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Serum bilirubin has an important role in multiple clinical applications

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Abstract: Bilirubin is a natural end-product of heme metabolism, and it has been traditionally used as a diagnostic marker in hepatobiliary diseases and its related complications. Recently, accumulating data have demonstrated that serum bilirubin has anti-oxidative, anti-inflammatory and immunosuppressive functions in the human body. In this review, we summarized the studies concerning serum bilirubin and its effects on various diseases, as well as its clinical implications. We found that serum bilirubin is closely related to human health. However, the results from available studies are heterogenous, most likely due to the presence of some confounding factors, which interfere the association between bilirubin and human disease have. Therefore, there is immense need of larger, prospective and possibly randomized controlled studies to clearly delineate the role of bilirubin in various disease processes.

Keywords: Serum bilirubin; cardiovascular diseases (CVD); autoimmune diseases; cancer; diabetes mellitus; inflammation; antioxidant

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Bilirubin has been deemed to be a natural end-product of heme metabolism in the body and has a neurotoxic effect in infants (1). However, accumulating data have demonstrated that serum bilirubin has anti-oxidative, anti-inflammatory and immunosuppressive functions in various diseases (2). Indeed, serum bilirubin has been found to be a predictor in some oxidative stress-mediated diseases, including atherosclerosis, rheumatism and neuropsychiatric disorders (3). Further, numerous studies have provided evidence that mildly elevated serum bilirubin concentrations are associated with better prognosis in cardiovascular, autoimmune and oncologic diseases (4). Serum bilirubin levels have been reported to be related to

type 2 diabetes mellitus (T2DM) and its complications (5). The relationships between serum bilirubin concentrations and essential trace elements status have also been revealed in an adult population since serum bilirubin maintains strong anti-inflammatory and anti-oxidative features even in general population (6). In fact, oxidative stress, inflammation, and immune response contribute to the pathology and physiology of clinical diseases and serve as triggers in these diseases (7). Therefore, it is reasonable to speculate that serum bilirubin is a promising biomarker to assess severity and prognosis of certain diseases in clinical laboratory medicine. In this article, we summarized the published studies in regard to levels of serum bilirubin and

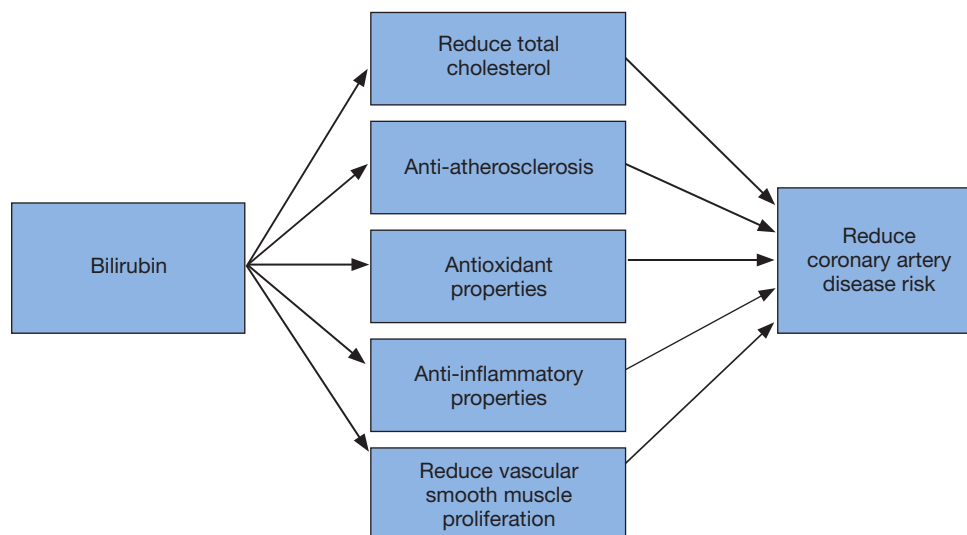


Figure 1 Proposed mechanisms between serum bilirubin and CVDs. CVD, cardiovascular disease.

its relation with severity and prognosis of clinical diseases and disorders, and its clinical implications are reviewed.

Serum bilirubin and cardiovascular diseases (CVD)

Bilirubin is considered as a non-traditional risk factor in patients with CVD owing to its anti-oxidative and anti-inflammatory actions. A relationship between serum bilirubin and CVD was first reported by Schwertner *et al.* (8) in 1994. Their study demonstrated that in adult males serum bilirubin is an independent risk factor for asymptomatic and angiographically proven coronary artery disease (CAD) even after adjusting for age, total cholesterol, smoking and systolic blood pressure (SBP). From a prospectively collected data on 7,658 middle-aged British males, followed for 11.6 years, Breimer *et al.* (9) found a negative association between serum bilirubin and ischemic heart disease. Since then, multiple studies have suggested that serum bilirubin plays an important role in the development of CVD.

Although the main mechanism related to an interaction of serum bilirubin and CVD is obscure, various theories have been proposed as shown in *Figure 1*. Hyperbilirubinemia reduces circulating plasma lipids such as cholesterol, triacylglycerols and low-density lipoprotein (LDL) cholesterol (10). Patients with higher bilirubin were found to have a lower risk of CVD events since its potential protective role against atherosclerosis process (11). Bilirubin could protect against atherosclerosis process due to its antioxidant

and anti-inflammatory properties as well as inhibition of vascular smooth muscle cell proliferation (12). Ko *et al.* (13) reported an inverse relationship between the levels of serum bilirubin and other known CVD risk factors such as smoking, obesity, SBP, glycated hemoglobin, triglycerides and LDL levels. de Sauvage Nolting *et al.* (14) found that in patients with familial hypertriglyceridemia, baseline serum bilirubin concentration is inversely associated with the presence of CVD even after adjusting for age, sex, HTN, and HDL cholesterol levels. In a cross-sectional cohort of healthy Japanese adults, it was found that high bilirubin levels are associated with less CVD and stroke prevalence in males and less prevalence of stroke in females (15) after adjusting common risk factors. Lower serum bilirubin has been found to be associated with all-cause mortality and cardiovascular mortality in patient with kidney dysfunction (16). Lin *et al.* (17) discovered that serum bilirubin is negatively related to SYNTAX score in patients with stable CAD, and can predict future cardiovascular events such as non-fatal myocardial infarction, target vessel revascularization, stroke and death. A large scale population studies have found an inverse relationship between serum bilirubin concentration and incidence of hypertension (18). *Ex vivo* studies on rats' heart have shown that pre- and post-treatment with bilirubin ditaurate provide significant cardioprotection, with a reduction in infarct size and oxidative damage (19). From the above evidences, it is clear that mildly elevated bilirubin level has cardioprotective effects and this relation should be

further studied in animal and human experimental trials.

Serum bilirubin and autoimmune disorders (AIDs)

AIDs are a group of disorders in which the immune system “attacks” itself due to exaggerated recognition and response to antigens, causing tissue damage and chronic inflammation. Continued oxidative stress, chronic inflammation, and immune response play a key role in the pathogenesis of AIDs. Because of its direct anti-oxidative, anti-inflammatory and immunomodulatory properties, mildly elevated bilirubin has been demonstrated to be beneficial in patients with AIDs (20). In a sample of 8,147 individuals in NHANES (National Health and Nutrition Examination Survey) study from 2003–2006, the prevalence of rheumatoid arthritis was inversely related to total serum bilirubin level (OR: 0.679; 95% CI 0.533–0.865) (21). In a study, it was found that serum bilirubin levels are significantly lower in newly diagnosed polymyositis patients when compared to healthy controls, and bilirubin levels negatively correlate to ESR, CK and LDH in patients with polymyositis (22). Moreover, serum bilirubin was found to be inversely correlated with disease activity and extent in patients with systemic lupus erythematosus (SLE) (20). Furthermore, each 1 $\mu\text{mol/L}$ decrease in serum bilirubin is associated with a 37% increase in the odds for a positive SLE status (OR: 1.37; 95% CI 1.28–1.47, $P < 0.00001$) (23). Another study in SLE patients showed significantly decreased total, indirect and direct bilirubin levels but only lower direct bilirubin levels show an independent association with renal involvement due to lupus (24). It was proposed that conjugated bilirubin can be filtered by glomeruli which could exert local (renal) anti-oxidative and anti-inflammatory effects while unconjugated bilirubin cannot (25). Serum bilirubin levels were found to be significantly lower ($P < 0.001$) in patients with multiple sclerosis (MS) when compared to healthy adults. However, authors also discovered that patients with longer duration of MS > 2 years, lower disability score and inactive disease on MRI had lower concentration of bilirubin. The authors could not explain if it was due to the primary deficit or increased consumption of bilirubin by free radicals. Similar findings were also observed in patients with myasthenia gravis, Takayasu arteritis and rheumatoid arthritis (5,26,27). Serum bilirubin levels were also found to be significantly lower in patient with Crohn’s disease and it was dependent on UDP-glucuronosyl transferase (UGT1A1) allele homozygosity (28).

Similarly, in many other AID such as neuromyelitis optica (29) primary biliary cirrhosis (PBC) (30) insulin dependent diabetes mellitus (IDDM) (31), higher bilirubin levels have found to be associated with lesser severity and a favorable prognosis. However, most of these evidences come from retrospective case-control studies, therefore further prospective high-quality cohort studies are needed in order to make full use of the protective characteristics of bilirubin in AID.

Serum bilirubin and cancer

The relationship between serum bilirubin and cancer has been revealed in recent years. Molecular studies on human cancer cells have shown that anticancer effects of bilirubin are due to its ability to drastically increase free radical levels inside the tumor cells, thereby alleviating the oxidative stress. Increased reactive oxygen species damage DNA structure and alters gene expression reducing cell proliferation (32).

In a large prospective study of 68,676 Korean population who were followed for 10 years, serum bilirubin levels consistently showed a protective effect on the risk of development of lung cancer in both never and current smokers. Smokers with bilirubin level 0.2–0.7 mg/dL had 6 times higher risk of development of lung cancer than never-smokers with bilirubin > 1.0 mg/dL (33). However, previous studies have demonstrated that smoking is inversely associated with serum bilirubin (34). Wen *et al.* (35) reported that bilirubin is a risk predictor for increased incidence and mortality of lung cancer in smokers. They found that with every 0.1 mg/dL decrease in bilirubin, incidence and mortality of lung cancer in male smokers increased by 5% and 6%, respectively ($P < 0.001$). Smokers with a history of ≥ 30 pack years with bilirubin level of < 0.75 mg/dL had 31% higher risk of lung cancer when compared to bilirubin level of > 1 mg/dL. In a retrospective study on 1,617 patients with curatively resected non-small cell lung cancer, moderately elevated pretreatment bilirubin is associated with improved longer-term survival (36). In a larger cohort study from UK primary care research database (the health improvement network) comprising of 504,206 adults, an inverse association between bilirubin and lung cancer is found. Authors estimated that for every 0.1 mg/dL increase in bilirubin, decrease in incidence rate of lung cancer was 8% (95% CI, 5–11%) in men and 11% (95% CI, 7–14%) in women (37).

In vitro studies have also shown that bilirubin induced

apoptosis of colon adenocarcinoma cells by directly dissipating mitochondrial membrane potential and this effect occurs at bilirubin concentration normally present in the intestinal lumen (38). However, clinical and epidemiological studies have shown contradictory results on the effect of bilirubin on colorectal cancer. In a study from NHANES from 1988 to 1994 with 20,216 adult subjects, it was found that each 1 mg/dL increase in bilirubin is associated with decreased prevalence of colon cancer (OR =0.257; 95% CI 0.254–0.260) (39). In a case-control study performed by Jirásková *et al.*, it was showed that patients with sporadic colorectal cancer had lower bilirubin compared to healthy adults and each 0.058 mg/dL (1 μ mol/L) decrease in bilirubin is associated with a 7% increase in colorectal cancer risk ($P<0.001$) (40). In a retrospective case control study, it was found that direct bilirubin level was independently associated with lymph node metastasis in rectal cancer and poor prognosis (41). In a study on NHANES III [1998–1994] data, an inverse correlation between bilirubin levels and history of colorectal cancer is found (39). On the contrary, in another study from NHANES-I [1971–1974], baseline serum total bilirubin concentrations are not associated with the incidence of colorectal cancer (42). The discrepancy in these results could be due to the fasting status of patients, as NHANES-I patients were not asked to fast before the collection of the blood samples as opposed to NHANES III data. In addition, the levels of serum bilirubin have also been used as a biomarker to predict the prognosis in patients with pancreatic cancer (43). In a study of 2,425 newly diagnosed non-metastatic breast cancer in female Caucasians, high bilirubin levels are significantly associated with 5-years overall survival and nearly 40% reduction in risk of death (HR: 1.42; 95% CI 0.45–0.85) (44). Above studies have shown that bilirubin level could predict prognosis in patients with various cancers but there are no prospective or randomized trials which could conform these results.

Serum bilirubin and T2DM

In recent years, interest has been extended to explore the effect of serum bilirubin on T2DM. Emerging evidence has shown that the serum bilirubin concentrations are related to the development of T2DM and its complications. In a middle aged and elderly Japanese cohort, Deetman *et al.* (45) found an inverse association between serum bilirubin levels and HbA1C, and prevalence of T2DM. Authors proposed that higher serum concentration of bilirubin suppresses the

development of T2DM via its anti-oxidative effects (45). However, Wang *et al.* performed a cross-sectional analysis in two Chinese cohorts and found that serum bilirubin level does not protect against the development of T1DM and direct bilirubin levels were actually associated with increased risk of T2DM (46).

A negative relationship between serum bilirubin and metabolic syndrome has been found in patients with T2DM (47), and serum bilirubin was found to be associated with glycemic variability in females patients with T2DM (48). In a recent meta-analysis of observational studies on 23,141 subjects and 7,944 patients with diabetic nephropathy, Zhang *et al.* found that bilirubin in diabetic nephropathy groups is lower than non-diabetic nephropathy group and there is significant negative relationship between bilirubin and the risk of diabetic nephropathy (OR: 0.86; 95% CI 0.82–0.90) (49). Authors proposed that bilirubin could be used as a biomarker of diabetic nephropathy. In another meta-analysis by Hamamoto *et al.* a negative nonlinear association between bilirubin and the risk of diabetic complications such as diabetic nephropathy, retinopathy and neuropathy is identified (50).

Furthermore, lower serum bilirubin has been reported to be associated with other cardiovascular complications in patients with T2DM, such as autonomic neuropathy, arterial stiffness, peripheral neuropathy, retinopathy and carotid atherosclerosis (51–55). However, data from multiple prospective cohort studies and retrospective case-control studies are conflicting because of the presence of multiple confounders which could affect bilirubin (56).

Serum bilirubin in other human disorders

In addition to the aforementioned diseases, serum bilirubin has also been found to have prognostic value in other diseases. Serum bilirubin has been found to be inversely related to the C-reactive protein in patients with migraine (57), and increased serum bilirubin levels can reduce oxidative stress response in patients with HIV (58). In an interesting study, higher serum bilirubin concentrations were demonstrated to be associated with decreased postoperative liver's ischemia/reperfusion injury (IRI) in patients with live donor liver transplantation (59). Serum bilirubin has also been proposed to be a useful marker to differentiate cardioembolic stroke from other subtypes of strokes (60). Recently, high serum bilirubin levels were found to be significantly associated with the fatal outcome in patients infected with Ebola virus (61). Serum bilirubin plays a

significant role in anti-inflammatory response in patients with psoriasis vulgaris and hypothyroidism disease (62,63). Serum bilirubin is an important biochemical parameter to assess depressive conditions and may improve its complete management (64). However, its protective concentrations may be limited in a certain range.

Conclusions

Bilirubin has an important role in multiple clinical applications and appears to be a promising biological parameter to predict prognosis. It possesses anti-oxidative, anti-inflammatory and immunosuppressive properties (65). In fact, these characteristics have been thought to act as a central link in the pathogenesis of many diseases (3). Hence, we should consider that serum bilirubin is closely related to human health, although its exact mechanism remains largely unknown. Bilirubin is affected by many factors such as smoking, age, gender, fasting status, alcohol use and undiagnosed liver diseases which could be the reason for discrepancies in the results of some of the studies. There is potential heterogeneity due to aforementioned reason in the cut off value of serum bilirubin which could be used in clinical practice. Therefore, there is immense need of larger, prospective and possibly randomized controlled trials to clearly delineate the role of bilirubin in various disease processes.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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