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Study of Serum Bilirubin Level in Coronary Artery Disease

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Abstract

Background: *Bilirubin is a strong antioxidant under physiological conditions and suppresses the oxidation of lipids and low density lipoproteins and prevents free radical injury. Lesser serum bilirubin levels are associated with Protein Kinase C activation, inflammation, and oxidative stress, which are known mediators of endothelial and microvascular dysfunction. The aim of the study was to assess the serum bilirubin levels and coronary artery disease in comparison with controls without coronary artery disease and its relation with ACS sub types such as STEMI, NSTEMI and unstable angina.*

Methods: *A hospital based analytical study was conducted for a period of two years in our medical college hospital. Patients attending casualty with STEMI, NSTEMI and Unstable Angina confirmed by ECG, ECHO and cardiac markers were taken as cases. Controls were selected and matched with age, gender and other co-morbid conditions. Total of 110 subjects were included in the study with 55 cases and 55 controls. General and systemic examination was conducted on all study subjects including laboratory investigations like complete blood count, renal function test, lipid profile, CKMB, Troponin I, HBsAg, HCVIgM, SGOT, SGPT, total bilirubin, direct bilirubin, in direct bilirubin, albumin and globulin levels. A 12 lead ECG and a trans thoracic echocardiogram was performed for all patients.*

Results: *Risk factors like diabetes mellitus, hypertension, smoking history, family history, fasting lipid profile and liver function tests were compared between the cases and controls and it was found that the serum bilirubin levels which includes total bilirubin, direct bilirubin and indirect bilirubin were found to be lower among the case group compared to the control group and this difference was found to be statistically significant ($p<0.05$). Bilirubin levels in people with STEMI were lower than NSTEMI and bilirubin levels in people with NSTEMI were lower than people with Unstable angina but the difference was not statistically significant.*

Conclusions: *This study confirmed a significant inverse association between the reduced serum bilirubin levels and the occurrence of Coronary artery disease. Thus total bilirubin may serve as a protective biomarker of CAD.*

Keywords: *Coronary artery disease, Risk factor, Serum bilirubin, STEMI, NSTEMI, unstable angina.*

Introduction

In recent years, the incidence of cardiovascular disease has increased gradually in developing nations.[1] Coronary artery disease has received most attention from medical workers because of its high fatality rate, especially the acute onset of coronary artery disease. The current scenario necessitates the recognition of novel risk factors and screening of individuals who are at risk of developing CAD.[2] In spite of detailed studies on many established risk factors like diabetes mellitus, hypertension, smoking, dyslipidemia etc, the studies on serum bilirubin and its pre disposition to CAD are worth a consideration.

Postulated cardio protective effects of bilirubin are

- Has antioxidant properties that inhibit oxidation of LDL and lower LDL levels[3]
- Preserves vascular nitric oxide that maintains vessel wall elasticity
- Has anti-inflammatory benefits and inihibits platelet activation and aggregation properties that prevent thrombus formation suppresses matrix metalloproteinases and maintains vascular integrity

Several studies have concluded inverse correlations between CAD and total serum bilirubin levels.[4] Also inverse correlation between serum bilirubin and smoking, increased LDL cholesterol, diabetes and increased BMI have been documented. Lesser serum bilirubin levels are associated with Protein Kinase C activation, inflammation, and oxidative stress, which are known mediators of endothelial and micro vascular dysfunction.[5]

Very few studies in India had been conducted to prove the association between serum bilirubin levels and coronary artery disease and so the present study was undertaken to assess the association between these two variables by comparing it with a control group.

The aim of the study was to assess the serum bilirubin levels and coronary artery disease in comparison with controls without coronary artery disease and its relation with ACS sub types such as STEMI, NSTEI and unstable angina.

Methods

A hospital based analytical study was conducted for a period of two years in our medical college hospital. The study was started after getting the clearance from the institutional human ethical committee.

Patients attending casualty with STEMI, NSTEMI and Unstable Angina more than 40 years of age confirmed by ECG, cardiac markers and ECHO were taken as cases.

Patients with symptoms of congestive cardiac failure, chronic kidney disease, chronic liver disease, autoimmune diseases, COPD and malignancy were excluded from the study. Controls were selected and matched with age, gender and other co-morbid conditions. Total of 110 subjects were included in the study with 55 cases and 55 controls. Informed consent was obtained from all subjects involved in the study.

A complete socio-demographic details were obtained from all the subjects including the dietary habits and smoking/alcohol history. General and systemic examination was conducted on all study subjects including laboratory investigations like complete blood count, renal function test, lipid profile, CKMB, Troponin I viral markers such as HBsAg, HCVIgM and liver function test which includes total bilirubin, direct bilirubin, indirect bilirubin, liver enzymes, albumin and globulin levels. A 12 lead ECG and a transthoracic echocardiogram were performed for all patients.

Total serum bilirubin was measured in the laboratory by spectrophotometry method. In the Jendrassik-Grof allied methods, total bilirubin is reacted with diazotized sulfanilic acid in an acidic medium to form azobilirubin. The absorbance of the azo pigment is then measured as direct bilirubin and the total bilirubin is measured after treatment with alkaline tartrated solution, which shifts the maximum absorption of the azo pigment towards longer wavelength.

Statistical analysis

All the data were entered and analysed using SPSS version 22. Mean and standard deviation

were derived for all the parametric variables and the parametric variables between the two groups (cases and controls) were compared using unpaired student T test and comparison between the frequencies was done by using chi-square test considering p <0.05 as statistically significant.

Results

The mean age among the cases and controls were 59 and 56 years. The male subjects were more than the females with a male: female ratio of 2:1 among both the cases and controls. So, it shows that the cases and controls did not show any significant difference with respect to age and gender which implies that the controls were age and sex matched.

The most common risk factors for CAD like diabetes, hypertension, smoking, obesity and family history of CAD were found to be slightly higher among the cases than the control group but it was not found to be statistically significant.

The various liver function tests were compared between the cases and controls. It was found that the serum total bilirubin, direct bilirubin and indirect bilirubin levels were found to be lower among the case group compared to the control group and this difference was found to be statistically significant, whereas the other parameters like SGOT and SGPT levels did not show much difference. Moreover, the serum bilirubin levels in people with STEMI were lower than those with NSTEMI and the serum bilirubin levels in people with NSTEMI were lower than those with unstable angina but the differences were not statistically significant.

Graph 1: Gender wise Distribution

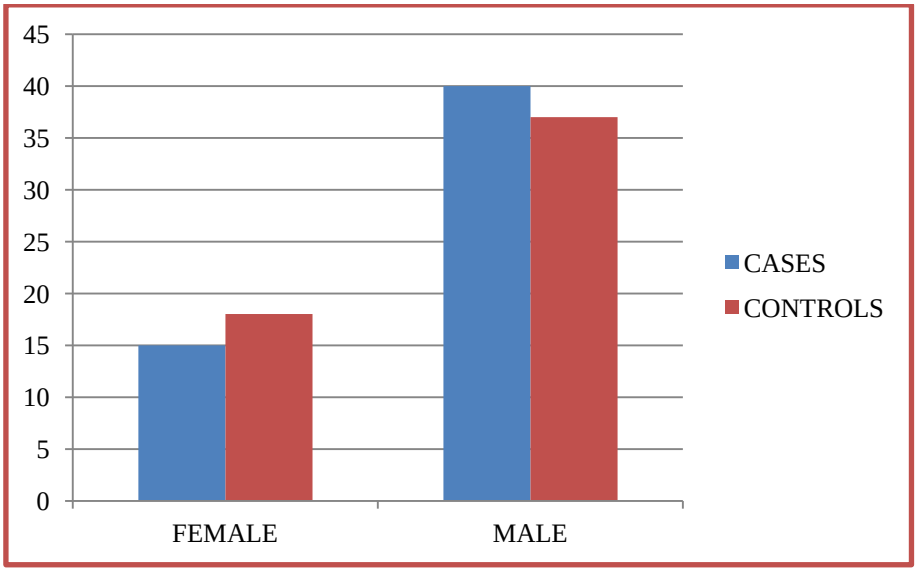


Table-1: Age wise Distribution

Group	N	Mean	Std. Deviation	Std. Error Mean
Case	55	59.727	9.6599	1.3025
Controls	55	56.945	10.3984	1.4021

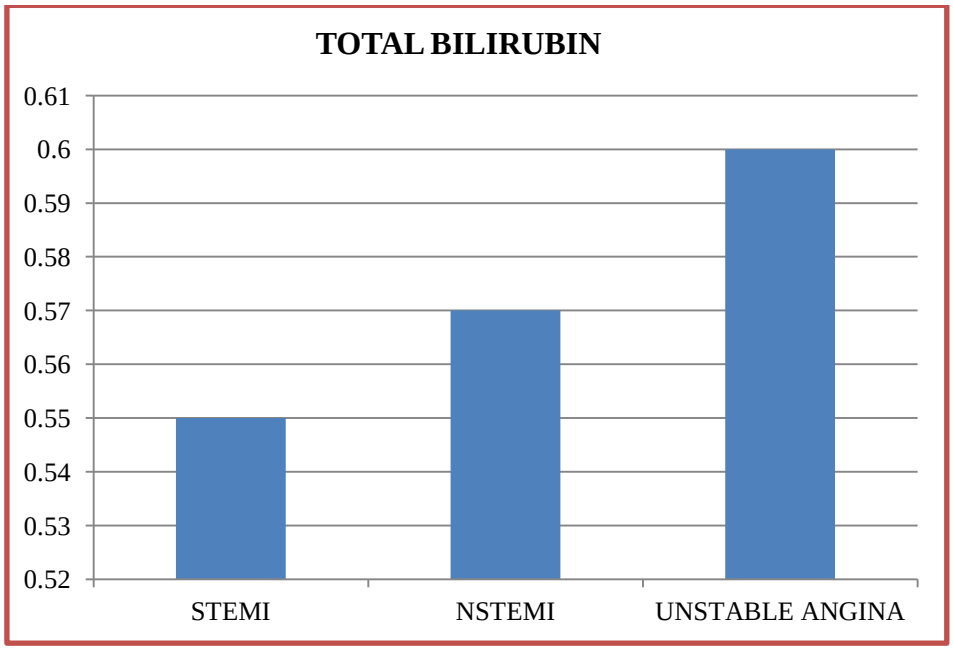
Table-2: Distribution of Risk Factors

Risk Factors	Cases (n = 55)	Controls (n =55)	P Value
Diabetes	17 (15%)	12 (11%)	0.279
Hypertension	20 (18%)	16 (14.5%)	0.416
Family history	14 (12%)	11 (10%)	0.340
Smoking history	13 (11%)	9 (8%)	0.495

Table-2: Comparison of liver function test parameters

LFT	Cases (mean)	Controls (mean)	P Value
Total bilirubin	0.56	0.80	<0.001
Direct bilirubin	0.16	0.19	<0.001
Indirect bilirubin	0.40	0.61	<0.001
SGOT	38.03	37.49	0.524
SGPT	33.94	29.52	0.731

Graph 1: Comparison of Total bilirubin in ACS patients



Discussion

Atherosclerosis is viewed as the most widely recognized fundamental reason for the coronary artery disease (CAD), which is the significant reason for mortality and morbidity worldwide.[6] Bilirubin, being a waste metabolite produced during heme catabolism is in reality a strong physiological anti oxidant agent that offers significant defence against atherosclerosis and inflammation.[7] Heme oxygenase (HO) which is a rate limiting enzyme in the heme catabolism has a significant play in cell protection during the events of oxidative stress. The end products of the catabolic reaction like bilirubin, carbon monoxide and iron have a defensive role in atherogenesis. The other significant role of bilirubin is the inhibition of Vascular cell adhesion molecule -1 thus counteracting the multiplication of the vascular smooth muscle cells and the transendothelial relocation of the white blood cells.[8]

Male gender is one of the most significant risk factors for CAD. The same was found in our study. Males were predominant in cases and so we matched the controls accordingly thereby removing the confounding factors responsible for the low plasma bilirubin.[9]

The inverse relationship between the risk factors like smoking, diabetes, hypertension, obesity and CAD denotes the oxidative stress underlying in them, but in the present study we did not observe such correlation as most of the risk factors between the cases and controls are matched. Schwertner et al was the first to note the inverse association between plasma bilirubin and occurrence of CAD.[4]

Our study found a significant inverse association between serum bilirubin levels and CAD. Bilirubin levels were found to be significantly lower in CAD patients in comparison with the controls ($p < 0.001$)[(11,12)] and a similar sort of findings were also inferred by Zhang et al. In their

study they found a significant negative association between the bilirubin levels and coronart artery calcification score by doing a coronary angiogram. So it seems that higher bilirubin levels offer a potential protective effect against coronary artery disease.[10]

In 2018 Rong. fu et al did a study and it revealed that the serum bilirubin levels in groups STEMI, NSTEMI and UA were lower than those in the normal control group, and the serum bilirubin levels in patients of STEMI and NSTEMI were lesser than those in people with unstable angina [13].Similar results were achieved in our study in a fashion that the serum bilirubin levels in people with STEMI were lower than those with NSTEMI and the serum bilirubin levels in people with NSTEMI were lower than those with unstable angina but the difference is not statistically significant.

As of late, low serum bilirubin levels have been proposed as a valuable biomarker to anticipate cardiovascular hazard and it recommends the fact that bilirubin proves to be a strong physiological antioxidant and anti thrombotic agent. Studies have demonstrated that raised serum bilirubin focuses to give significant defence against atherosclerosis. Many researchers have recommended that bilirubin possesses a potential job in prevention of lipid oxidation. Many authors have accounted inverse correlation between bilirubin and coronary atherosclerosis, peripheral vascular disease and carotid intimal and media thickness. Low normal plasma bilirubin levels are often related with significant coronary artery disease and morbidity.[14]

One of the significant limitations of this study is that it was not done in a prospective way to precisely distinguish the causal relationship between plasma bilirubin levels and CAD. Furthermore, relationship of the severity of CAD with bilirubin levels by doing a coronary angiogram study was not done.

Conclusion

This study has demonstrated a critical relationship between the decreased serum bilirubin levels and the event of CAD; in this manner, bilirubin level can fill in as a prognostic factor, together with other significant factors for recognizing an individual who is in the peril of coronary artery disease. Further studies with a bigger sample size and a prospective design would illuminate bilirubin's role as a risk factor for coronary artery disease.

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