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Original Research Article

Study on relationship of total bilirubin with acute coronary syndrome (ACS) and associated risk factors

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ABSTRACT

Background: Cardiovascular risk factors for ACS are on the rise in people of Indian origin and ACS is now the leading cause of death. More recent evidence suggests that bilirubin is a potent physiological antioxidant that may provide important protection against atherosclerosis and inflammation. Substantial evidence has documented that the development of CAD involves lipid oxidation and formation of oxygen radicals as atherosclerosis and inflammation are associated with formation of oxygen and peroxyl radicals. Keep of these points in mind, the present study was undertaken to find relation between Serum Bilirubin and Acute Coronary Syndrome.
Methods: The present descriptive cross-sectional study conducted at A.J Institute of Medical Sciences and Research Centre, Mangaluru from October 2016 to April 2017. A detailed history, general physical examination, systemic examination and investigations was performed on all patients who fulfill the inclusion criterion and age >18yrs, both sexes who are admitted in CCU.
Results: Hypertension had statistically significant correlation with ACS. All risk factors were more associated with STEMI compared to unstable angina or NSTEMI. On Correlation of LDL and Total leucocyte count with bilirubin both were statistically significant when compared to bilirubin levels.
Conclusions: The study showed an inverse correlation of bilirubin with ACS, which in shows fact that bilirubin acts as an antioxidant and has cardioprotective action and patients with ACS have lower levels of bilirubin. This can use as a factor for screening individuals who have high risk for ACS and preventive strategies applied in them before the onset of overt ACS.

Keywords: Acute coronary syndrome, Hypertension, Risk factor, Serum bilirubin

INTRODUCTION

It is predicted that more than half the worldwide cardiovascular disease (CVD) risk burden will be borne by the Indian subcontinent in the next decade according to recent epidemiological studies and will be the largest cause of death and disability in India by 2020.[1,2] Coronary Artery disease (CAD) accounts for the greatest proportion of CVD and Acute Coronary Syndrome (ACS) a common complication of CAD.[3,4] Cardiovascular risk factors for ACS are on the rise in people of Indian origin, and ACS is now the leading cause of death.[5]

Most cases of ACS are caused by rupture of an atherosclerotic plaque in a coronary artery, resulting in the formation of a thrombus.[6] Atherosclerosis appear to result from an over balance between radical generating, compared with radical scavenging systems, a condition called oxidative stress.[7,8] Reactive Oxygen Species (ROS) can damage endothelial cells in many ways, either directly or indirectly.[9] They can also increase endothelial

cell permeability and there by accelerate the accumulation of atherogenic factors, such as Low Density Lipoprotein (LDL) in the sub endothelial space.[10]

Total anti-oxidant status (TAS) in human serum reflects the balance between oxidants and antioxidants in each system. Oxidative stress has been implicated in the pathogenesis of coronary diseases.[11,12] Increased production of ROS will result in reduced antioxidant levels.[13]

Bilirubin was considered to be a waste product of the heme oxygenase action but now among various benefits, it is found to have strong relation with coronary artery lesion types.[14] This is because of its major antioxidant action under physiological conditions by inhibiting both lipid and protein oxidation.[15] As little as 10nM of bilirubin is enough to protect cells against a 10000-fold higher concentration of oxidants through rapid generation of bilirubin by biliverdin reductase.[16] Additionally, bilirubin exerts anti-inflammatory effects on vasculature and inhibits proliferation of vascular smooth muscle cells.[17,18] Hence bilirubin was proved to act against plaque formation and subsequent atherosclerosis.[19]

The recently concluded Interheart study emphasized on early detection of persons with risk factors and as reduced levels of bilirubin were shown to be associated with higher prevalence of coronary artery disease vice versa as individuals with gilbert syndrome who have mildly elevated bilirubin levels were found to have ischemic heart disease rate of 2% compared with 12.1% in general population.[20-22] Treatment and outcomes of Acute Coronary Syndromes in India (CREATE) registry has provided contemporary data on 20,468 patients with ACS from 89 centers from 10 regions and 50 cities in India and found higher 30-day mortality than developed countries.[23]

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 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 as atherosclerosis and inflammation are associated with formation of oxygen and peroxyl radicals.[7-12,14,17-19,24-27] Hence, making bilirubin as emerging potential risk factor marker. Objective was to find relation between total serum bilirubin levels and acute coronary syndrome, and associated risk factors with its components.

METHODS

The present descriptive cross-sectional study conducted at AJ Institute of Medical Sciences and Research Centre, Mangaluru from October 2016 to April 2017. Institutional ethical clearance was obtained prior beginning of the study and informed consent was obtained from patients. The patients who fulfill the selection criteria were included in the present study during study duration. A detailed history, general physical examination, systemic examination and investigations was performed on all patients who fulfill the inclusion criterion and age >18yrs, both sexes, who are admitted in CCU.

Inclusion criteria

The non-ST segment elevation MI, ST segment elevation MI and Unstable anginas are selected on basis of history, examination and relevant investigations.

Exclusion criteria

- Hepatitis of any cause.
- On drugs like Vitamin C, Amiodarone
  -Oral Hypoglycemics: Acarbose, Pioglitazone,
  -Anti-seizure drugs: Carbamazepine, Felbamate, ValproicAcid, and Phenobarbitol,
  -Anti-fungal drugs: Itraconazole, Ketoconazole and Terbinafine,
  -Anti-tuberculosis: Isoniazid, Pyrazinamide, and Rifampicin,
  -Antiretroviral drugs: Ritonavir, Nevirapine.
- Non-cardiac chest Pain,
- Cirrhosis of Liver,
- Bile duct obstruction,
- Recent (less than 3months old)
  -Major trauma,
  -Surgery,
  -Burns,
- Myocardial Re-Infarction patient,
- Haemolytic jaundice.

Sample Size

The prevalence of coronary artery disease in India is 8%.[20] At 95% confidence interval and margin error +5, the sample size is 113 using the statistical formula:

$n = (1.96)^2 \times p \times q/d^2$

p= prevalence of acute coronary syndromes
q= (100-p)
d= Margin error $\pm$ 5

Laboratory

Principle

Sulfanilic acid reacts with sodium nitrite to form diazotized sulfanilic acid. Total Bilirubin reacts with diazotized sulfanilic acid in the presence of DMSO (Di Methyl Sulf Oxide) to form azobilirubin.

Normal range

0.2 to 1.0 mg/dl, Mean 0.6 mg/dl

Sample

Serum/plasma (free of haemolysis)

Procedure

Total bilirubin reagent-1000µL, Serum-50µL

Mix well and incubate for 5minutes exactly. Measure the absorbance of the sample against the respective sample blank at 546 or 532nm

Calculation

For semi auto with factor:

Total bilirubin = OD of test-OD of sample blank × Factor

With artificial standard:

Total bilirubun concentration = OD of test-OD of sample blank/OD of standard

Statistical analysis

Descriptive statistics such as mean, SD and percentage were used to present the data. Correlation between the variables was evaluated by Pearson's correlation coefficient and association risk factors were assessed by chi-square test. A p-value less than 0.05 were considered as significant. Data analysis was performed by using software SPSS v16.

RESULTS

In the 113 patients with acute coronary syndrome (ACS) studied 72.6% were male and 27.4% females. The age ranged from 26 to 95 years of age. The mean age of the group was 54.5+13.19 SD. The patients in the age group of 55 to 65 years had the highest incidence of ACS. Mean (SD) = 54.5 (13.19) (Table 1).

Table 1: Basic characteristics.

Characteristics	Frequency	Percentage
Gender		
Male	82	72.6
Female	31	27.4
Age (years)		
25-35	7	6.2
35-45	12	10.6
45-55	19	16.8
55-65	36	31.9
65-75	30	26.5
>=75	9	8.0

Correlation of LDL and total leucocyte count with bilirubin

Total Leucocyte count (TC) in ACS is usually high as infarction of the myocardium is an inflammatory process. In our study the mean TC was 13785.7+5140.27 SD. The minimum TC was 2000cells/cumm and maximum was 30730cells/cumm.

Mean LDL was 172.07+46.57 which was higher than the normal considering the cut off value with existing risk factors. The minimum LDL value was 70mg/dl whereas the maximum was 291.8mg/dl. Both TC and LDL were statistically significant when compared to bilirubin levels (Table 2).

Table 2: Distribution of LDL, TC and total bilirubin.

Variable	Minimum	Maximum	Mean	SD
LDL	70	291.8	172.07	46.57
TC	2000	30730	13785.7	5140.27
Total bilirubin	0.1	2.1	0.48	0.28

Table 3: Correlation between total bilirubin with LDL and TC.

	Pearson's correlation coefficient value (r)	P-value
LDL	-0.755	<0.0001
TC	-0.787	<0.0001

There was statistically strong negative correlation between total bilirubin with LDL (p<0.0001) and TC (p<0.0001) (Table 3 and Figure 1 and 2).

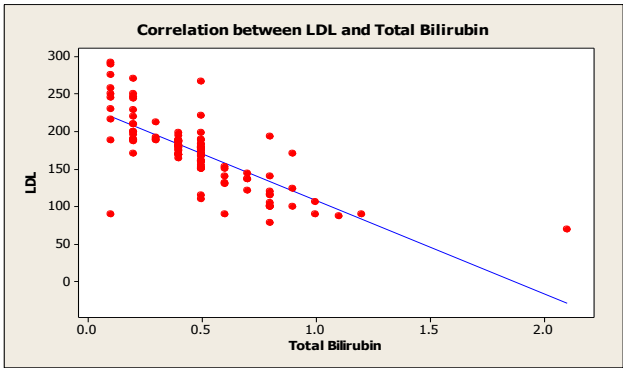

Figure 1: Correlation between total bilirubin and LDL.

Relation of total bilirubin with ACS

The Table 4 shows, the average total bilirubin value in ACS components. For STEMI, the mean total bilirubin value was 0.48±0.3, for NSTEMI the mean total bilirubin value was 0.45±0.17 whereas for unstable the mean Total Bilirubin value was 0.53±0.29. One-sample comparison with standard normal mean bilirubin value = 0.6.

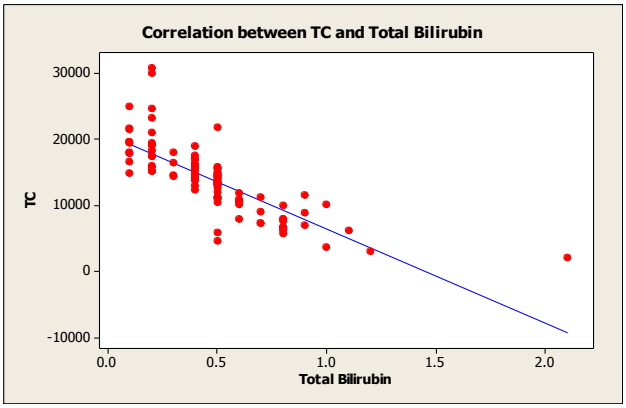

Figure 2: Correlation between total bilirubin and TC.

There is statistically highly significance, less total bilirubin of ACS than standard normal mean bilirubin value (0.6) ($p<0.0001$) (Table 5).

The known risk factors of ACS like smoking status, tobacco chewing, diabetes mellitus, family history of ACS and hypertension were studied and correlated. 37.2% of all ACS patients were smokers, 31% chewed tobacco, 24.7% had diabetes mellitus, 8% had family history of ACS and 31.8% were hypertensive.

Hypertension and smoking had statistically significant associated risk factors with ACS. All risk factors were more associated with STEMI compared to unstable angina or NSTEMI (Table 6).

Table 4: Distribution of total bilirubin with components of ACS.

Total bilirubin	N	Mean	Std. deviation	Minimum	Maximum
STEMI	82	0.484146	0.3069039	0.1000	2.1000
NSTEMI	21	0.452381	0.1691717	0.2000	0.8000
Unstable	10	0.530000	0.2869379	0.1000	1.0000
Total	113	0.482301	0.2832308	0.1000	2.1000

Table 5: Comparison of total bilirubin in patients with ACS and standard normal mean bilirubin (=0.6).

	ACS	Mean difference	95% ci of difference	T-value	P-value
Total bilirubin	0.48 $\pm$ 0.28	0.12	0.06 – 0.17	4.42	P<0.0001

Table 6: Relation of risk factors with components of ACS.

	ACS					
Parameters	**Unstable**	**NSTEMI**	**STEMI**	**Total**	**X^2 value**	**P-value**
Smoking	3	3	36	42	5.80	0.02
Tobacco chewer	5	9	21	35	4.18	0.12
Diabetes status	3	7	18	28	1.32	0.52
Family history	1	3	5	9	1.42	0.23
HTN	8	12	16	36	22.62	<0.0001

DISCUSSION

This study was conducted on 113 patients admitted with acute coronary syndrome at AJ Institute of Medical Sciences and Research Centre, Mangaluru from October 2016 to April 2017.

Gender

Of the study group 72.6% were male and 27.4% were female. The male preponderance was similar to other studies like Sahen O et al were 66% of participants were male and 34% were female. Hopkins et al had 75.6% males and 24.4% females.[28,29]

Age

The age ranged from 26 to 95years of age. The mean age of the group was 54.5+13.19 SD. The patients in the age group of 55 to 65years had the highest incidence of ACS. This finding was similar to other studies and accepted fact that the incidence of ACS increases with age.

Relation of total bilirubin with ACS

Total leucocyte count (TLC) in ACS is usually high as infarction of the myocardium is an inflammatory process. In our study the mean TLC was 13785.7+5140.27 SD.

Mean LDL was 172.07+46.57 which was higher than the normal considering the cut off value with existing risk factors. Both TLC and LDL were statistically significant when compared to bilirubin levels and hence our study was similar to other studies in this regard.

Bilirubin has been long postulated to have antioxidant properties and thus its correlation with ACS is of interest. This study tried to find association of serum total bilirubin levels in patients with acute coronary syndrome.

The mean bilirubin values in mg/dl for STEMI was 0.48+0.30 SD, for NSTEMI it was 0.45+0.16 and for unstable angina it was 0.28+0.1 SD.

The mean total bilirubin in patients with ACS was 0.48+0.28SD mg/dl compared to bilirubin levels of 0.6mg/dl in normal population.

There is statistically significance less total bilirubin of ACS than normal standard mean value (0.6) ($p<0.0001$). Hence our research hypothesis accepted.

The results were comparable to Sahin O et al and Hopkins P N et al who also had decreased bilirubin levels in patients with ACS.[28,29]

Substantial evidence has documented that the development of CAD involves lipid oxidation and formation of oxygen radicals as atherosclerosis and inflammation are associated with formation of oxygen and peroxyl radicals.[7-12,14,17-19,24-27]

Bilirubin has proven to be a potent antioxidant under physiological conditions by inhibiting both lipid and protein oxidation.[15] In several studies it was found that different circulating forms of bilirubin are powerful antioxidants: Free bilirubin, albumin-bound bilirubin, conjugated bilirubin, and unconjugated bilirubin were all noted to be effective scavengers of peroxyl radicals and to be able to protect human LDL against peroxidation.[19] Additionally, bilirubin exerts anti-inflammatory effects on vasculature and inhibits proliferation of vascular smooth muscle cells.[17,18]

This has led to suggestions that mildly increased circulatory bilirubin may have a physiologic function to protect against disease processes that involve oxygen and peroxyl radicals or vice versa and many studies have shown relation with CAD.[25,26]

Reduced levels of bilirubin were shown to be associated with higher prevalence of coronary artery disease emerging as new potential risk factor marker.[20] The inverse association between serum bilirubin concentrations and CAD has been found in several studies

Troughton JA et al found bilirubin is a novel coronary heart disease risk marker in middle-aged men, with a U-shaped relationship observed between bilirubin concentration and coronary heart disease risk.[30]

Sahin O et al found high serum total bilirubin level is independently associated with severity of coronary artery disease in patients with NSTEMI.[28] Kim KM et al did cross-sectional study on 19,792 Koreans and found serum total bilirubin concentration inversely correlated with Framingham risk score and it may be helpful to decrease the future risk of Coronary artery disease.[31]

In India, Veerendra Kumar Arumalla et al found plasma bilirubin concentration could act as a provisional new marker of atherogenic risk that can be measured easily in the clinical laboratory and applied in medical practice.[32]

Also, Simmi Kharb found an inverse relationship between increase in total bilirubin and serum levels of LDL-C in Myocardial Infarction. Giving a possibility of bilirubin playing a role in the pathogenesis of coronary heart disease through LDL-C levels.[33] Song YS et al with the objective to investigate the effects of low serum bilirubin levels on the risk for future coronary artery disease (CAD) in a prospective cohort of 8,593 subjects found the addition of low serum bilirubin levels to the traditional risk factors for CAD, such as metabolic syndrome, may yield an improvement of risk prediction.[34]

The same association was also reported in a recent Taiwanese prospective study by Huang et al on patients with cardiac X syndrome followed for 5years, in which patients with the lowest serum bilirubin levels had a higher incidence of non-fatal myocardial infarction, ischemic stroke, rehospitalization for unstable angina and coronary revascularization procedures.[35]

Glucuronidation by UGT1A1 has a controlling effect on serum bilirubin levels.[36] Because the UGT1A1*28 Gilbert syndrome polymorphism results in higher (protective) serum bilirubin levels, it is expected to be associated with reduced CVD risk. Seven studies have addressed this, and all confirmed the association of UGT1A1*28 with higher bilirubin levels.[37]

Among them the strongest protective effect of elevated bilirubin on CVD was reported in a prospective population-based cohort study In the Framingham Heart Study by Jing-ping et al which included 1780 unrelated individuals who had been followed up for 24years found Homozygotes with UGT1A1*28 allele carriers with higher serum bilirubin concentrations exhibited a strong association with lower risk for Cardiovascular disease.[38]

Also in the large study by Horsfall et al demonstrated the association between reduced serum bilirubin levels and increased CVD risk is strong in both sexes and could act as an independent risk factor.[39] It seems likely that several factors are playing a role; antioxidant effects of bilirubin, heme oxygenase activity and consumption of bilirubin by oxidative processes could all be involved.

Risk factors

The known risk factors of ACS like smoking status, tobacco chewing, diabetes mellitus, family history of ACS and hypertension were studied and correlated. 37.2 % of all ACS patients were smokers, 31% chewed tobacco, 24.7 % had diabetes mellitus, 8 % had family history of ACS and 31.8% were hypertensive.

Hypertension and smoking had statistically significant associated risk factors for ACS. All risk factors were more associated with STEMI compared to unstable angina or NSTEMI. On comparing with similar studies all risk factors had positive correlation with ACS. In a study done by Hopkins P N et al 52.2 % were smokers, 47.2% had hypertension and 14.3% had diabetes mellitus.[29] Sahin O et al in their study had 36% smokers, 50% were hypertensive and 26% were diabetics.[28]

CONCLUSION

The present study revealed that, an inverse correlation of bilirubin with ACS. This reinforces the fact that bilirubin acts as an antioxidant and has cardioprotective action and patients with ACS have lower levels of bilirubin. This can use as a factor for screening individuals who have high risk for ACS and preventive strategies applied in them before the onset of overt ACS.

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