e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2023; 15(4); 1500-1504

Original Research Article

The Study of the Association between Serum Bilirubin Levels and the Risk of Heart Disease in Hospitalised Patients

Jigar Shaherawala[1], Ketan Mangukiya[2]

[1]Assistant Professor, Department of Biochemistry, Smt NHL Municipal Medical College, Ahmedabad Gujarat, India

[2]Professor & Head, Department of Biochemistry, Kiran Medical College, Surat, Gujarat, India

Received: 30-01-2023 / Revised: 27-02-2023 / Accepted: 30-03-2023

Corresponding author: Dr. Jigar Shaherawala

Conflict of interest: Nil

Abstract

Background: When Haemoglobin is broken down, bilirubin is produced ,a metabolic waste product that needs to be metabolized before it can be properly disposed of Low Level of bilirubin are linked to a decreased risk of cardiovascular and coronary heart disease.

Objectives: The major objective of the study was to establish a correlation between hospitalised patients' blood bilirubin levels and risk factors for heart disease.

Methodology: This cross sectional study includes total 120 Indian male of age group between 40-60 year who came to our medicine OPD .Among them 60 patients were came for health check up so that is considered in a control group and rest 60 were in Case Group. from all study subjects blood samples were collected for estimation of Lipid profile ,Serum Bilirubin level and blood sugar level. In order to calculate the p value and determine whether there was a significant difference, the acquired findings were statistically evaluated.

Results: The difference in HDL level between OPD and IPD individuals (28.50± 4.25, 43.92± 5.23) was statistically significant. Study demonstrated greater levels of FBS (123.23±4.2 mg/dl) and PP2BS (133.2±38.0 mg/dl) in OPD participants as compared to IPD patients, however the difference between them was not statistically significant. When blood LDL levels were compared, they were 165.86±15.29 and 134.43±10.39 in the control and case groups, respectively. The difference among them was highly significant and LDL having atherogenesis property so it leads to increase risk of cardiovascular disease. The level of Direct bilirubin was 0.36±0.21 mg/dl in control group and 2.80±1.72 mg/dl in case group. and difference among them was highly significant. The Level of Total bilirubin was 0.94±0.41 mg/dl in control group and 3.42±2.1 in case Group and difference among them was highly significant.

Conclusions: According to my findings, there is a substantial negative link between baseline bilirubin levels and incident CHD and CVD death, and serum bilirubin levels are an important component in determining cardiovascular disease risk.

Keywords: Atherosclerosis, Blilirubin, HDL, Coronary heart Disease(CHD), cardiovascular Disease(CVD)

Introduction

Coronary artery disease (CAD) is one of the most common causes of death worldwide. In 2010, about 7 out of total 53 million deaths were due to ischemic heart disease.[1]

Atherosclerosis is the disease primarily responsible for most acute coronary syndrome (ACS) cases. Approximately 90% of myocardial infarctions (MIs) result from an acute thrombus that obstructs an atherosclerotic coronary artery. Plaque rupture and erosion are considered to be the major triggers of coronary thrombosis [2,3]

Bilirubin has long been thought to be a cytotoxic waste product. Recent research has demonstrated that bilirubin has antioxidant, anti-inflammatory, vasodilatory, anti-apoptotic, and anti-proliferative properties. [4,5] These features may endow bilirubin with a novel protective role, particularly in coronary artery disease (CAD), which is a low-grade inflammatory condition aggravated by oxidative stress. In fact, current research indicates an inverse association between serum bilirubin content and the occurrence of CAD. In this article, we evaluate the current literature on the relationship between bilirubin levels and the risk of CAD. We conclude that the current evidence on the preventive impact of bilirubin on CAD is inconclusive. There is currently no evidence of a link between low blood bilirubin levels and an increased risk of CAD.

The ability of bilirubin to strengthen cells, which reduces lipid oxidation, particularly that of Low-Density Lipoprotein (LDL), and minimises accidental free radical-induced damage, is related to its protective impact. Lower blood bilirubin levels have been shown to be related to endothelial and microvascular dysfunction. [6,7]

Materials and Methods

This retrospective cross-sectional study, which involved 120 male participants aged 40 to 60, was conducted between January 2011 and January 2012 at the Govt Medical College, New Civil Hospital in Surat, Gujarat, India. The individuals underwent assessments of their lipid profile, serum bilirubin, and blood sugar (FBS and PPBS).

The study excluded participants who had signs of COPD, chronic renal disease, chronic liver disease, autoimmune illnesses, congestive heart failure, or cancer. Age, gender, and any co-morbid conditions were taken into account while choosing the controls.

Women were not included in this study.

Collection of blood sample: In a fasting state, 5 mL of venous blood was drawn from each participant. Blood was drawn from them and distributed in Flouride and plain vaccutainers for the assessment of several biochemical parameters.

Blood samples were centrifuged at 3000 RPM for 10 minutes after each participant was given a unique ID, and the same ID was written on the eppendorf cup to conceal the participants' identities.

In a fully automated biochemistry analyzer, blood glucose was measured using the Hexokinase technique from a fluoride sample. Cholesterol was measured using the CHOD-PAP method, TG using the GPO-PAP method, HDL using the Phospho tungstate precipitation method, and bilirubin using the diazotized sulfanilic acid method in a biochemistry analyzer with Randox quality control material.

Frieldwald's algorithm was used to calculate serum LDL and VLDL.

All obtained data were analysed stastatically by calculating p-value by using online student t-test calculator.

Results

The biochemical and lipid parameters levels

of both groups are represented in our study table.(Table 1)

Table 1: Comparison of Lipid profile and Blood sugar level between case and Control group

Parameter	Subject Group		P-value
	OPD(60)(Control)	IPD(60)(case)	
S.Cholesterol(mg/dl)	219.92 ± 30.21	204.45 ± 15.90	<0.001(S)
S.Triglyceride(mg/dl)	127.83 ± 24.90	130.52 ± 31.23	0.7475(NS)
S.HDL(mg/dl)	28.50.92±4.25	43.92±5.23	<0.001(S)
S.LDL(mg/dl)	165.86±15.29	134.43±10.39	<0.001(S)
S.VLDL(mg/dl)	25.56±10.19	26.10±10.29	0.7350
FBS(mg/dl)	123.23±4.2	118.12±4.5	0.0001(NS)
PP2BS(mg/dl)	133.23±8.0	129.23±5.2	0.0001(NS)

(P <0.001 significant)

Table 1 demonstrated that there was a significant difference in HDL levels between OPD and IPD individuals (28.50 ±4.25, 43.92 ±5.23).

Similarly, this table revealed a greater level of FBS 123.2±34.2 mg/dl and PP2BS 133.2±38.0 mg/dl in OPD participants as compared to IPD patients, but the difference was not significant.

The level of S. cholesterol in OPD participants was 219.92 ±30.21 compared to 204.45± 15.90 in IPD subjects, indicating that they were more vulnerable to CVD risk.(p = 0.001 significant)(Table 1)

There is no significant difference in serum Triglyceride levels between the two groups.

When blood LDL levels were compared, they were 165.86±15.29 and 134.43±10.39 in the control and case groups, respectively. The difference among them was highly significant and LDL having atherogenesis property so it leads to increase risk of cardiovascular disease.(Table 1)

Table 2: Showing the Bilirubin Level in case and control group

Parameter	Subject Group		P-value
	OPD(60)(Control)	IPD(60)(case)	
D.bilirubin(mg/dl)	0.36±0.21	2.80±1.72	0.0001(S)
T.bilirubin(mg/dl)	0.94±0.41	3.42±2.1	0.0001(S)

(P <0.001 significant)

Direct bilirubin levels were 0.36±0.21 mg/dl in the control group and 2.80±1.72 mg/dl in the case group. and the disparity between them was enormous. (Table 2)

Total bilirubin levels were 0.94±0.41 mg/dl in the control group and 3.42±2.1 in the case group, with a significantly significant difference between them. (Table 2)

Discussion

Up to one-third of all fatalities globally are caused by cardiovascular disease, primarily acute myocardial infarction [8]. It is also the leading cause of death in affluent nations. The striking incidence of cardiovascular disorders in modern society emphasises the need for risk factor identification and vulnerability screening when applying

preventative and therapeutic measures.

The advancement of atherosclerosis is aided by oxidative stress and DNA damage brought on by oxidised low-density lipoprotein (LDL) cholesterol and diet-induced hypercholesterolemia, despite the lack of substantial research into the pathophysiology of atherosclerosis [9]. Thus, by inhibiting the oxidative alteration of LDL cholesterol, antioxidants are believed to play a preventive effect against atherosclerosis and coronary artery disease [10].

In a cohort with untreated hypertension (n = 114), Ayaz *et al*[11] showed an independent positive correlation between bilirubin and left ventricular mass/hypertrophy. Total bilirubin was found to be an independent risk factor for CAD (P = 0.011) after running a linear and logistical regression. The authors explain this by saying that reactive oxygen species have been suppressed[12]. Preclinical rat studies that demonstrated a protective effect of increased bilirubin on left ventricular hypertrophy in spontaneously hypertensive rats demonstrated a similar effect. They proposed that bilirubin's suppression of liver growth factor played a part. However, more clarification on this relationship is still needed.

In 2013, Stojanov *et al* discovered that elevated bilirubin levels in 628 healthy subjects had cardiac beneficial effects. 442 men and 186 women between the ages of 18 and 52 made up the subjects. Based on the subjects' bilirubin levels, they split them into two groups. Subjects were categorised as having "low bilirubin" (0.95 mg/dL in women and 1.4 mg/dL in men) if their levels were below the upper limit of reference, and as having "high bilirubin" if their levels were beyond the upper limit of reference. Low levels of oxidised LDL (p 0.05) and greater levels of albumin and uric acid were seen in men with high bilirubin concentrations (>1.4 mg/dL). When bilirubin levels were high in females (>0.95 mg/dL), albumin levels were greater and thiobarbituric acid-reacting substances (TBARS) ($p < 0.05$). These findings support the evidence of an anti-oxidant effect of bilirubin secondary to inverse association with ox-LDL and anti-inflammatory effect secondary to direct correlation with albumin, which is a negative acute phase reactant in inflammatory response. [13]

Another study found a moderate but significant positive connection between direct bilirubin levels and the Gensini score in 221 patients who had coronary angiography for the assessment of CAD ($r = 0.158$, $p = 0.019$). Total bilirubin and the Gensini score did not, however, show a similar strong association. The small sample size (n = 221) of this investigation has limitations [14].

Additionally, Grosser *et al*[15] observed that statin and aspirin therapy resulted in the activation of heme oxygenase. The synthesis of bilirubin is increased when heme oxygenase is activated. As a result of their decreased ability to exclude bilirubin, people with UGT1A1 gene variations are more likely to accumulate bilirubin when taking statins and aspirin. This suggests that individuals with the UGT1A1 gene who have CAD or who are at increased risk of developing CAD with UGT1A1 gene polymorphism, on aspirin and statin should have increased levels of bilirubin. In that case, bilirubin might be looked upon as a marker of the drug activity.

Conclusion

Based on my findings, baseline bilirubin levels and incident CHD and CVD death have a significant negative relationship, and serum bilirubin levels are an important component in assessing cardiovascular disease risk.

References

1 Yamaguchi T, Terakado M, Horio F, Aoki K, Tanaka M, Nakajima H. Role of bilirubin as an antioxidant in an ischemia–reperfusion of rat liver and induction of heme oxygenase. Biochem Biophysical Res Communications. 1996 Jun 5;223(1):129-35.

2 Djoussé L, Rothman KJ, Cupples LA, Levy D, Ellison RC. Effect of serum albumin and bilirubin on the risk of myocardial infarction (the framingham offspring study). Am J Cardiol. 2003;91(4A):485-8.

3 Kim NH, Kim HC, Lee JY, Lee JM, Suh I. Active and Passive Smoking and Serum Total Bilirubin in a Rural Korean Population. Nicotine & tobacco research: official journal of the Society for Research on Nicotine and Tobacco. 2016;18(5):572–9.

4 Neuzil J, Stocker R. Free and albumin-bound bilirubin are efficient co-antioxidants for alpha-tocopherol, inhibiting plasma and low-density lipoprotein lipid peroxidation. J Biol Chem 1994; 269:16712–9.

5 Vitek L, Jirsa M, Brodanova M, Kalab M, Marecek Z, Danzig V, *et al* Gilbert syndrome and ischemic heart disease: a protective effect of elevated bilirubin levels. Atherosclerosis 2002;160:449 –56

6 Novotny L, Vitek L Inverse relationship between serum bilirubin and atherosclerosis in men: a meta-analysis of published studies. Exp Biol Med (Maywood). 2003;228:568–571.

7 Yamaguchi T, Terakado M, Horio F, Aoki K, Tanaka M, Nakajima H. Role of bilirubin as an antioxidant in an ischemia–reperfusion of rat liver and induction of heme oxygenase. Biochem Biophysical Res Communications. 1996 Jun 5;223(1):129-35.

8 Suh S, Baek J, Bae JC, Kim KN, Park MK, Kim DK, *et al*Sex factors in the metabolic syndrome as a predictor of cardiovascular disease. Endocrinologyand metabolism. 2014; 29(4): 522–9.

9 Freeman R. Hormone replacement therapy (estrogen and progesterone): is it necessary for heart disease prevention?. Preventive Cardiol. 2000 Jan;3(1):21-4.

10 Targher G. Risk of ischemic stroke and decreased serum bilirubin levels: is there a causal link?Arteriosclerosis, thrombosis, and vascular biology.2014;34(4):702–4.

11 Chen SM, Li YG, Wang DM Study on changes of heme oxygenase-1 expression in patients with coronary heart disease. Clin Cardiol.2005;28:197–201.

12 Neuzil J, Stocker R. Free and albumin-bound bilirubin are efficient co-antioxidants for alpha-tocopherol, inhibiting plasma and low-density lipoprotein lipid peroxidation. J Bio Chem. 1994;269(24):16712-9.

13 Stojanov K, Golmohammadi A, Parvizi R, Kezerlou AN, Separham A, Hosnavi Z. The relation of serum bilirubin level with coronary artery disease based on angiographic findings. Crescent J Med Biol Sci. 2015;2(4):130-4.

14 Troughton JA, Woodside JV, Young IS, Arveiler D, Amouyel P, Ferrières J, *et al* Bilirubin and coronary heart disease risk in the Prospective Epidemiological Study of Myocardial Infarction (PRIME). Eur J Cardiovasc Prevent Rehabilitation. 2007 Feb;14(1):79-84.

15 Grosser J, Koo BK, Cho NH, Moon MK. Effect of low serum total bilirubin levels (</ = 0.32 mg/dl) on risk of coronary artery disease in patients with metabolic syndrome. The American journal of cardiology. 2014;114(11):1695–700.