

Research Article

Serum Bilirubin level in metabolic syndrome

Neha Shah* and H. B. Sirajwala

Department of Biochemistry, Baroda Medical College, Vadodara, Gujarat, India

***Correspondence Info:**

Neha Shah
Department of Biochemistry,
Baroda Medical College, Vadodara, Gujarat, India
E-mail: nehashah_2289@yahoo.com

Abstract

Introduction: Metabolic syndrome (MS) is a broadly defined concept that seeks to describe the interactions and mutual synergism of risk factors such as central obesity, impaired glucose tolerance, hypertension, and hyperlipidemia, which are known to be causes of cardiovascular disease, and are the basis for the design of currently used preventive measures against cardiovascular disease. Bilirubin has got a potential antioxidant, antiinflammatory and cytoprotective effect. It has been shown that its concentration inversely related to metabolic syndrome. The aim of this study was to evaluate the association of total serum bilirubin level.

Method: This is observational case control study involving 50 controls and 50 patients who were admitted in S.S.G. Hospital, Baroda. Physical examination and laboratory tests including serum total bilirubin, plasma glucose and serum triglyceride levels were performed.

Result: Physiological normal levels were associated with increased prevalence of metabolic syndrome. When each metabolic abnormality was analyzed separately, the serum total bilirubin was significantly associated with hypertriglyceridemia and hyperglycemia in both sexes and with abdominal obesity.

Conclusion: These results suggest that serum bilirubin levels are at higher side of normal range and serum bilirubin level along with plasma glucose and serum triglyceride level can be added as a good additional marker in patients with metabolic syndrome.

Keywords: Total bilirubin, Metabolic syndrome, Antioxidant

1. Introduction

Bilirubin belongs to the super family of tetrapyrrolic compounds, which is one of the most highly conserved groups of molecules in nature. Bilirubin is the end product of heme catabolism in the systemic circulation. It is formed by the action of heme oxygenase (HMOX), an enzyme that splits cyclic tetrapyrrole heme into biliverdin, carbon monoxide, and ferrous iron. Biliverdin is subsequently reduced to bilirubin by biliverdin reductase (BLVRA). HMOX 1, a highly inducible isoform responsible for reactions of acute phase immediate response against oxidative stress, and a constitutive isoenzyme HMOX2, playing important roles in the brain and testis. The third member of the HMOX family (HMOX3) has also been described, but generally believed that HMOX3 is only represented by a pseudogene, with no coding function.¹

Bilirubin is water insoluble, carried by albumin in the blood, taken up across the basolateral membrane of hepatocytes, predominantly by SLCO1B1 (Soluble Carrier Organic anion transporter family member 1B1), and is conjugated in the hepatocytes by UGT1A1 (Bilirubin UDP-Glucuronosyl Transferase 1 family, polypeptide A1). Bilirubin conjugates are then actively secreted into the canaliculi by ABC2 [member-ATP-Binding Cassette subfamily (CFTR/MRP) member 2].²

From the metabolic point of view, there are several crucial enzymatic steps in particular those catalyzed by HMOX1, BLVRA and UGT1A1 enzymes which play an important role in bilirubin homeostasis with subsequent impacts on the risk of metabolic diseases including cardiovascular diseases (CVD), diabetes, Metabolic syndrome, arterial hypertension and obesity.³

1.1 Biological properties of bilirubin:

- i. Bilirubin has been recognized as a substance with potent antioxidant properties. The bilirubin has shown to be more effective at protecting lipids from oxidation than the water-soluble antioxidants such as glutathione, which primarily protect proteins from oxidation. However, bilirubin has also been demonstrated to be almost 30 times more potent toward the prevention of LDL oxidation compared to a vitamin E analog. Even more importantly, serum bilirubin has been demonstrated to be a major contributor to the total antioxidant capacity in humans.⁴⁻⁶
- ii. Additionally, bilirubin has been proven to have anti-inflammatory properties. Bilirubin inhibited tumor necrosis factor α -induced up-regulation of E-selectin, vascular cell adhesion molecule-1 (VCAM-1), and intercellular adhesion molecule (ICAM-1) in vitro.^{7,8}

The lower bilirubin levels are at increased risk of both coronary and peripheral atherosclerotic disease. Serum bilirubin concentrations were also found to be negatively related to coronary artery calcification.⁷⁻¹⁰

1.2 Bilirubin, Diabetes, and Metabolic syndrome:

Negative associations between serum bilirubin concentrations and abnormal glucose tolerance tests have also been found. Additionally, serum bilirubin concentrations were shown to be inversely correlated with urinary albumin excretion in patients with type 2 diabetes as well as with the prevalence of the metabolic syndrome.^{11,12}

1.3 Bilirubin and Body mass Index:

A negative association between bilirubin concentration and abdominal obesity, consistent with the inverse relationships between serum bilirubin concentrations and metabolic syndrome. Moreover, since weight reduction is known to reduce several cardiovascular risk factors, each percent decrease in weight loss was associated with a linear increase in serum bilirubin concentration.¹²⁻¹⁴

1.4 Bilirubin and Arterial Hypertension:

Serum bilirubin concentrations are inversely related to blood pressure have shown that serum bilirubin concentrations are significantly decreased in patients with untreated hypertension.²

2. Methods

In observational case control study was analysis in S.S.G. Hospital, Baroda. 50 Controls and 50 Patients were studied.

2.1 Exclusion Criteria

Smokers and Alcohol abuser were excluded.

2.2 Inclusion Criteria

Subjects were taken according to the guidelines of National Cholesterol Education Program Adult Treatment Panel III. Metabolic syndrome was diagnosed for participants that had any three of the following five features:

Waist circumference ≥ 90 cm in men and ≥ 85 cm in women; Triglycerides ≥ 150 mg/dL; HDL cholesterol < 40 mg/dL in men and < 50 mg/dL in women; Systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg or on hypertensive drug treatment in a patient with a history of hypertension ;Fasting glucose ≥ 100 or on drug treatment for elevated glucose.

Fasting blood samples were taken. Serum level of total bilirubin with Diazo method-end point, protein by biuret method, albumin by BCG Dye method- end point, creatinine by Jaffe’s method, AST and ALT by modified IFCC method, Lipid profile i.e. TG by GPO/PAP method and plasma glucose by GOD- POD method was measured.

3. Result

The comparison of serum bilirubin was done in case and control group as well as comparison was also done for Plasma Glucose and Serum Triglyceride in case group and control group to indicating diabetes mellitus and cardiac diseases. Statistical analysis was done and p value was calculated using t-test.

Table 1: Shows the mean and p-value of different parameter in case and control groups with metabolic syndrome

Parameters	Controls	Subjects	P Value
Glucose (mg/dL)	97±16	138±37	<0.0001
Triglyceride (mg/dL)	124±48	172±75	0.0002
Total bilirubin (mg/dL)	0.72±0.1	0.95±0.3	<0.0001
Waist circumference			
Men(cm)	85±07	101±18	0.0001
Females(cm)	76±07	90± 10	<0.0001

p < 0.0001 is considered highly significant.

Figure 1: Shows the linear relationship of serum Bilirubin level with Serum T

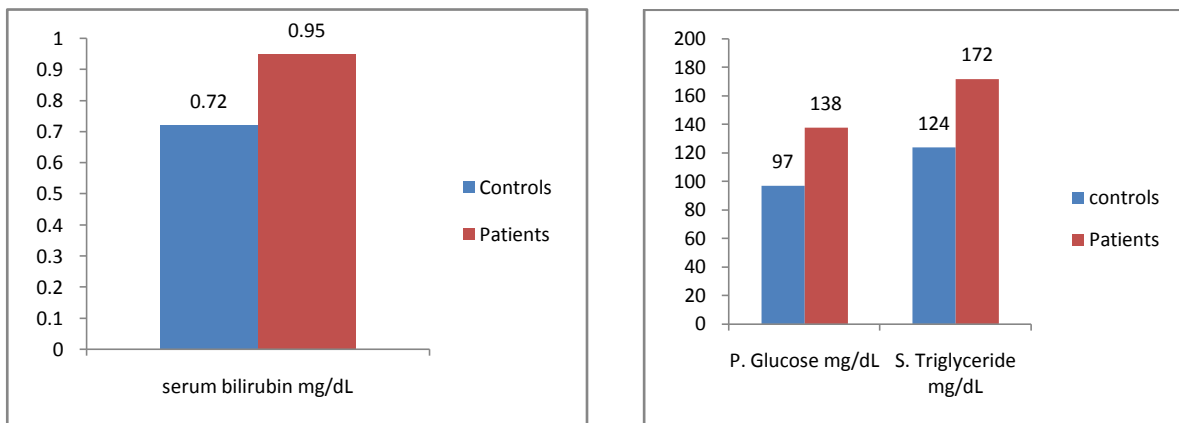
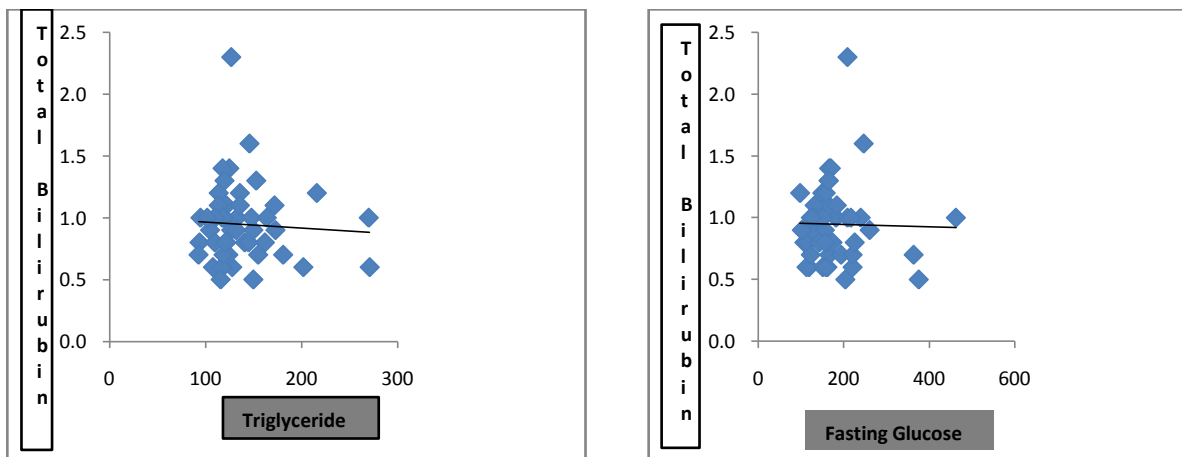


Figure 2: shows the linear relationship of serum Bilirubin level with Plasma Glucose.



The total bilirubin is significantly associated with Serum triglyceride (p<0.0001) and Plasma glucose (p<0.0001).

The study shows correlation of serum bilirubin with plasma glucose and with serum triglyceride. All these parameters rise together in metabolic syndrome.

4. Discussion

The study was conducted to document the serum bilirubin levels in patient with metabolic syndrome whether there is any correlation. The results of this study showed that all the three studied variables (Serum bilirubin, plasma glucose, serum triglyceride) were significant in the study population than in the control group (P value <0.05).

Few studies have been conducted on metabolic syndrome. These included, by Choi et al (2013) on the serum total bilirubin levels showed that within physiological range, the serum total bilirubin level was associated with metabolic syndrome in subjects. Another by Guzek et al (2012) and by Kwon et al (2011) showed that there is inverse association of serum bilirubin with metabolic syndrome and insulin resistance.¹⁵⁻¹⁷

5. Conclusion

The serum total bilirubin level is at higher side of normal range in patients with metabolic syndrome. Serum bilirubin level along with plasma glucose and serum triglyceride level can be added as additional marker when these entire parameter altogether shows rise in there levels in patients with metabolic syndrome.

References

- Hayashi, S., Omata, Y., Sakamoto, H., Higashimoto, Y. Hara, T. Sagara, Y., Noguchi, M. Characterization of rat heme oxygenase-3-gene. Implication of processed pseudogenes derived from heme oxygenase-2 gene. *Gene* 2004; 336:241-50.
- Jing-Ping Lin, Libor Vitek, Harvey Schwertner. Serum bilirubin and genes controlling bilirubin concentrations as biomarkers for cardiovascular disease. *Clinical Chemistry* 2010; 56:10 1535-43.
- Libor Vitek. The role of bilirubin in diabetes, metabolic syndrome, and cardiovascular diseases. *Frontiers in Pharmacology* 2012 April; 3(55):1-7.
- Sedlak TW, Saleh M, Higginson DS, Paul BD, Juluri KR, Synder SH. Bilirubin and glutathione have complementary antioxidant and cytoprotective roles. *Proc Natl Acad Sci USA* 2009; 106:5171-6.
- Yesilova Z, Serder M, Ercin CN, Gunay A, Kilciler G, Hasimi A, et al. Decreased oxidation susceptibility of plasma low density lipoproteins in patients with Gilbert's syndrome. *J Gastroenterol Hepatol* 2008; 23:1556-60.
- 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.
- Vitek L., and Schwertner, H.A. The heme catabolic pathways and its protective effects on oxidative stress-mediated diseases. *Advance Clinical Chemistry*. 2007b; 43:1-57.
- Mazzone, G. L., I. Rigato, Ostrow, J. D., F. Bossi, A. Bortoluzzi, Sukowati C. H., Tedesco, F., and Tiribelli, C. Bilirubin inhibits TNF alpha-related induction of three endothelial adhesion molecules. *Biochem. Biophys. Res. Commun.* 2009; 386:338-344.
- Vitek L., and Ostrow J.D. Bilirubin chemistry and metabolism; harmful and protective aspects. *Curr. Pharm. Des.* 2009; 15: 2869-83.
- Tanaka M., Fukui M., Tomiyasu K., Akabame S., Nakamura N. Low serum bilirubin concentration is associated with coronary artery calcification(CAC). *Atherosclerosis* 2009; 206:287-91.
- Fukui M, Tanaka M, Shiraishi E, Harusato I, Hosoda H, Asano M, et al. Relationship between serum bilirubin and albuminuria in patients with type 2 diabetes. *Kidney Int* 2008; 74:1197-201.
- Lin LY, Kuo HK, Hwang JJ, Lai LP, Chiang FT, Tseng CD, Lin JL. Serum bilirubin is inversely associated with insulin resistance and metabolic syndrome among children and adolescents. *Atherosclerosis* 2009; 203:563- 8.
- Bhuiyan AR, Srinivasan SR, Chen W, Sultana A, Berenson GS. Association of serum bilirubin with pulsatile arterial function in asymptomatic young adults: the Bogalusa Heart Study. *Metabolism* 2008; 57:612- 6.
- Andersson C, Weeke P, Fosbol EL, Brendorp B, Kober L, Coutinho W, et al. Acute effect of weight loss on levels of total bilirubin in obese, cardiovascular high-risk patients: an analysis from the lead-in period of the Sibutramine Cardiovascular Outcome trial. *Metabolism* 2009; 58:1109-15.
- Choi SH, Yun KE, Choi HJ. Relationships between serum total bilirubin levels and metabolic syndrome in Korean adults. *Nutr Metab Cardiovasc Dis.* 2013 Jan; 23(1):31-37.
- Guzek M, Jakubowski Z, Bandosz P, Wyrzykowski B, Smoczyński M, Jabłońska , Zdrojewski T. Inverse association of serum bilirubin with metabolic syndrome and insulin resistance in polish population. *Przegl epidemiol.* 2012; 66(3):495-501.
- Kwon KM, Kam JH, Kim MY, Chung CH, Kim JK, Linton JA, Eom A, Koh SB, Kang HT. Inverse association between total bilirubin and metabolic syndrome in rural Korean women. *J Women's Health (Larchmt)*. 2011 Jun; 20(6):963-9.