Original Research Article

Association of low serum bilirubin and peripheral arterial disease in coronary heart disease patients

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Abstract

Background : High serum bilirubin is considered to be an unfavourable prognostic factor in hepatobiliary disorders. Evidence that low serum bilirubin is associated with myasthenia gravis, Alzheimer's disease, ulcerative colitis, Crohn's disease, diabetic complications, and immunological disorders has suggested the possibility that endogenous bilirubin, presumably owing to its antioxidant properties, may act protectively against conditions that develop or progress due to redox imbalance. A recent study has shown that administration of bilirubin suppresses atherosclerotic formation in an animal model. However, information on the association between serum bilirubin and peripheral arterial disease (PAD) seems to be limited. The study aims to find the association between low serum bilirubin and peripheral arterial disease in coronary artery heart disease patients. **Materials and methods:** Cardiac patients with history of Angioplasty and Bypass surgery in Chengalpattu Medical College Cardiology department were taken as subjects after obtaining Institutional Ethics Committee approval. Subjects were divided into two groups with 30 subjects in each. Group I of patients with coronary artery heart disease alone and Group II of patients with coronary artery heart disease and peripheral arterial disease. Both groups include patients of both gender and 30 – 55 yrs of age. Inclusion criteria was patients having coronary artery heart disease. Exclusion criteria were persons with liver pathologies, cardiac failure, filariasis, trauma lower limbs. Study was done in Department of Physiology, Chengalpattu Medical College. The research study was carried after obtaining written and informed consent from the participants. **Results :** The results show that the mean serum bilirubin of group I was 0.48 ±0.13 and the mean serum bilirubin of Group II was 0.29±0.10. These results show a significant p value of less than 0.05, which confers that low serum bilirubin level, may be associated with peripheral arterial disease in coronary artery disease patients. **Conclusion :** Our study found a significant association between low serum bilirubin and increased incidence of peripheral arterial disease in coronary artery disease patients.. This is suggestive of reduced bilirubin's antioxidant effect resulting in peripheral arterial disease.

Key Words: antioxidant effect, coronary artery disease, serum bilirubin

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Introduction

Atherosclerosis is the leading factor that predisposes to many disorders like coronary artery and other peripheral artery disorders. The reason for atherosclerosis is the injury to endothelium of vessels that leads to exposure of subendothelial tissues[1]. The oxidants released recruits inflammatory cells, followed by deposition of platelets. This leads to plaque

formation, which builds up blocking the cross sectional area of the vessels. This occlusion or break of thrombus from the plaque leads to the thrombo-embolic complications in all systems.

High serum bilirubin is considered to be an unfavorable prognostic factor in hepatobiliary disorders. On the other hand, evidence that low serum bilirubin is associated with myasthenia gravis, Alzheimer's disease, ulcerative colitis, Crohn's disease, diabetic complications, and immunological disorders has suggested the possibility that endogenous bilirubin, presumably owing to its antioxidant properties, may act protectively against conditions that develop or progress due to redox imbalance[2].

Patients with higher serum bilirubin concentrations, within the normal range, were less likely to have PAD, and this association was independent of various confounding variables including sex, age, smoking, HbA1C, serum lipid data, diabetic medication, and statin use.

Low serum total bilirubin is associated with increased risk of coronary artery disease, carotid atherosclerosis and arterial stiffness. However, information on the association between serum bilirubin and peripheral arterial disease (PAD) seems to be limited.

Methodology

This is a cross sectional study done in Chengalpattu Medical College. Informed written consent was obtained from all patients after getting approval from Institutional ethics committee (9/8/18). Rules of modified Helsinki's declaration were followed. 60 coronary artery disease patients of age, gender, blood sugar & blood pressure matched were chosen from inpatient ward of Medicine Department. They were divided into 30 subjects with coronary artery heart (CAD) disease as group I and 30 subjects with coronary artery disease along with peripheral arterial (CAD & PAD) disease as group II. Care was taken that both groups were gender matched. Patients with pathologies leading to RBC destruction and a rise in hemoglobin destruction leading to bilirubin rise were excluded from the study. Patients with liver pathologies that may interfere with bilirubin metabolism like cirrhosis are also excluded from the study. Patients with history of trauma of lower limbs, pathologies leading to edema of legs like filariasis, cirrhosis, renal failure & cardiac failure on treatment were excluded from the study.

Patients diagnosed with myocardial infarction, with blocks in any of the coronary arteries diagnosed by Angiogram and confirmed by Cardiologist were selected as subjects. Those who were having peripheral arterial disease were grouped separately. Patients with Ankle Brachial index[3] of <0.90, by systolic blood pressure measurement, were considered of having peripheral arterial disease.

Patients with random blood sugar >200mgs% and already on treatment for glycemic control were taken as Diabetes. Patients with blood pressure of systolic >140mmHg and diastolic pressure of >90mmHg and hypertensive patients already on treatment were taken as hypertensive patients. Serum bilirubin total, direct and indirect was done for all subjects by serum bilirubin kits.

Result

Results of two groups were analyzed by student independent unpaired 'T' test using (IBM) SPSS software -23. In both groups 15 persons were having type II Diabetes mellitus, 5 persons were having isolated hypertension and 15 persons were having both diabetes and hypertension. P<0.05 was taken as significant.

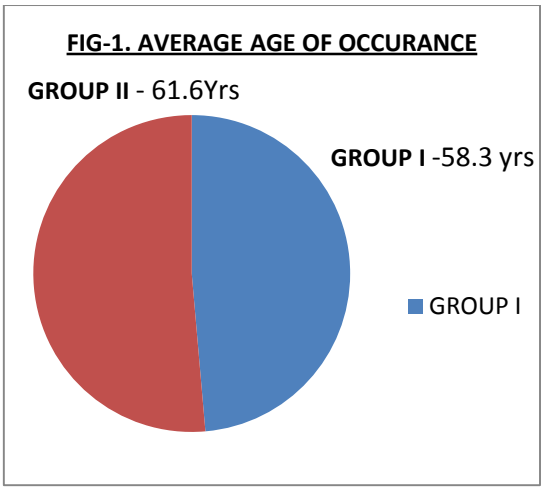
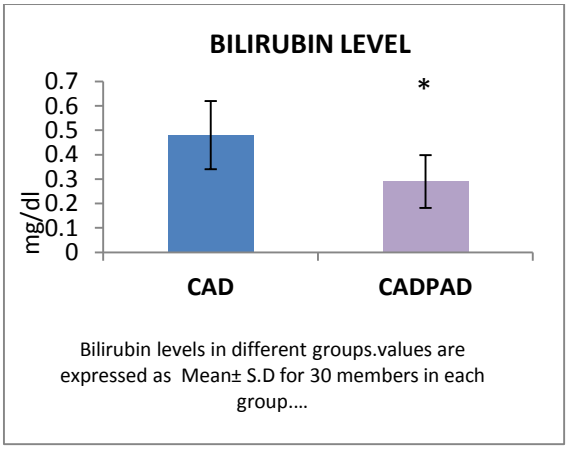


Table-1.Parameters taken for comparison

	GROUP I		GROUP II	
	MEAN	SD	MEAN	SD
1.Random Blood sugar	236.3	64.7	223.4	64.3
2.Ankle Brachial Index	1.13	0.15	0.80	0.05
3.Serum Bilirubin	0.48	0.13	0.29	0.10

Fig 2 .Status of Bilirubin level



Bilirubin levels in different groups.values are expressed as Mean± S.D for 30 members in each group....

*significant p<0.05 comparing group II with group I.

The results show that the mean serum bilirubin of group I was 0.48 ±0.13 and the mean serum bilirubin of Group II was 0.29±0.10. These results show a significant P value of less than 0.05, which confers that low serum bilirubin level, may be associated with peripheral arterial disease in coronary artery disease patients.

Discussion

In current scenario bilirubin measurement is only done to assess the effective functioning of liver.The fact that it is anti oxidative and cytoprotective suggests that it has antiatherogenic properties. As demonstrated, bilirubin has a comparable anti oxidative capacity as vitamin E [4] and alleviates the atherogenic stress of lipid per oxidation by preventing oxidative modification of LDL [5].It is possible that the protective effects seen with higher bilirubin levels are possibly mediated through hemeoxygenase or by other substrates involved in the pathway of bilirubin production, namely, biliverdin and carbon monoxide[6].

Bilirubin requires vitamin E as the co-oxidant, hence patients with a high bilirubin and deficiency of vitamin E, have less atheroprotective effect that weakens the inverse association between elevated bilirubin levels and the risk of CAD[7].

Bilirubin sub-fractions (Bu and Bc) have demonstrated inhibition of low-density lipoproteins oxidation, which in turn retards the peroxidation of lipids, hence could potentially restrict the progression of atherosclerosis. Increasing pile of evidence suggests that bilirubin is a highly bioactive molecule having deep impact on prognosis of cardiovascular and other diseases. Due to recent discoveries of bilirubin binding to specific nuclear receptors[8] (besides PPARα, aryl hydrocarbon receptor (AhR)), and taking into account its production in remote organs, bilirubin behaves in certain circumstances as a hormone. It is interesting to note that similar endocrine effects have been recently discovered for bile acids, which were also considered for long time as negligible molecules [9].

Pre-clinical studies have observed this effect to be mediated by preservation of vascular nitric oxide, which mediates endothelial relaxation. Decreased levels of nitric oxide impair the ability of the coronary vessels to dilate during exercise or stress, thus, provoking myocardial ischemia in CAD patients. Besides vaso-relaxation, nitric oxide also inhibits leukocyte adhesion to endothelium, vascular smooth muscle cell migration and proliferation, platelet aggregation and neointimal formation[10].

When wild type rats were pretreated with the bilirubin precursor biliverdin before injury, neointimal formation was also significantly reduced. Cultured vascular smoothmuscle cells from rats showed a significantly reduced proliferation when treated with bilirubin (Öllinger et al., 2005). These properties and bilirubin's ability to scavenge peroxyl radicals indicate a protective role of bilirubin against vascular ageing and associated atherosclerotic diseases (Schwertner et al., 2008). This is in line with epidemiological studies reporting low serum bilirubin levels to be associated with an increased risk for

coronary artery disease (CAD) or other atherosclerosis outcomes (Schwertner et al., 1994; Hopkins et al., 1996; Hunt et al., 2001.). A recent study has shown that administration of bilirubin suppresses atherosclerosis formation in an animal model.

In humans, a relationship between serum bilirubin and atherosclerotic disorders has been demonstrated in only few studies. The serum bilirubin of group I (Coronary artery disease) patients alone were found to be in higher range, when compared to group II patients of having coronary artery disease with peripheral artery disease. Several studies have shown the association of low serum bilirubin with occurrences of atherosclerosis related arterial diseases. Whether interventions that increase serum bilirubin will influence the progression of atherosclerosis requires future investigations.

A study in healthy individuals grouped by low, intermediate and high serum bilirubin levels revealed that elevated bilirubin concentrations protect from coronary flow reserve impairment, coronary micro vascular dysfunction, and possibly coronary atherosclerosis[11].

We found that patients with higher serum bilirubin concentrations, even those within the normal range, were less likely to have PAD, and this association was independent of various confounding variables including sex, age, smoking, HbA1C, serum lipid data, diabetic medication, and statin use[12].

Schwertner et al was the first to report this protective effect of high level of bilirubin in CAD. They compared 619 subjects in training set (complete data on all risk factors considered was available) vs. 258 subjects in test set (some risk factor data was not available). They observed a statistically significant inverse association between bilirubin and CAD. Fifty percent reduction in total bilirubin was associated with 47% increased odds of CAD, both univariate and multivariate after adjustment for other risk factors.

In another study [13] in 2012, 179 patients undergoing angiography were analyzed to evaluate for CAD. Out of them, 110 patients had good collateral formation and 69 had poor collateral development. Higher serum bilirubin levels were associated with good collateral development as compared to poor collateral development (0.80 ± 0.27 mg/dL vs. 0.53 ± 0.19 mg/dL, $P < 0.001$).

Low bilirubin levels can be indicative of decreased hemeoxygenase activity (a powerful antioxidant) or could be indicative of high oxidative stress in patients leading to consumption of the natural antioxidants including bilirubin. Hence, lower levels of bilirubin are perhaps not the causal factor for CAD but may indicate patients at an increased risk of developing CAD[14, 15]

Conclusion

Our study found a significant association between low serum bilirubin and increased incidence of peripheral arterial disease in coronary artery disease patients. This is suggestive of reduced bilirubin's antioxidant effect resulting in peripheral arterial disease. Hence bilirubin must be assessed along with other cardiac parameters in cardiac patients. This would significantly reduce the morbidity and mortality in these patients.

Limitations

Further course of the study is planned in assessing peripheral vascular diseases by Doppler in a larger sample size, in future to substantiate the effect of serum bilirubin in various arterial disease patients.

Doppler study for peripheral arterial disease and lipid profiles analysis will be taken up in the prospective studies.

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Conflict of interest: Nil

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