Use of the Informatics for Integrating Biology and the Bedside (i2b2) Population to Test Serum Bilirubin Levels and Risk for Inflammatory Bowl Diseases and the Involvement of Uridine Glucuronosyltransferase Genes

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ABSTRACT

Chronic inflammation associated with inflammatory bowel disease (IBD) results in increased oxidative stress that damages the colonic microenvironment. A low level of serum bilirubin, an endogenous antioxidant, has been associated with increased risk for Crohn's disease (CD), but no study has tested another common IBD ulcerative colitis (UC). Bilirubin is metabolized in the liver by uridine glucuronosyltransferase 1A1 (UGT1A1) exclusively. Genetic variants cause functional changes in UGT1A1 which result in hyperbilirubinemia, which can be toxic to tissues if untreated and results in a characteristic jaundiced appearance. Approximately 10% of the Caucasian population is homozygous for the microsatellite polymorphism *UGT1A1*28*, which results in increased total serum bilirubin levels due to reduced transcriptional efficiency of *UGT1A1* and an overall 70% reduction in UGT1A1 enzymatic activity. The aim of this study was to examine whether bilirubin levels are associated with the risk for ulcerative colitis (UC). Using the Informatics for Integrating Biology and the Bedside (i2b2), a large case-control population was identified from a single tertiary care center, Penn State Hershey Medical Center (PSU). Similarly, a validation cohort was identified at Virginia Commonwealth University Medical Center. Logistic regression analysis was performed to determine the risk of developing UC with lower concentrations of serum bilirubin. From the PSU cohort, a subset of terminal ileum tissue was obtained at the time of surgical resection to analyze *UGT1A1* gene expression (which encodes the enzyme responsible for bilirubin metabolism). Similar to CD patients, UC patients also demonstrated reduced levels of total serum bilirubin. Upon segregating serum bilirubin levels into quartiles, risk of UC increased with reduced concentrations of serum bilirubin. These results were confirmed in our validation cohort. *UGT1A1* gene expression was up-regulated in the terminal ileum of a subset of UC patients. Lower levels of the antioxidant bilirubin may reduce the capability of UC patients to remove reactive oxygen species leading to an increase in intestinal injury. One potential explanation for these lower bilirubin levels may be up-regulation of *UGT1A1* gene expression, which encodes the only enzyme involved in conjugating bilirubin. Therapeutics that reduce oxidative stress may be beneficial for these patients.

CCS CONCEPTS

• **Medical Informatics**

KEYWORDS

health informatics, bedside, IBD

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