels might be the link in the correlation between hemoglobin levels and nephropathy progression (65).

A longitudinal study reported that serum bilirubin levels were negatively associated with the incidence of MetS in healthy Korean men (66). Among individual components of MetS, bilirubin was significantly associated with only incident hypertriglyceridemia (66). Another longitudinal study reported that decreased serum bilirubin levels predicted MetS in healthy middle-aged non-smoking Taiwanese men (67). It is reported that genotype-phenotype relationships regarding obesity traits were influenced by smoking status (68,69). Effects of genotypes linked to TB levels on incidence of MetS, diabetes and CVDs may be different between smokers and non-smokers. However, the author found that serum bilirubin levels could not predict the development of MetS in a Japanese population (48). Lee *et al.* also reported that no association was observed between baseline TB and incident MetS in men, but a significant inverse association was observed in women, which became insignificant after adjusted for insulin resistance (70).

A retrospective longitudinal study reported that serum bilirubin levels predicted diabetes in healthy Korean men (71). However, the authors of that study did not include baseline fasting glucose in the adjusted covariates of their multivariable-adjusted models (71). The author observed that incident prediabetes was not significantly associated with the quintiles of serum bilirubin but was positively associated with a 1 SD increase in serum bilirubin levels in non-smoking men, although serum bilirubin levels were significantly negatively associated with prevalent prediabetes in non-smokers (36). Therefore, a negative association between serum bilirubin levels and incident prediabetes seemed to be unlikely (36).

These conflicting results in longitudinal studies on the association between serum bilirubin and metabolic and atherosclerotic diseases are summarized in *Table 2*.

Considerable fluctuation of bilirubin levels

Serum bilirubin levels are determined both genetically and environmentally and fluctuate throughout one's life, as illustrated in *Figure 1*. The annual changes in the serum total bilirubin levels of 2,512 apparently healthy subjects who visited our medical check-up center are presented in *Figure 2*. Considerable changes were observed in serum bilirubin levels over the course of one year.

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Table 2 Conflicting results in longitudinal studies on the association between serum bilirubin and metabolic and atherosclerotic diseases

Studies (reference)	Subjects	Follow-up periods	Risk factors	Outcomes	Results
Breimer *et al.* (49)	7,685 men	11.5 years	Serum bilirubin	Coronary heart disease	U-shaped association
Troughton *et al.* (50)	10,593 men	5 years	Serum bilirubin	Coronary heart disease	U-shaped association
Bosma *et al.* (53)	185 cases vs. 370 controls	Case-control study	UGT1A1*28	Myocardial infarction	No significant association
Lin *et al.* (54)	1,780 individuals	Mendelian randomization	UGT1A1*28	Coronary heart disease	Negative association
McArdle *et al.* (55)	868 individuals	Mendelian randomization	UGT1A1*28	CVD risk factors	No significant association
Stender *et al.* (57)	67,068 individuals	Mendelian randomization	UGT1A1 rs6742078	Coronary heart disease	No significant association
Song *et al.* (58)	8,593 individuals	4 years	Serum bilirubin	Coronary heart disease	Negative association
Mahabadi *et al.* (59)	3,553 individuals	9.1 years	Serum bilirubin	Cardiovascular events	No significant association
Kimm *et al.* (60)	41,054 men†	13 years	Serum bilirubin	Ischemic stroke	Negative association
	37,670 women†	13 years	Serum bilirubin	Ischemic stroke	No significant association
Oda *et al.* (61)	6,251 patients	1 year	Serum bilirubin	ESKD	Negative association
Sakoh *et al.* (62)	279 CKD patients	21 months	Serum bilirubin	Progression of CKD	Negative association
Riphagen *et al.* (63)	1,498 diabetics in RENAAL	3.4 years	Serum bilirubin	Progression of DN	Negative association
	1,707 diabetics in IDNT	2.6 years	Serum bilirubin	Progression of DN	Negative association
Okada *et al.* (64)	320 diabetics	3.2 years	Serum bilirubin	Proteinuria	Negative association
Mashitani *et al.* (65)	2,511 diabetics	1.4 years	Serum bilirubin	Macroalbuminuria	Negative association
	Adjusted for hemoglobin				No significant association
Lee *et al.* (66)	6,205 men	4 years	Serum bilirubin	Metabolic syndrome	Negative association
Huang *et al.* (67)	377 nonsmoking men	7.6 years	Serum bilirubin	Metabolic syndrome	Negative association
Oda *et al.* (48)	2,558 men and women	4 years	Serum bilirubin	Metabolic syndrome	No significant association
Lee *et al.* (70)	6,890 men	5 years	Serum bilirubin	Metabolic syndrome	No significant association
	4,723 women	5 years	Serum bilirubin	Metabolic syndrome	Negative association
	Adjusted for insulin resistance				No significant association
Jung *et al.* (71)	5,960 men	4 years	Serum bilirubin	Diabetes	Negative association
Oda (36)	2,149 individuals	6 years	Serum bilirubin	Prediabetes	No significant association

†, excluding Gilbert's syndrome. UGT1A1, uridine diphosphate glucuronosyltransferase1A1; CVD, cardiovascular disease; ESKD, end-stage kidney disease; CKD, chronic kidney disease; RENAAL , Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan Study; IDNT, Irbesartan Diabetic Nephropathy Trial; DN, diabetic nephropathy.

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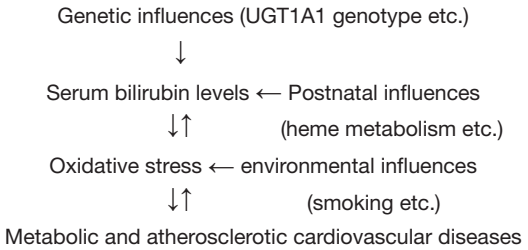

Figure 1 Various factors that influence serum bilirubin levels.

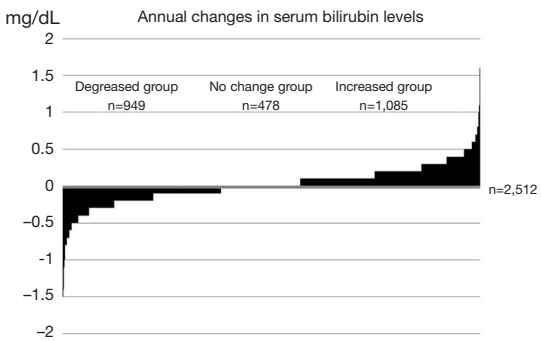

Figure 2 Annual changes in the serum bilirubin levels among apparently healthy individuals.

Conclusions

The above-mentioned cross-sectional and longitudinal studies suggest that postnatal metabolic and atherosclerotic diseases sometimes cause oxidative stress and reduce serum bilirubin levels, and antioxidant agents such as bilirubin do not always prevent metabolic and atherosclerotic diseases, although certain genetically hyperbilirubinemic individuals may have lower CVD risk than the general population. A similar situation has been documented for antioxidant vitamins and is called the antioxidant paradox. Further prospective studies are required to confirm whether serum bilirubin prevents the development of non-communicable disease such as MetS, diabetes and CVD.

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Footnote

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jxym.2017.07.05). The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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