BILIRUBIN AS A MARKER OF OXIDATIVE STRESS AND NON-COMMUNICABLE DISEASE: CHICKEN OR THE EGG?

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Oxidative stress has been implicated in most non-communicable diseases: That is, metabolic syndrome (MetS), atherosclerosis, and cancer. Low-density lipoprotein cholesterol is rendered more atherogenic by oxidative modification [1], and many carcinogens create free oxygen radicals that damage DNA and other cellular structures, initiating and promoting tumor development [2]. Therefore, antioxidant agents have been extensively evaluated in the prevention of cardiovascular disease and cancer. Vitamin E has been shown to reduce atherosclerotic lesions in animals [3], smooth muscle cell proliferation [4], platelet adherence and aggregation [5]. Epidemiological data indicate an inverse association between cardiovascular or cancer risk and vitamin E intake from dietary sources and/or supplements [6]. However, most randomized controlled trials have failed to confirm a role for vitamin E supplementation in cardiovascular prevention [7-11]. Vitamin E had no significant effect on myocardial infarction, stroke, cardiovascular death, unstable angina, revascularization, and total mortality. Trials of cancer chemoprevention have also been disappointing [12,13].

Bilirubin has been recognized as a potent antioxidant. Bilirubin suppresses the oxidation of lipid in liposomes more than vitamin E, which is regarded as the best antioxidant of lipid peroxidation [14,15]. The water-soluble glutathione primarily protects water-soluble proteins, whereas the lipophilic bilirubin protects lipids from oxidation [16]. Serum bilirubin has been demonstrated to be a major contributor to the total antioxidant capacity in blood plasma [17] and proven to have anti-inflammatory properties [18]. Serum bilirubin was shown to be associated with cross-sectional MetS in Chinese children, adolescents, and adults [19,20] as well as Korean men and women [21,22]. Patients with Gilbert syndrome whose serum bilirubin levels are high had low levels of oxidative stress associated with enhancement of endothelium-dependent vasodilation [23]. Serum bilirubin has been demonstrated to be negatively associated with cardiovascular disease [24-26], hemoglobin A1c [27], and albuminuria [28]. The author previously suggested that serum bilirubin might be a negative predictor of end-stage kidney disease [29]. Others reported that serum bilirubin predicted MetS [30,31]. However, the author demonstrated that serum bilirubin cannot predict the development of MetS and suggested that a decreased serum bilirubin was not a cause of MetS but a marker of oxidative stress [32] which is closely related to inflammation [18] and endothelial dysfunction [23], both of which are thought to be underlying mechanisms of MetS [33]. Hence, further prospective studies are required to conclude whether a decrease in serum bilirubin is a risk factor for non-communicable disease such as MetS [34].

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