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Original Research article: A Study of Serum Bilirubin as a Marker of Oxidative Stress in Hypertensive and Normotensive Subjects

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Abstract
Background: Oxidative stress is found to be one of the causes of hypertension. Serum Bilirubin is found to be an antioxidant and participates in defense mechanism against oxidative stress.
Aims & Objectives: To see relation between serum bilirubin and hypertension along with MDA (Malondialdhyde).
Methodology: In the present study serum MDA and Serum bilirubin was measured in 25 patients with hypertension and 25 normotensive healthy adults showing family history of CAD.
Results: The mean concentration of S.bilirubin (mg/dl) in hypertensive study group is 1.13±0.2 and that of control group is 0.56±0.3. The mean concentration of S.MDA (mmol/L) in hypertensive study group is 5.1±1.3 and that of control group is 1.5±1.1.
Conclusion: The subjects with higher bilirubin level showed a lower incidence of hypertension than did the subjects with lower bilirubin level. In humans, the effects of mildly increased serum bilirubin levels have been reported to be a decreased risk for the development of coronary artery disease and atherosclerosis.

Keywords: Bilirubin, Oxidative stress, Antioxidant, Hypertension, MDA

Introduction

Heme oxygenase (HO) is the rate limiting enzyme for the breakdown of heme to generate carbon monoxide, iron, and biliverdin. Biliverdin is rapidly converted to bilirubin by biliverdin reductase **[1]**. Experimental evidence suggests that the induction of HO-1, the inducible isoform of HO, is an important endogenous mechanism for cytoprotection and the downstream products of heme degradation may mediate the beneficial effects, such as antioxidant, anti-inflammatory properties, etc. Induction of HO-1 has also been demonstrated to lower blood pressure in several animal models [2, 3]. The mechanism by which HO-1 induction lowers blood pressure is decreasing vascular resistance by the HO-driven carbon monoxide. Reactive oxygen species (ROS) have been known to be an important factor in the pathogenesis of hypertension **[4]**. The increased ROS production in the renal medulla is a key component of angiotensin II-dependent hypertension **[5, 6]**. Induction of hemeoxygenase has been demonstrated to lower blood pressure in various experimental studies. Bilirubin is a potent antioxidant [7]. We evaluated the levels of serum bilirubin level on the patients of both hypertensive and normotensive subjects.

Materials and Methods

The study was carried in the department of Biochemistry of SMS medical college and attached hospital, Jaipur, Rajasthan, India. In the present study, we investigated the relationship between serum bilirubin level and the incidence of hypertension in normotensive subjects who had undergone repeated routine health check-ups and hypertensive subjects with family history of CAD in both cases.
Cases- 25 hypertensive patients
Controls- 25 normotensive controls

The blood samples were drawn and collected in a clean, disposable plastic tube from anterior cubital vein under aseptic condition for estimation of serum bilirubin and serum MDA (Malondialdehyde) levels.
Serum bilirubin and S.MDA were assessed by using semi-automated analyzer ERBA chem 5 Plus V2.
Blood pressure was measured by standard techniques using sphygmomanometer, using 140/90 mmHg for diagnosis of hypertension.

Statistical analysis

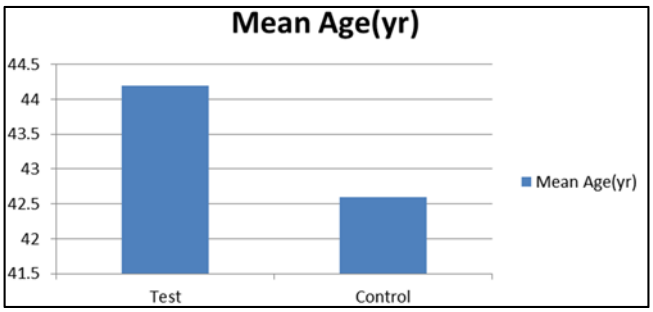
It was done by using online student t-test calculator.

Result

The mean age of the patients for this study was 44.2±2.3 and controls were 42.6±3.2. The results in this study showed significant decrease in serum bilirubin levels in hypertensive patients as compared to controlled normotensive group (p = 0.001)as shown in Table 1.
There was a significant increase in the levels of serum MDA levels in hypertensive subjects as compared to normotensive (P = 0.0001) as shown in Table 2.
Average Blood pressure of both group was mentioned in Table 3.

Table 1: Age wise distribution of participant

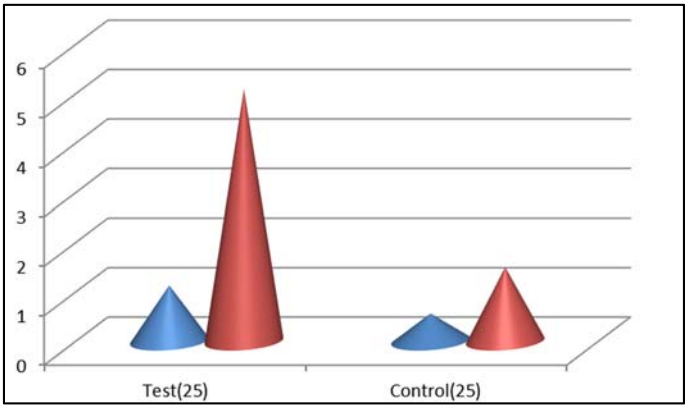
Group	Number(n)	Age(yr)(Mean± SD)
Test	25	44.2±2.3
Control	25	42.6±3.2



Graph 2: Graphical presentation of Age group of participants

Table 2: The Mean concentration of S.MDA and S.bilirubin in both groups

Parameter	Test(25)	Control(25)	p-value
S.Bilirubin(mg/dl)	1.13±0.2	0.56±0.3	<0.05(Significant)
S.MDA(mmol/l)	5.1±1.3	1.5±1.1	<0.05(Significant)



Graph 1: Graphical presentation of the Mean concentration of S. Bilirubin and S.MDA in test and control Group

Table 3: Average Blood pressure in both test and control group

Group	Number(n)	BP(Mean± SD)
Test(Hypertensive)	25	190/90±10
Control	25	130/80±9

Discussion

In this study, the serum bilirubin level assigned to discriminate the risk of hypertension was 1.1 mg/dL. Endothelial dysfunction is the initial step in the pathogenesis of atherosclerosis, leading to cardiovascular complications. Oxidative stress also plays an important role in the pathogenesis and development of cardiovascular diseases. Normal endothelial function is maintained by a balance of oxidative stress and nitric oxide (NO). One mechanism of endothelial dysfunction is an increase in oxidative stress, which inactivates NO [9].

Although bilirubin at a high concentration acts as a cytotoxic metabolite, bilirubin at a low concentration is a potent endogenous antioxidant [9]. Serum bilirubin should be one of the key mediators of the antioxidant system in humans.

Clinical studies have shown that serum concentrations of bilirubin inversely correlate with risk of cardiovascular diseases and peripheral arterial disease.

In the cardiovascular system ROS play a physiological role in controlling endothelial function, vascular tone, and cardiac function, and a pathophysiological role in inflammation, hypertrophy, proliferation, apoptosis, migration, fibrosis, angiogenesis, and rarefaction, all of which are important processes contributing to endothelial dysfunction and cardiovascular remodeling in hypertension. A major source for cardiovascular ROS is a family of nonphagocytic nicotinamide adenine dinucleotide phosphate (NADPH) oxidizes (Nox1, Nox2, Nox4, and Nox5). Other sources include mitochondrial enzymes, xanthine oxidize, and uncoupled NO synthase (NOS).Biomarkers of excess ROS are increased in patients with hypertension and oxidative damage is important in the molecular mechanisms associated with cardiovascular and renal injury in hypertension.

Conclusion

The subjects with higher bilirubin level showed a lower incidence of hypertension than did the subjects with lower bilirubin level. In humans, the effects of mildly increased serum bilirubin levels have been reported to be a decreased risk for the development of coronary artery disease and atherosclerosis.

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