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Liver News Elsewhere

Protective effects of serum bilirubin on peripheral vascular disease

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Abstract

Background: **Bilirubin, with recently recognized antioxidant and anti-inflammatory activity, has emerged as a candidate for atheroprotection. We hypothesized that higher levels of bilirubin would reduce susceptibility to peripheral arterial disease (PAD).** ***Methods and results:*** **We analyzed 7,075 adults with data available on the ankle brachial index, serum total bilirubin level, and PAD risk factors in the National Health and Nutrition Examination Survey (1999 to 2004), a nationally representative cross-sectional examination of the United States population. A 0.1 mg/dL increase in bilirubin level was associated with a 6% reduction in the odds of PAD (OR 0.94 [95% CI 0.90 to 0.98]) after adjustment for age, gender, race/ethnicity, smoking status, diabetes, hypertension, hypercholesterolemia, chronic kidney disease, CRP, and homocysteine. This result was not dependent on bilirubin levels above the reference range, liver disease, or alcohol intake. The inverse association of bilirubin with PAD tended to be stronger among men (OR 0.90 [95% CI 0.85 to 0.96]) compared with women (OR 0.97 [95% CI 0.91 to 1.04]; P (interaction) = 0.05), and was stronger among active smokers (OR 0.81 [95% CI 0.73 to 0.90]) compared with nonsmokers (OR 0.97 [95% CI 0.93 to 1.02]; P (interaction) < 0.01).** ***Conclusions:*** **Increased serum total bilirubin level is associated with reduced PAD prevalence. This result is consistent with the hypothesis that bilirubin is protective from PAD.**

Key words: Bilirubin, antioxidant, atherosclerosis, peripheral artery disease.

Comment

Serum bilirubin, a potent endogenous antioxidant, has been linked to a number of oxidative stress-mediated diseases including atherosclerosis, cancer, certain rheumatological as well as to neurodegenerative diseases.[1] Additional evidence supporting the inverse association of bilirubin and atherosclerosis has been recently reported by Drs. Perlstein *et al*.[2] In that study, they retrospectively studied the relationship between serum bilirubin levels and peripheral artery disease (PAD) in more than 7,000 adults from the National Health and Nutrition Examination Survey (NHANES). After adjustment for possible confounding factors, each 0.1 mg/dL increase in serum bilirubin level was found to be associated with 6% reduction in the odds of having PAD. This association was even stronger in men (OR 0.90 [95% CI 0.85-0.96]) and active smokers (OR 0.81 [95% CI 0.73-0.90]).

Results of this, so far the largest study of bilirubin and PAD, extends the evidence that bilirubin is a marker for atherosclerosis. The data provided are consistent with other (not discussed) reports showing that increased serum bilirubin levels are associated with a reduced prevalence of PAD.[3-11] Although Perlstein and colleagues in their paper warn of possible U-shape relationship between serum bilirubin and PAD, this warning is based largely on two previous reports[12,13] in which inproper[12] or no[13] adjustment for underlying liver disease was performed. When proper adjustment for elevated liver function tests in Breimer *et al.´*s study[12] was performed, the U-shape relationship disappeared.[14] Moreover, several more recent studies have demonstrated that mildly elevated se-

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rum unconjugated bilirubin levels protects from both coronary[15] and peripheral atherosclerotic disease.[8,10] It should be also noted that elevated aminotransferase activity, a surrogate marker of liver damage, occurs in about 10% of the US population,[16] and is directly related to CHD risk.[17-19] As a result, elevated aminotransferase activity could be concealing the protective effects of mild isolated hyperbilirubinemia. In this respect it is important to note that the protective effects of bilirubin on PAD in the Perlstein *et al.´*s study were detected in both individuals with supraphysiological bilirubin concentrations as well as in subsets of individuals that did not have underlying liver disease.[2]

Therefore, it appears likely that additional large well-designed prospective studies that adjust for all possible confounding factors including liver disease will establish that higher levels of serum bilirubin are indeed protective.

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