Is Serum Bilirubin a Risk Factor for Coronary Artery Disease?

Coronary artery disease (CAD), a major cause of morbidity and death in North America, has several known risk factors, e.g., history of cigarette smoking, obesity, age, diabetes mellitus, systolic blood pressure, and increased serum lipids. As far as lipids are concerned, animal studies have long shown a liaison between hypercholesterolemia and the presence of an inflammatory reaction that seems to characterize vascular smooth muscle cell proliferation in atherosclerosis. This has engendered an intense interest in the role of lipid oxidation in atherogenesis (1). As early as 1980, Brown and Goldstein showed that, during the above-mentioned chronic inflammatory process, macrophages have a very limited ability to ingest native low-density lipoprotein (LDL), but they bind chemically modified LDL by a high-affinity receptor also called a scavenger receptor (2). In fact, there is a family of related scavenger receptors, of which one is a high-affinity receptor for oxidized LDL (3). Because of their chemical composition, lipoproteins, particularly LDL, are highly susceptible to oxidations in vitro and in vivo. Subsequently, several lines of evidence in humans and animals have lent credence to the proposal that oxidized LDL is taken up by intimal macrophages, which contribute to formation of lipid-rich foam cells (3). These and related data have consolidated the suggestion that oxidized LDL is a risk factor for the development of atherosclerosis.

In the current issue of Clinical Chemistry, Schwertner et al. present an unexpected finding that serum bilirubin is an inverse and independent risk factor for CAD (4). They examined serum bilirubin and various liver-function enzymes as possible risk factors for angiographically confirmed CAD in 619 men with complete data for all risk factors considered and in 268 men with incomplete data for risk factors. All subjects were US Air Force pilots and navigators. From statistical analyses of the data according to various hypotheses, the authors deduced that a 50% decrease in bilirubin was associated with a 47% increase in the probability of being in a more severe CAD category.

The finding of an inverse relationship between serum bilirubin and the risk of CAD is novel simply because it has never been so suggested. That novelty is even more striking against the background that bilirubin has, since more than a century ago, been used as a marker for many hepatobiliary disorders but not for any heart conditions. If further substantiated, bilirubin may be a welcome addition to the barrage of tests for CAD risk. It will also necessitate a revision in current concepts about bilirubin.

The paper by Schwertner et al. (4) raises a number of interesting questions. For example, because total bilirubin (TBIL) in serum comprises multiple subfractions (5)—unconjugated bilirubin (Bu), mono- and di-sugar bilirubin conjugates, and delta bilirubin (Bd or BP)—one wonders if one or more bilirubin fractions were involved in this putative relationship with CAD. To explore this issue, we will apparently first have to separately quantify bilirubin fractions at concentrations well below the “normal” value for serum TBIL (e.g., 17–22 μmol/L). This is not an impossible challenge. Monoclonal antibodies targeted against serum Bu and Bd have recently been prepared (Wu et al., unpublished).

As a plausible mechanism for their observations, Schwertner et al. (4) suggested that bilirubin, which behaves as an antioxidant (see below), may prevent oxidation of LDL and hence reduce accumulation of cholesterol plaque (3). The idea that bilirubin is an antioxidant is not new. Several groups of workers (e.g., 6–8) had advanced this concept since the 1950s. The key finding was that Bu either in chloroform or in multilamellar liposomes protects phospholipids against damage from in situ-generated peroxyl radicals (8). However, most of these studies were not performed in the presence of living cells or in vivo. Albumin-bound Bu (especially Bd) was first demonstrated in 1991 to protect cultured hepatocytes and rat livers from oxyradical damage (9, 10). Also in 1991, the same bilirubins were shown to be substantially more effective protectors of human ventricular myocytes than several known antioxidants such as vitamin C and a vitamin E analog called Trolox (11). However, the fact that bilirubin is a cytoprotective antioxidant does not necessarily mean that it must protect LDL from oxidation. This is a critical point that must await further experimental testing. For example: (a) Is there concrete physicochemical evidence of bilirubin's being consumed in vitro and in vivo so as to preserve LDL from oxidative damage? (b) If so, is the effect reflected by angiography and at least some other risk factors of CAD? Eventually, it will be important to ascertain what is the relative impact of bilirubin in the total endogenous anti-LDL activity of the body, in the context of the other known native antioxidants, some of which are effective in preserving LDL integrity (3). There may even be other, less obvious, metabolic linkages between bilirubin and cholesterol/bile acids involved here.

Most of the serum Bu is strongly adsorbed, whereas all of the bilirubin in Bd is irreversibly bonded to albumin, the most abundant protein in serum and a qualitatively important antioxidant (5, 11). Against this
background, it seems logical to ask: Does albumin contribute to the body’s ability to prevent LDL oxidation and therefore play a role in protecting LDL? Although in vivo evidence is wanting, our group has shown that albumin profoundly modulates the antioxidant activity of bilirubin in human cardiomyocytes (11) and erythrocytes (10). Eventually, this question must be answered more directly by studying the physicochemical interaction between purified LDL and bilirubin fraction(s) in the presence or absence of albumin. Overall, Schwertner et al. (4) have provoked our thinking about serum bilirubin in the important context of CAD. Bilirubin may be more closely linked to the heart than we have been taught.

References

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