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Original Article

To study inverse relationship between serum total bilirubin levels and severity of disease in patients with stable coronary artery disease as assessed by coronary angiography and syntax score

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ABSTRACT

Objectives: Many studies have shown that bilirubin may protect against atherosclerosis. Lipid oxidation and formation of oxygen radicals are important elements of arterial plaque formation and atherosclerosis, and are involved in the pathophysiology of coronary artery disease (CAD). Because bilirubin has antioxidant properties, it has been suggested that it may have a protective role in the atherosclerotic process. In the present study, we assess the association between serum total bilirubin levels and the severity of CAD as assessed by angiography and Syntax score.

Methods: This is a prospective study which included Patients who underwent coronary angiography for **Chronic stable angina pectoris (CSAP)** from august 2013 to July 2014 at our centre. Serum bilirubin levels were determined. The patients were divided into tertiles according to their Syntax score and bilirubin levels were analysed.

Results: Total of 319 patients were registered for the study. The total bilirubin levels in the low Syntax score group were significantly higher than those of the other groups. serum bilirubin levels were identified as independent correlates of a high Syntax score and severity of cad.

Conclusions: Serum bilirubin concentrations in the upper portion of the reference value (0.61–1.0 mg/dl) reduce atherogenic risk and provide protection against CAD. In contrast, serum bilirubin concentrations in the lower portion of the reference value (0–0.60 mg/dl) may be associated with increased risk of CAD. The evidence presented in our study supports the concept that bilirubin, via its antioxidant potential, has antiatherogenic properties and that an inverse relationship exists between circulating bilirubin concentrations and risk of CAD.

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1. Introduction

Coronary artery disease [CAD] remains the major cause of morbidity and mortality in all developed countries in the world and in India. Major CAD risk factors do not predict subsequent myocardial infarction accurately and do not fully explain social class differences in Indians as Indians have a high incidence of CAD which is not fully explained by conventional risk factors. The search for CAD risk factors that might explain these variations has been stimulated by the evidence that free radicals are involved in the pathogenesis of atherosclerosis and that antioxidants, both dietary and endogenous may be important protective factors.^{1–3} For many years, the bile pigment bilirubin was considered a toxic waste product formed during heme catabolism. However, more recent evidence suggests that bilirubin is a potent physiological antioxidant that may provide important protection against atherosclerosis, CAD and inflammation. It is generally accepted that oxidative reactions are involved in the pathophysiology of these disease processes. Substantial evidence has documented that the development of CAD involves lipid oxidation and formation of oxygen radicals and that atherosclerosis and inflammation are associated with formation of oxygen and peroxy radicals. The antioxidant capacity of bilirubin and its ability to provide potent scavenging of peroxy radicals have led to suggestions that mildly increased circulatory bilirubin may have a physiologic function to protect against disease processes that involve oxygen and peroxy radicals. Increased activity of haeme oxygenase (HO) enzyme may account for the antiatherogenic through increased elimination of heme and reducing tissue iron. Increased tissue iron because of decreased activity of haem oxygenase can trigger inflammation. This may explain the association of low serum bilirubin levels in the atherosclerotic process.^{4,5,6}

Gilbert's syndrome is caused by a mutation that increases the level of bilirubin. The mutation carriers show a strong association with a lower risk of cardiovascular disease.⁷ The Syntax score is based on a visual assessment of coronary lesions by coronary angiograms and is used to evaluate the severity of coronary artery disease (CAD). It also provides information about prognosis and appropriate revascularization. Therefore, the Syntax score is important in the management of the complexity of CAD.⁸

In the present study, we assess the association between serum total bilirubin levels and the severity of CAD as assessed by angiography and the Syntax score in chronic stable angina patients (CSAP).

2. Material and methods

This cross-sectional prospective study included 319 patients who presented to the emergency/OPD in department of cardiology at SMSH JAIPUR with diagnosis of chronic stable angina from August 2013 till July 2014. Patients with known hemodynamic instability, acute coronary syndrome, autoimmune disease, neoplastic disease, chronic kidney disease, chronic hepatic disease, previous coronary artery bypass surgery or percutaneous coronary intervention, chronic or

current infections, presence of the thalassemia trait, and any systemic disease that could cause high bilirubin concentrations were excluded. The study was approved by the ethics committee at our centre. A clinical history of risk factors – such as age, sex, diabetes mellitus, hypertension, and smoking was recorded. Blood glucose, haemoglobin, serum creatinine, low-density lipoprotein (LDL) cholesterol and transaminase enzyme levels were determined. Serum bilirubin concentrations were determined by the enzymatic colorimetric method using a clinical chemistry autoanalyzer at our pathology lab. Another Cardiologist blinded to the study analyzed angiograms using a quantitative coronary angiographic system and syntax score was verified. The online latest updated version was used for the calculation of the Syntax scores (www.Syntaxscore.com). Each coronary lesion with a diameter stenosis of at least 50%, in vessels of at least 1.5 mm, was scored. Patients were divided into two groups according to bilirubin levels 0.0 to 0.60 and 0.61–1.0 mg/dl. The patients were also divided into tertiles according to their Syntax score.

2.1. Statistical analysis

Qualitative variables were expressed as percentages. Quantitative variables were expressed as mean \pm SD. A comparison of parametric values between the two groups was performed using a two-tailed Student's t-test. Categorical variables were compared by the Fisher's exact test $p \leq 0.05$ was taken as significant. Spss 20.0 version was used for all statistical analysis.

3. Results

Patients who fulfilled all the inclusion and exclusion criteria (319 patients) were registered for the study at our centre. [Tables 1 and 2](#) presents the baseline clinical characteristics of patients across the Syntax score tertiles and other variables which were studied. Compared with the other groups, group 1 was younger and had significantly lower LDL levels. However, the total bilirubin levels in this group were significantly higher than those of the group 3. There was less severe CAD in the form of single vessel disease (svd) (42.6%) and double vessel disease (dvd) (52.3%) in those with bilirubin (0.61–1.0 mg/dl) with p values (0.0087 & 0.0001) respectively ([Table 4](#)). There was increasing occurrence of triple vessel disease (tvd) in those with lower bilirubin levels (0–0.60 mg/dl) which could not reach significance in this study (see [Table 3](#)).

Patients with high syntax score were smokers, diabetics and older and had significantly higher fasting blood glucose, LDL, and lower total bilirubin values ([Tables 1 and 2](#)).

4. Discussion

To best of our knowledge, this is the first study from north India to examine the relationship between total bilirubin levels and the severity of disease in patients with stable CAD as assessed by coronary angiography complexity using syntax score. A higher baseline of serum bilirubin levels was independently associated with the coronary complexity of CAD as

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