Bilirubin Concentration, UGT1A1*28 Polymorphism, and Coronary Artery Disease

An inverse association between serum bilirubin and cardiovascular disease has been shown in numerous retrospective and prospective studies (1–8) as well as in a metaanalysis study (9). Schwertner et al. (1) first reported that fasting serum bilirubin concentrations are inversely related to coronary artery stenosis in men. Low serum bilirubin concentrations were found to be associated with an increased risk of coronary artery disease (CAD), whereas bilirubin concentrations near the upper end of the reference interval were associated with a low risk of CAD. The strength of the association between bilirubin and CAD was similar to that of smoking, systolic blood pressure, and HDL-cholesterol.

Hopkins et al. (2) confirmed the findings in a retrospective case-controlled study of men and women with early familial CAD. Individuals in the top quintile of serum bilirubin concentrations had an 80% reduction in CAD risk compared with individuals in the lowest quintile. Low bilirubin concentrations also have been found in individuals with peripheral vascular disease (PVD) (3) and ischemic heart disease (IHD) (6–8).

Several prospective studies have shown that low serum bilirubin predicts future cardiovascular disease. In 1995, Breimer et al. (6) performed a prospective study of 7685 middle-aged men enrolled in the British Regional Heart Study (BRHS) and found that both low and high bilirubin concentrations were associated with an increased risk of CAD. In a prospective study of serum bilirubin and myocardial infarction (MI) in the Framingham Offspring Study (7), higher total serum bilirubin concentrations were associated with a lower risk of MI, CAD, and any cardiovascular disease event in men; in contrast, there was only suggestive evidence for a lower CAD risk in women.

**Protective Effect of Increased Bilirubin Concentrations**

Although most studies of serum bilirubin and CHD have included participants with normal serum bilirubin concentrations [≥17.1 μmol/L (≥1.0 mg/dL)], several studies have included individuals with moderately increased bilirubin concentrations (1, 3, 6, 8). We found protective effects for angiographically documented CAD (1) at these higher concentrations, and Ishizaka et al. (3) found protective effects for carotid atherosclerosis. More recently, Vitek et al. (8) reported on the prevalence of IHD in individuals with Gilbert syndrome. Such individuals have mildly increased fasting serum unconjugated bilirubin concentrations. The individuals were selected on the basis of chronic unconjugated hyperbilirubinemia in the absence of any hemolytic or altered hepatic function. Individuals with Gilbert syndrome were found to have an IHD prevalence rate of 2% compared with 12.1% in the general population.

A metaanalysis of 11 studies has shown a negative relationship between serum bilirubin concentrations and severity of atherosclerosis in men (r = -0.31; P < 0.0001) (9). Nonparametric, regression, and stratified analyses all reliably demonstrated an inverse and dose–response relationship between serum bilirubin concentrations and atherosclerotic processes ranging from subclinical to clinical outcomes. A serum bilirubin concentration of 10.0 μmol/L (0.58 mg/dL) discriminated higher and lower cardiovascular risk.

In this issue of Clinical Chemistry, Bosma et al. (10) investigated the risk of MI in individuals with the UGT1A1*28 allele. The study is important in that it is the first to examine the role of this genetic polymorphism in cardiovascular disease and because it provides much needed information on CAD risk associated with moderately increased bilirubin concentrations. The studies could also have significant population implications for future CAD prevention because ~12% of the population has the UGT1A1*28 mutation (10). The UGT1A1*28 allele, however, did not provide protection despite the fact that it led to bilirubin concentrations that have previously been shown to be associated with a lower CAD risk. Moreover, low serum bilirubin concentrations were not found to be associated with an increased risk of CAD.

The study involved elderly individuals enrolled in the Rotterdam longitudinal population-based study. Although the study appears to have been carefully performed, the relatively small sample size, the largely “normal” bilirubin concentrations in the groups with the UGT1A1*28 allele, and the nonstandardized blood collection procedures could have influenced the results. The authors correctly state that a protective effect might have been missed because of the lack of power to detect such an effect and that an increased association between bilirubin concentrations and CAD incidence may have been missed because of the nonstandardized blood collection procedures (10).

Because of the small population sizes, it is not possible to determine whether there is a relationship between serum bilirubin concentrations and CAD within a group, nor is it possible to determine how many of the cases in the 6/7 and 7/7 genotypes could be attributable to or related to low serum bilirubin concentrations. It also would have been helpful to have information on the odds ratios of the other risk factors because such information is important in evaluating the relationships between the various risk factors.

Although a protective effect was not found between the UGT1A1*28 mutation and MI in the total population, opposite trends appeared to occur for the 6/6 and 6/7 genotypes. Serum bilirubin concentrations, for example, appeared to be higher in the controls than in the cases of the 6/6 and 6/7 genotypes. Therefore, bilirubin may be exerting a protective effect in these groups, but not in the total population. Although these are post hoc findings that could be the result of chance, they need to be
considered when evaluating the study, especially in light of the small population size and the normal bilirubin concentrations.

The results of Bosma et al. (10) are similar to several other studies that have shown a slight, nonsignificant increase in CAD risk at higher bilirubin concentrations (2, 6, 7). Liver disease, however, could have contributed to the increase in CAD risk in the studies of Hopkins et al. (2) and Djousse et al. (7). Hopkins et al. (2), for example, did not adjust for liver function tests, and Djousse et al. (7) used a relatively high cutoff value for liver transaminase activities, 1.33 μkat/L, which could have led to greater inclusion of individuals with liver disease.

The results are at variance with several other studies that showed a protective effect with moderately increased bilirubin concentrations (1, 3), including the study of individuals with Gilbert syndrome mentioned above (8). In the latter study, serum bilirubin concentrations in individuals with Gilbert syndrome were 32.6 ± 13.5 μmol/L (1.9 ± 0.79 mg/dL); those in the 7/7 genotypes were 14.8 ± 5 μmol/L (0.87 ± 0.29 mg/dL) (10). The results also appear to be at variance with those of Hunt et al. (4) and Kronenberg et al. (5), who found an inverse association between a bilirubin-related gene and CAD, and with the results of a metaanalysis performed by Novotny and Vitek (9). The latter study provided strong evidence that increased bilirubin concentrations provide protection against CAD.

The studies to date indicate a protective effect with Gilbert syndrome, but not with the UGT1A1*28 mutation. The studies also indicate a protective effect of moderately increased bilirubin concentrations if adjustments are made for liver disease and if fasting, morning blood samples are used. These observations will have to be confirmed in larger populations and in individuals with symptomatic and asymptomatic CAD and PVD. Studies also need to be performed to determine whether the bilirubin concentration has a role in other chronic diseases and whether it is associated with cardiovascular and all-cause mortality. Nonfasting conditions and standardized collection times should be used to minimize biological variability. Because increased liver enzymes and liver disease are more prevalent in individuals with increased serum bilirubin concentrations, abnormal liver enzymes should be included in models when assessing the association between bilirubin concentrations and CAD. In such studies, the preponderance of evidence supports the presence of an inverse relationship between serum bilirubin concentrations and CAD incidence, but the genetic and mechanistic relationships are still obscure.

References
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