Serum Bilirubin and Genes Controlling Bilirubin Concentrations as Biomarkers for Cardiovascular Disease

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BACKGROUND: Serum bilirubin has been consistently shown to be inversely related to cardiovascular disease (CVD). Recent studies showed serum bilirubin to be associated with CVD-related factors such as diabetes, metabolic syndrome, and body mass index. Although the association of serum bilirubin with CVD has been found in both retrospective and prospective studies, less information is available on the role of genes that control bilirubin concentrations and their association with CVD.

CONTENT: In this review, we provide detailed information on the identity of the major genes that control bilirubin concentrations and their association with serum bilirubin concentrations and CVD risk. We also update the results of the major studies that have been performed on the association between serum bilirubin, CVD, and CVD-related diseases such as diabetes or metabolic syndrome. Studies consistently indicate that bilirubin concentrations are inversely associated with different types of CVD and CVD-related diseases. A conditional linkage study indicates that UGT1A1 is the major gene controlling serum bilirubin concentrations, and this finding has been confirmed in recent genomewide association studies. Studies also indicate that individuals homozygous for UGT1A1*28 have a significantly lower risk of developing CVD than carriers of the wild-type alleles.

SUMMARY: Serum bilirubin has a protective effect on CVD and CVD-related diseases, and UGT1A1 is the major gene controlling serum bilirubin concentrations. Pharmacologic, nonpharmacologic, or genetic interventions that increase serum bilirubin concentrations could provide more direct evidence on the role of bilirubin in CVD prevention.

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Biological Properties of Bilirubin

Bilirubin has been shown to be an effective antioxidant both in vitro (1–3) and in vivo (4). As an antioxidant, it has been shown to suppress the oxidation of lipids and lipoproteins, especially LDL cholesterol (5), and to be directly related to the total serum antioxidant capacity in humans (4). Recent studies indicate that the lipophilic bilirubin is more effective at protecting lipids from oxidation than the water-soluble antioxidants such as glutathione, which primarily protect proteins from oxidation (6). Deletion of heme oxygenase-2, which produces biliverdin, in mice was also found to result in greater lipid oxidation than protein oxidation, whereas the reverse was found for glutathione. These results indicate that depletion of biliverdin and glutathione augments cell death in an oxidant-specific fashion (6). In addition, there is some evidence that bilirubin has antiinflammatory properties (7) that inhibit tumor necrosis factor α(8) (TNF-α)–induced upregulation of E-selectin, vascular cell adhesion molecule 1 (VCAM-1), and intercellular adhesion molecule 1 (ICAM-1) in vitro (8). This is consistent with findings by Tapan et al. (9), who found significantly lower concentrations of soluble forms of CD40 ligand and P-selectin in subjects with Gilbert syndrome (GS). Because of its antioxidant, antiinflammatory, and other biological properties, higher bilirubin concentrations could possibly prevent plaque formation and subsequent atherosclerosis (10, 11).

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Nonstandard abbreviations: TNF-α, tumor necrosis factor α; VCAM-1, vascular cell adhesion molecule 1; ICAM-1, intercellular adhesion molecule 1; GS, Gilbert syndrome; CAD, coronary artery disease; CAC, coronary artery calciumification; NHANES, National Health and Nutrition Examination Survey; PAD, peripheral arterial disease; CVD, cardiovascular disease; GWAS, genome-wide association study; EURLIC, Ludwigshafen Risk and Cardiovascular Health; SNP, single nucleotide polymorphism; ECTIM, Étude Cas Témoins de l’infarctus du Myocarde; CAVASIC, Cardiovascular Disease in Patients with Intermittent Claudication.
Bilirubin, Coronary Artery Disease, and Coronary Artery Calcification

The first indication that serum bilirubin concentrations might be related to coronary artery disease (CAD) was reported in 1994 (10). In that study, low serum bilirubin concentrations were found to be related to an increased risk of CAD, whereas high-normal concentrations were found to be associated with a decreased risk of CAD. The strength of the association with CAD was found to be similar to that of smoking, systolic blood pressure, and HDL cholesterol (10, 12–14). Studies by Hopkins et al. (12) confirmed that serum bilirubin concentrations were inversely related to the severity of CAD and that this inverse association occurs in both men and women.

In a recent cross-sectional study of 398 men and 239 women, serum bilirubin concentrations were found to be strongly related to coronary artery calcification (CAC) scores and independent determinants of CAC in both men and women (P < 0.0001) (15). An increase in serum bilirubin of 1 μmol/L led to a 14% decrease in odds for having a CAC score >400 after adjustment for several other major risk factors (15).

Bilirubin, Peripheral Arterial Disease, and Stroke

In the past year, 3 important studies have shown an inverse relationship between serum bilirubin concentrations and peripheral vascular disease or stroke (16–18). Kimm et al. (16) found that men with higher serum bilirubin concentrations had a lower hazard ratio for ischemic stroke after adjustment for multiple confounding factors compared with men in the lowest bilirubin quartile (P = 0.016). Perlstein et al. (17) found similar results in a cross-sectional cohort study that consisted of 7075 adults enrolled in the National Health and Nutrition Examination Survey (NHANES) and included both sexes and various racial groups. In their study, they found that each 0.1 mg/dL (1.7 μmol/L) increase in serum bilirubin led to a 6% reduction in the odds of having peripheral artery disease (PAD). Rantner et al. (18) found similar results in a retrospective case control study that compared 255 men with intermittent claudication to 255 matched controls. In their study, each 0.1 mg/dL (1.7 μmol/L) increase in bilirubin was associated with an 11.5% decrease in PAD. These results confirmed earlier studies performed on 1741 individuals in Japan (19). In that study, each 0.1 mg/dL (1.7 μmol/L) increase in bilirubin was found to decrease the risk of carotid artery plaque by 3.7%. In another study, Vitek et al. (20) found a marked delay in progression of intima-medial thickness of carotid arteries in subjects with GS compared with normobilirubinemic individuals. Although these studies provide substantial evidence that serum bilirubin may play an important role in PAD prevention, they need to be confirmed.

Bilirubin and Other Forms of Cardiovascular Disease

Similar inverse associations have now been shown in prospective studies of individuals with myocardial infarction (21, 22) as well as in various forms of cardiovascular disease (CVD) (23). In the Framingham Offspring Study involving 4276 men and women, higher serum bilirubin concentrations were found to be associated with a lower risk of myocardial infarction, coronary death, and any cardiovascular events in men; however, the inverse association was only suggestive in women. A metaanalysis of 11 studies involving men has shown that each 1.0 μmol/L increase in serum bilirubin is associated with a 6.5% decrease in CVD risk (24).

Although low concentrations of serum bilirubin have been shown to be associated with an increased risk of CVD, less information is available on the effects of moderately increased concentrations of serum bilirubin. Vitek et al. (4) were the first investigators to conduct studies of CAD risk in individuals with GS. In that study, individuals with mild increases in fasting serum unconjugated bilirubin concentrations [mean (SD) 33 (14) μmol/L] were found to have a marked reduction in CAD risk (4).

Bilirubin, CVD Mortality, and Acute Medical Conditions

Most of the studies to date have been on the association of serum bilirubin and various forms of CVD. Less is known about the possible protective effect of bilirubin and CVD mortality and all-cause mortality. Likewise, there is limited information on a possible protective role for bilirubin in acute medical conditions such as sepsis and oxidative stress after surgery. There is some evidence in animal models that bilirubin and biliverdin prevent vascular complications associated with coronary artery bypass surgery and percutaneous transluminal angioplasty such as vein graft surgery failure and restenosis (25).

Bilirubin, Diabetes, and Metabolic Syndrome

Recent studies by Inoguchi et al. (26) indicate that patients who have both diabetes and GS have a lower prevalence of vascular complications than individuals with diabetes alone. In their study, the prevalence of GS among 5080 consecutive diabetes patients was only 1.9%, which is far less than would be expected in a general population.
Negative associations between serum bilirubin concentrations and abnormal glucose tolerance tests have also been found (27). Additionally, serum bilirubin concentrations were shown to be inversely correlated with urinary albumin excretion in patients with type 2 diabetes (28) as well as with the prevalence of the metabolic syndrome (29).

**Bilirubin and Body Mass Index**

A negative association between bilirubin concentrations and abdominal obesity has been shown in 2 recent studies (29, 30), consistent with the inverse relationships between serum bilirubin concentrations and metabolic syndrome (29). Moreover, since weight reduction is known to reduce several cardiovascular risk factors, it is interesting to note that each percent decrease in weight loss was associated with a linear increase in serum bilirubin concentration (31).

**Bilirubin and Arterial Hypertension**

Several studies have shown that serum bilirubin concentrations are inversely related to blood pressure. Papadakis et al. (32) have shown that serum bilirubin concentrations are significantly decreased in patients with untreated hypertension. In another study on asymptomatic young adults, serum bilirubin concentrations were found to be significantly and positively related to large- and small-artery pulsatile arterial function and inversely related to body mass index, blood pressure variables, triglycerides, and insulin resistance index (30).

In addition, in a study by Fukui et al. (28) on patients with type 2 diabetes, a significant inverse correlation was found between serum bilirubin concentrations and pulse wave velocity. In studies on healthy subjects, increased serum bilirubin concentrations were also reported to prevent coronary microvascular dysfunction (33).

**Genes Controlling Bilirubin Concentrations**

In humans, serum bilirubin concentrations are highly heritable (34–36). Bilirubin is a breakdown product of heme-containing proteins and mainly originates from hemoglobin in aging red blood cells. HMOX1 [heme oxygenase (decycling) 1] converts heme to biliverdin, which is reduced by BLVRA (biliverdin reductase A) to bilirubin. Bilirubin is water-insoluble, carried by albumin in the blood, taken up across the basolateral membrane of hepatocytes predominantly by SLC01B1 (solute carrier organic anion transporter family member 1B1), and conjugated in the hepatocyte by UGT1A1 (bilirubin UDP-glucuronosyl transferase 1 family, polypeptide A1). Bilirubin conjugates are then actively secreted into the canaliculi by ABCC2 [membrane ATP-binding cassette subfamily C (CFTR/MRP), member 2]. Therefore, the genes involved in bilirubin metabolism as well as red blood cell life span, such as G6PD (glucose-6-phosphate dehydrogenase), are important candidate genes for the control of serum bilirubin concentrations.

**UGT1A1**

Segregation studies have suggested that there is a major gene with the rarer allele associated with increased total serum bilirubin (22, 34). Furthermore, linkage genomewide analyses identified chromosome 2q37 as the major locus with a large effect on serum bilirubin concentrations (35, 36). Under the linkage peak is the gene encoding hepatic UGT1A1.

Of the genes involved in bilirubin metabolism, UGT1A1 has been the most widely studied because of its essential role in hepatic bilirubin glucuronosylation. Many polymorphisms have been identified. Some rare mutations in the coding region of the gene are responsible for the severe childhood form of hyperbilirubinemia, Crigler-Najjar syndrome type I and II, characterized by absent or very low UGT1A1 activity (37–39). Although the hyperbilirubinemia in subjects with GS is milder than in other forms of hyperbilirubinemia, it exists in 5%–10% of the general population (40). Two types of genetic variants related to GS are known. In whites, GS mainly results from a TA insertion in the TATA box in the promoter [normal (TA)7TAA], resulting in the sequence (TA)6TAA, designated as UGT1A1*28 (41), whereas in Asians it is mainly related to missense mutations in coding sequences, such as G211A (UGT1A1*6).

In whites, the allele frequency of UGT1A1*28 is about 40% (41). Most GS subjects appeared to be homozygous for (TA)7. This insertion reduces the transcription of the gene to 18%–33% of normal (41), resulting in a decrease of hepatic bilirubin glucuronosylating activity by 70% in homozygous subjects (42). A linkage scan conditional on the TA repeat association demonstrated that the TA repeat accounts for the genetic linkage signal observed (43). This is further supported by a recent association study in a white population (44). Thirteen functional variants within the UGT1A1 gene were tested. When conditional on the TA repeat, no other variant was shown to be signif-
icantly associated with bilirubin. The results confirmed that in whites, the TA insertion is the major locus that controls total serum bilirubin concentrations in the general population. Recently, another variant in the T-3279G phenobarbital-responsive enhancer module of this gene was found to reduce transcriptional activity as well (45). The T-3279G and TA repeat are in linkage disequilibrium (46–48); therefore, it is difficult to distinguish their effect through association studies.

In addition to UGT1A1, SLCO1B1 on chromosome 12p12 and G6PD on chromosome Xp28 have been repeatedly reported to be related to bilirubin concentrations.

**SLCO1B1**

Together with a reduction of UGT1A1 activity, impaired bilirubin uptake from the blood circulation into the liver has been suggested to contribute to hyperbilirubinemia (49). Uptake of bilirubin into human hepatocytes, the first step of its hepatic disposition, is mediated by SLCO1B1, a major transport protein localized on the basolateral membrane of hepatocytes. SLCO1B1 has been reported to be associated with the hepatic uptake of many clinical drugs as well as endogenous substrates including bilirubin. A series of functional variants have been identified within the coding area and regulating regions (50–52). These variants occur at relatively high frequencies and markedly reduce uptake of bilirubin (53). A study showed that the change of amino acid at either codon 130 (Asn130Asp) or codon 174 (Val174Ala) of SLCO1B1 may reduce elimination of unconjugated bilirubin (54). Another study demonstrated that the SLCO1B1 variant is 1 of the independent predictors of serum bilirubin concentrations, and the pattern of bilirubin increase caused by the SLCO1B1*15 allele is very similar to that in GS (55).

**G6PD**

G6PD is the key enzyme of the pentose phosphate pathway and provides the NADPH essential for cells including erythrocytes. With G6PD deficiency, for example, the mean life span of red blood cells may be shortened, and low-grade hemolysis occurs, leading to the increased production of bilirubin. G6PD deficiency is well known to be associated with neonatal hyperbilirubinemia. Similar associations between G6PD deficiency and bilirubin concentrations were also seen in adults (54).

**HMOX1**

The (GT)n repeat variant in the HMOX1 promoter region was associated with CVD in some (56–61), but not all (62–64), studies; however, the association between (GT)n repeat and bilirubin concentrations was inconsistent (62, 64). Potentially beneficial effects of the short HMOX1 allele on lipid profile and serum bilirubin was observed in 1 study; in that study, however, there was no association with CVD risk (57). Likewise, the HMOX1 genotypes were not found to be associated with serum bilirubin or CVD in the recent large LURIC (Ludwigshafen Risk and Cardiovascular Health) study (58). Therefore, if HMOX1 plays a role in the pathogenesis of CAD, it likely involves mechanisms independent of the serum bilirubin concentrations, such as vascular or cell signaling effects of carbon monoxide (65).

**BLVRA AND ABCC2**

Several studies of genetic variants of BLVRA and ABCC2 on serum bilirubin concentrations have been reported (66–68); however, there was no evidence of association between those variants and serum bilirubin concentrations.

**GENOMEWIDE ASSOCIATION STUDIES**

Recently, 2 genomewide association studies (GWASs) for serum bilirubin concentrations have been carried out in white populations. One tested 2.5 million autosomal SNPs (single nucleotide polymorphisms) for association with serum bilirubin concentrations in 9464 individuals (69). The metaanalysis results revealed 2 loci reaching genomewide significance: UGT1A1 and SLCO1B1. Very strong association (rs6742078, $P < 5.0 \times 10^{-324}$) was observed in SNPs physically close to the UGT1A1 TATAA box polymorphism, which accounted for approximately 18% of the variation in total serum bilirubin. For SLCO1B1, the most significant SNP (rs4149056, $P = 6.7 \times 10^{-14}$) was located in exon 6 and results in an amino acid change (Val174Ala) that accounts for approximately 0.6% of the variation in total serum bilirubin concentrations. The same missense variant has been reported to affect transporter function and variation in serum bilirubin concentrations (54–56, 66, 70). Conditional on the UGT1A1 top SNP association, the metaanalysis revealed that SNPs in SLCO1B1 alone remained significant genomewide.

Another study in 4300 Sardinians tested 500 000 SNPs, including SNPs on the X chromosome, for association with serum bilirubin concentrations and identified 3 loci with genomewide significance (71). The strongest association was also observed on the SNP in the promoter of UGT1A1 (rs887829, $P = 6.2 \times 10^{-62}$). The second significant locus was on the X chromosome near the G6PD gene (rs766420, $P = 9.4 \times 10^{-50}$). The third was found to be on chromosome 12p12.2, the same chromosome region of SLCO1B1 (69). However, the association was found in SNPs of another gene in the same gene family, SLCO1B3 (rs2117032, $P = 4.7 \times 10^{-48}$). When the functional SNP of the SLCO1B1, rs4149056, from the abovementioned GWAS was
tested in this population, only a nominal association with total bilirubin was detected. In addition, when including these functional SNPs of \( \text{SLCO1B1} \) as covariates in the model, SNPs at the \( \text{SLCO1B3} \) locus still remain highly significant, supporting the hypothesis that the association signal observed in the \( \text{SLCO1B3} \) is not modulated by an indirect effect of those variants of \( \text{SLCO1B1} \). Bilirubin and biliverdin are known substrates for at least 2 of the transporters, \( \text{SLCO1B1} \) and \( \text{SLCO1B3} \), and both of them have been shown to be expressed in liver tissue and share >80% amino acid identity (72). The different contribution of the 2 transporters may be owing to population-specific genetic features.

The findings provide strong confirmation of the major genetic effects of \( \text{UGT1A1} \) variants and suggest that given the effect size, this locus is the main contributor to bilirubin concentrations in the general population. In addition, the effects of \( \text{SLCO1B1} \) or other transporter genes within the same chromosome location such as \( \text{SLCO1B3} \), as well as X-linked \( \text{G6PD} \), were confirmed. None of the tests for epistasis between the top SNPs at the 3 loci \( \text{UGT1A1}, \text{SLCO1B1}, \) and \( \text{G6PD} \) was significant after correction for multiple testing (71), indicating that these 3 genes affect bilirubin concentrations independently.

No GWAS on bilirubin concentrations in populations other than whites has been reported. However, a study of 4 bilirubin metabolism genes, \( \text{HMOX1}, \text{BLVRA}, \text{SLCO1B1}, \) and \( \text{UGT1A1} \), with serum bilirubin was carried out in 3 Asian populations including Han, Kazak, and Uyghur (67). The Kazak and Uyghur are genetically derived from East Asians and whites, whereas the Han are of Asian descent and the major ethnic group in China. The same \( \text{UGT1A1} \) was found to have a predominant effect on serum bilirubin concentrations in all 3 community-based populations. For \( \text{UGT1A1} \), 2 common genetic variants within the \( \text{UGT1A1} \) were tested, (TA)n and G211A. In the Han population, the (TA)7 and G211A explained 7.1% and 9.8% of the total variation of serum bilirubin concentrations, respectively. The combination of the 2 variants totaled 17%, which is similar to the effect of the 18% (TA)7 effect in whites.

The (TA) repeat and G211A appear to be 2 major variants controlling bilirubin concentrations in whites and Asians. Although there is clear heterogeneity in the \( \text{UGT1A1} \), it is the major gene in controlling bilirubin concentrations.

**\( \text{UGT1A1} \) and CVD**

Because individuals with higher bilirubin concentrations have been found to have lower risk of CVD, and \( \text{UGT1A1} \) has a predominant effect on bilirubin concentrations, studies have been performed to determine if CVD risk varies with the different \( \text{UGT1A1} \) genotypes. The studies performed to date are outlined in Table 1. In the Rotterdam study, the risk of myocardial infarction in individuals with the \( \text{UGT1A1*28} \) allele was examined, however, no protective effect in individuals homozygous for the \( \text{UGT1A1*28} \) allele was found (73). The authors acknowledged that a protective effect might have been missed because of a lack of power to detect such an effect. The ECTIM (Étude Cas Témoins de l’Infarctus du Myocarde) case-control study involving 2 white male populations showed similar results in that the \( \text{UGT1A1*28} \) allele was not found to be protective (74). The CAVASIC (Cardiovascular Disease in Patients with Intermittent Claudication) study was a case-control study of PAD (18). There was a clear association between \( \text{UGT1A1*28} \) and bilirubin concentrations in both the case and control groups, and individuals with PAD had significantly lower bilirubin concentrations than the controls. However, the case and control groups showed no differences with respect to genotype frequencies. Another case-control study was carried out on bilirubin concentrations, \( \text{UGT1A1*28} \) as well as T-3279G phenobarbital-responsive enhancer polymorphism, and CAD. The \( \text{UGT1A1} \) variants were found to be associated with bilirubin concentrations but not with CAD (47). A recent small Chinese case-control study on CAD demonstrated similar results in that the \( \text{UGT1A1} \) variants were associated with bilirubin concentrations but not with CAD (75). It is also important to note that in 3 of the 5 studies (47, 73, 74), possible underlying liver disease (10, 20) was not controlled for. The negative association between the \( \text{UGT1A1} \) polymorphism and atherosclerotic disease observed in these studies could be the result of the low penetrance (approximately 50%) of \( \text{UGT1A1*28} \) allele carrier status. Therefore, homozygosity of the \( \text{UGT1A1*28} \) allele might exert its protective effect only if associated with increased serum bilirubin concentrations. Unfortunately, stratification of genotype according to bilirubin status was not performed in any of the above retrospective studies.

An association of serum bilirubin, \( \text{UGT1A1} \) genotypes, and CVD was found in a recent study of 1780 individuals participating in the Framingham Offspring Study (76). Serum bilirubin and other risk factors were measured at baseline using data from the Framingham Offspring Examination 1. The mean age at baseline was 36 years, and CVD and CAD events were followed for 24 years. This was the first time that a significantly decreased risk of CVD and CAD was found for subjects with the \( \text{UGT1A1*28} \) homozygosity ((TA)7/TA)7 genotype. Individuals with this genotype had significantly higher serum bilirubin concentrations and one-third risk of CVD and CAD than the carriers with the
(TA)6/(TA)6 and (TA)6/(TA)7 genotypes. Although there was a similar trend between UGT1A1*28 and myocardial infarction, the association was not significant \((P = 0.08)\), possibly because of the inadequate power associated with the low number of incident myocardial infarctions. CVD, CAD, and myocardial infarction risks decreased by 10%, 13%, and 13%, respectively, for each 0.1 mg/dL (1.7 \(\mu\)mol/L) increase in serum bilirubin when the genotype was not included in the Cox regression model. Allele (TA)7 was significantly associated with higher serum bilirubin concentrations, and the gene explained a large proportion (18%) of the variation in serum bilirubin. When both serum bilirubin and genotype were included, only the bilirubin effect remained in the model and the UGT1A1*28 genotype was no longer significant. This result suggests that serum bilirubin concentrations are probably more closely associated with CVD and CAD than the genotype, and may be an intermediate phenotype for CVD and CAD events. This study is important in that it is the first well-designed study to show that individuals homozygous for UGT1A1*28, (TA)7/(TA)7, have both higher bilirubin concentrations and a significantly lower risk of CVD and CAD than individuals with the wild type.

In another study, UGT1A1 genotypes and CAD risk was investigated in 1320 CAD patients and 1060 controls in a Chinese Han population who underwent coronary angiography (68). Eight common tag SNPs were selected from the phase II HapMap Han Chinese population, which captured 30 of 30 (100%) common SNPs of UGT1A1 at \(r^2 > 0.8\). A SNP, UGT1A1 G364A (located between the TA repeat and G211A), showed association with male CAD only (odds ratio 0.24, 95% CI 0.10–0.60, \(P = 0.0014\)). In this study, an inverse relationship between serum bilirubin concentrations and CAD was observed in men but not in women, which is consistent with 1 other study (62).

In all studies involving bilirubin, UGT1A1, and CVD, clear associations between UGT1A1*28 and bilirubin concentrations were found. Serum bilirubin concentrations were also found to be associated with CVD outcomes in most of the studies; however, the UGT1A1*28 genotype was found to be associated with CVD in only the prospective Framingham Heart Study (76) and the large Han Chinese case-control study (68) (Table 1). The major difference between the Framingham Study (76) and these retrospective studies on CVD is that the Framingham Study was a prospective population-based cohort study followed for 24 years with an mean age of 36 years at baseline, whereas the other studies were case-control studies with much higher mean ages at recruitment, mostly 60 years or older. A survival bias due to older ages at recruitment could account for the results, because up to half of the incident cases do not survive the first half-year after a...
major CAD event and thus were not available for inclusion into the studies. CVD in those individuals could be more severe owing to stronger genetic effects. Second, genetic heterogeneity at this locus is clear. If participants have different genetic background and only 1 genetic variant was tested, the association may not be revealed. Third, statistical power may not be adequate except for the large Han Chinese case-control study, which had 4–6 times the number of CAD patients as the other studies. This may be the major reason why positive results were found only in this case-control study.

Pharmacologic, Nonpharmacologic, and Genetic Interventions

Drugs that inhibit UGT1A1 activity or inhibit the transport of bilirubin could be effective in increasing serum and tissue bilirubin concentrations. Among substances having UGT1A1-inhibiting activity is a uricosuric drug probenecid (77). Likewise, inhibition of SLCO1B1 transport activity, such as from rifampicin action, might result in increased serum bilirubin concentrations (78). As with all drugs, safety considerations will need to be taken into consideration, in that inhibition of UGT1A1 or SLCO1B1 activity could adversely impact the conjugation and clearance of other drugs, toxins, and carcinogens.

Serum bilirubin concentrations might also be increased through nonpharmacologic means. Smoking has been shown to be associated with lower serum bilirubin concentrations (13). As a result, smoking cessation should result in increased serum bilirubin concentrations. As mentioned previously, there is some indication that weight loss is associated with increases in serum bilirubin concentrations (31). Likewise, altitude is known to increase serum bilirubin concentrations (79).

SUMMARY

In this review, we have discussed the retrospective and prospective studies that show that low serum bilirubin concentrations are associated with an increased risk of CVD, severity of CVD, and CVD-related diseases. Genetic studies demonstrated that UGT1A1, SLCO1B1, and G6PD are important genes in controlling serum bilirubin, and UGT1A1 has a predominant effect over the other 2 genes. The UGT1A1 gene has been shown to be associated with CVD. The most recent studies involving the 1780 individuals in the Framingham Offspring Study indicates that individuals homozygous for UGT1A1*28 had only one-third the risk for CVD and CAD as the carriers of the wild-type allele. Similar results have been found in a study of the UGT1A1 genotypes and CAD in a Chinese Han population.

Methods to increase serum bilirubin concentrations have not been investigated, especially with regard to atherosclerosis and CVD prevention. Studies involving various bilirubin-enhancing drugs appear warranted and may provide much needed evidence that slightly increased bilirubin concentrations are beneficial.

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