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Elevated serum bilirubin levels are inversely associated with nonalcoholic fatty liver disease

Byoung Kuk Jang

Department of Internal Medicine, Keimyung University School of Medicine, Daegu, Korea

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Nonalcoholic fatty liver disease (NAFLD) has similar pathologic findings of alcoholic fatty liver but occurs in patients who drink little or no alcohol.[1] Accumulation of excess fat in the liver is regarded as a clinical feature of insulin resistance and is known to be associated with metabolic syndrome components such as abdominal obesity, hypertension, type 2 diabetes and dyslipidemia.[2,3] For this reason, NAFLD is currently considered as a form of metabolic syndrome occurring in the liver.[4] NAFLD can progress from simple steatosis to nonalcoholic steatohepatitis (NASH) and cirrhosis which are accompanied with hepatic cellular destruction.[5] It can even develop to hepatocellular carcinoma.[6] As a result, patients with liver cirrhosis often have concomitant metabolic diseases such as diabetes and coronary heart disease and the major causes of their mortality are reported to be coronary vascular disease (CVD), extrahepatic malignancy and cirrhosis related events.[7]

Bilirubin is the end product of heme catabolism. Heme is degraded to biliverdin, cabon monoxide and ferrous iron by heme oxygenase (HMOX) and biliverdin is reduced to bilirubin by biliverdin reductase. Bilirubin is bound to albumin in the plasma and is delivered to the liver in the form of albumin-bound bilirubin. Albumin-bound bilirubin is conjugated with glucuronic acid by UDP-glucuronosyltransferase (UGT1A1) and is excreted to biliary duct in the form of bisglucuronosyl bilirubin.[8] Bilirubin used to be regarded as a toxic metabolite in the central nerve system.[9] However, in recent years, cytoprotective effects of bilirubin have been reported in a few studies.[10-12] Frei et al reported that serum bilirubin significantly contributes to total antioxidant capacity.[11] It was discovered that bilirubin had anti-inflammatory effects as well as acts as scavengers of reactive oxygen species, as it was mentioned above.[13] In addition to bilirubin, experimental studies have found that enzymes involved in bilirubin metabolism also have several effects. In an experiment conducted with an animal model, it was shown that HMOX1 stimulated insulin products and reduced insulin resistance.[14] It was also reported that biliverdin reductase has multiple functions affecting cell signaling and modulating immune system response[15,16]

In clinical practice, it has been reported that the level of serum bilirubin is related to several diseases. There have been a number of studies reporting a negative relation between serum bilirubin and CVD since Schwertner et al reported a negative relationship

Abbreviations:

CVD, coronary vascular disease; HMOX, heme oxygenase; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; UGT1A1, UDP-glucuronosyltransferase

Corresponding author : Byoung Kuk Jang
Department of Internal Medicine, Keimyung University School of Medicine, 56 Dalseong-ro, Jung-gu, Daegu 700-712, Korea
Tel. +82-53-250-7088, Fax. +82-53-250-7088
E-mail; jangha106@dsmc.or.kr

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between serum bilirubin level and coronary artery disease.[17,18] In addition, it was also reported that a high level of serum bilirubin reduced the risk of diabetes mellitus and diabetic nephropathy.[19] Cheriyath et al reported that increased total bilirubin (≥10 μmol/L) was associated with 26% reduction in diabetes risk.[20] In recent years, it was reported that serum bilirubin had a negative relation with metabolic syndrome, abdominal obesity and NAFLD.[21,22] A study conducted with Taiwanese children showed that UGT1A1 promoter variants related to Gilbert syndrome was associated with the low risk of NAFLD and the levels of serum bilirubin were low in the patients with NAFLD.[23]

In this study by Kwak et al, they conducted a retrospective study with 17,348 people undergoing health checkups to examine the relationship between serum bilirubin levels and NAFLD. The prevalence of NAFLD decreased as a serum bilirubin level increased and a multivariate analysis confirmed a negative relation between serum bilirubin levels and the prevalence of NAFLD (odds ratio [OR] 0.88, 95% confidence interval [CI], 0.80-0.97). This study was conducted with a large number of people undergoing health checkups and included both men and women and it reconfirmed the result of previous studies. However, there were a few limitations that needed to be addressed in this study. The first limitation was that alcohol consumption might not be accurately assessed since this study was conducted as a retrospective study with people undergoing health checkups. It is generally known that people tend to underestimate their alcohol consumption when answering a survey.[24] Therefore, it was possible that a large proportion of alcoholic fatty liver patients might have included in this study.

The second limitation was that the level of total bilirubin was only measured and analyzed instead of measuring unconjugated bilirubin and conjugated bilirubin separately. Chang et al reported that the level of serum conjugated bilirubin was related to the occurrence of NAFLD and Kumar et al and Hjelkrem et al reported that the level of serum unconjugated bilirubin was related to the severity of NAFLD.[25-27] In other words, currently, it is not clear that what type of bilirubin is associated with NAFLD. Therefore, further researches to identify this matter will be required in the future.

Summarizing several research results reported to date, serum bilirubin has protective effects on various diseases. Accordingly, studies have been conducted to find methods to artificially increase serum bilirubin. In some studies, UGT1A1 activity was partially inhibited by probenecid and atazanavir to induce iatrogenic Gilbert syndrome.[28,29] In some other studies, it was reported that curcumin and sylimarin induced HMOX induction and subsequently increased insulin secretion in diabetes animal models resulting in the improvement of laboratory markers.[30]

In conclusion, this study, conducted with a large number of healthy populations, confirmed the inverse relationship between serum bilirubin level and the occurrence of NAFLD. Based on this result, further clinical studies on the disease prevention and treatment by controlling serum bilirubin level will be required in the future.

Conflicts of Interest

The author has no conflicts to disclose.

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