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Mannose binding lectin as a marker for coronary artery disease in hypertension

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ABSTRACT

Background

According to The Framingham Heart Study and the Epidemiology of Cardiovascular Diseases hypertension is an independent risk factor for cardiovascular disease (1). Inflammation plays a major role in atherosclerosis. Markers of innate immunity have been shown to predict the development of coronary artery disease. MBL (Mannose binding lectin) being a component of innate immunity can be used as a marker of cardiovascular risk in hypertension.

Aim & Objectives:

The study was conducted to evaluate the risk of coronary artery disease in recently diagnosed hypertensive patients by estimating serum mannose binding lectin levels

Materials & Methods:

This cross sectional case control study was conducted among 180 subjects who were divided into three groups as follows

Group A : 60 recently diagnosed hypertensive patients (< 6 months duration)

Group B : 60 hypertensive patients who had myocardial infarction recently (< 7 days)

Group C : 60 age & sex matched healthy controls

Serum levels of MBL was evaluated in the three groups using ELISA technique. Collected data were analysed statistically.

Results & Conclusion:

The serum MBL levels were significantly elevated in hypertensive patients (mean = 823.45 ng/mL; Range – 772 to 875 ng/mL) and in hypertensive with myocardial infarction (mean = 1163.39 ng/mL; Range – 945 to 1381 ng/mL) as compared with control population (mean = 607.15 ng/mL; Range – 513 to 701 ng/mL) with p value of 0.001. From the ROC curve, it has been determined that MBL has sensitivity of 93% & specificity of 96%) with a positive predictive value of 96% & negative predictive value of 84.65%.

Our findings suggested the determination of MBL status may serve as a potential marker for early identification of patients at risk of cardiovascular complications, pending further validation studies.

Keywords: Mannose binding lectin (MBL) • Hypertension • Coronary artery disease • Atherosclerosis • Inflammation

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INTRODUCTION

Cardiovascular disease is one of the leading cause of morbidity and mortality worldwide. Epidemiological investigations pointed out that hypertension is a powerful cardiovascular risk factor. According to World Heart Federation High Blood Pressure is responsible for 47% of coronary artery disease worldwide. In India the prevalence rate is 29.8%.About 23% of men and 22.6% of women above 25 years suffer from hypertension. Relationship between elevated blood pressure and risk of cardiovascular events is continuous, consistent and independent of other risk factors (2). Inflammation plays a major role in all phases of atherogenesis from plaque initiation to plaque rupture(3).Excessive production of ROS (Reactive Oxygen Species), outstripping antioxidant mechan(ism, decreased bioavailability of NO (Nitric Oxide) in the vasculature and kidneys and ROS mediated cardiovascular remodelling plays an important pathophysiological role in development of hypertension. Mannose binding lectin (MBL) is an important component of the innate immune system(18). It has opsonic activity and in cooperation with MBL – associated serine proteases (MASPs) has the ability to activate complement via the lectin pathway. Since innate immunity has been implicated in atherogenesis , MBL has been suggested to play a role in the formation of atherosclerotic plaque(5,6). MBL plays an important role in other systemic processes including coagulation, inflammation and tissue injury (7,23). MASP (MBL-associated serine proteases) – 1 and – 2 may participate in activation of the coagulation system. However studies examining the relations between serum levels of MBL and coronary artery disease risk have reported equivocal results .Based on the data reviewed MBL has a ambiguous role in the development of coronary artery disease. Studies done by Pesonen et al, Haahr-Pedersen et al, Schoos et al & Trendelenburg et al reported high MBL levels in acute Myocardial Infarction but the studies done by Saevarsdottir et al & Vengen et al reported high serum level associated with decreased risk of Myocardial Infarction (24).At present,no conclusive data are available about the relationship between serum MBL levels and coronary artery disease risk in hypertensive patients. Hence it is proposed to study the association of serum levels of MBL in the development of coronary artery disease in hypertensive patients.

MATERIALS AND METHODS:

The study protocol was approved by the Institutional Ethics Committee of Madras Medical College, Chennai. 180 subjects were selected for the study .They were divided into three groups as follows.

- Group A - 60 Recently diagnosed hypertensive patients of 6 months duration of age 30 years and above from the outpatients attending hypertension clinic in Rajiv Gandhi Government General Hospital, Chennai
- Group B - 60 Hypertensive patients who had myocardial infarction recently (< 7 days duration) of age 30 years and above from the Inpatients admitted in the cardiology department in Rajiv Gandhi Government General Hospital, Chennai.
- GROUP C – 60 Age and sex matched apparently healthy subjects who were staffs of Madras Medical College, their relatives and friends.

Exclusion criteria:

- Patients with Diabetes mellitus
- Patients with renal disorders.
- Patients with Liver diseases.
- Patient with acute illness / infection.
- Chronic Smokers and alcoholics.
- Other endocrinological disorders.

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5 mL of blood sample was collected from all subjects after overnight Fasting and transferred to serum tubes. The blood was allowed to clot and the serum was separated after centrifugation at 3000 RPM for 15 minutes. About 0.5 mL of serum was stored in eppendrof at – 20°C for the analysis of mannose binding lectin. MBL was analysed by ELISA technique (non-competitive, sandwich).BT LAB ELISA Kit (Lot No: E0335Hu) was used. The measurable range for the kit ranges from 10ng / mL – 3000 ng / mL with sensitivity of 5.16 ng/mL, inter assay CV < 10% & intra assay CV < 5%. Collected data were statistically analysed.The data analysis techniques were aligned with contemporary best practices.

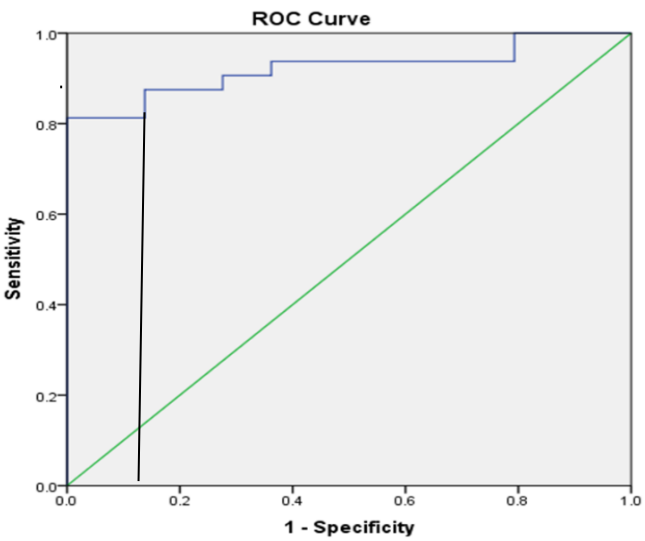
RESULTS:

The mean age in control was 54.03 ± 8.39 years, in hypertension was 52.37±8.15 years and in hypertension with myocardial infarction was 54.17 ± 9.67 years. There were 56 % of males in hypertension & 53% in both hypertension with myocardial infarction and in controls. The mean MBL of hypertension group was 823.45 (99.9% CI: 801.48 – 845.42) ± 51.72, hypertension with MI group was 1163.39 (99.9% CI: 1070.67 – 1256.11) ± 218.24 and control group was 607.15 (99.9% CI: 567.14 – 647.16) ± 0.7 (expressed in ng /mL). Statistically significant p-value of 0.001 was obtained by unpaired Students t-test.

Table 1: Mean MBL (Mannose binding lectin) among study groups

Variable	Study Group	N	Mean	SD	p – Value
MBL	Hypertension	60	823.45	51.72	0.001* Highly significant
	Control	60	607.15	94.18	
	Hypertension with MI	60	1163.39	218.24	0.001* Highly significant
	Control	60	607.15	94.18	

ROC for Mannose Binding Lectin



Optimal cut off – 730 ng/mL
Sensitivity – 92.72 %
Specificity – 95.30 %

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From the ROC analysis it has been determined that Area Under Curve (AUC)	0.924
Optimal cut off value	730.00
Sensitivity	92.72 %
Specificity	95.30 %
Positive Predictive value	96.32 %
Negative Predictive value	84.65 %

Area Under the Curve

Test Result Variable(s): MBL

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.924	.037	.000	.850	.994

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

Discussion

Hypertension and hypertensive end organ damage are mediated by innate and adaptive immune responses. Inflammatory responses mediate the cardiac dysfunction induced by hypertension (4).Recently, evidence has emerged concerning the role of Mannose Binding Lectin (MBL) in the development of atherosclerosis(7). It is a part of complement cascade and plays an important role in the first line of defense of the innate immune system (17).

MBL as an atherogenic agent:

- MBL activates complement system
    - Endothelial oxidative stress activates complement via lectin complement pathway(8).Binding of the MBL-MASPs

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complex to the target structure, lead to the activation of MASPs which causes cleavage of C_4 and C_2 and thus the initiation of the complement cascade(17,18).

- MBL - potent regulator of inflammatory pathway(9,10)

MBL enhance the production of chemokines by macrophages leading to enhanced leukocytes & phagocytes recruitment to the sub endothelium (11,12).MBL plays an important role in atherogenesis, plaque destabilisation and the development of coronary events (16, 25). Hence high MBL levels can influence the atherosclerotic process in sub endothelium (15,21). In this study the serum Mannose Binding Lectin (MBL) levels were measured for predicting cardiovascular risk in hypertensive patients. So that it is possible to treat the patients at an earlier stage and prevent the progression of cardiovascular disease.The MBL levels were significantly elevated in hypertensive patients when compared with the control group but are more significantly elevated in hypertensive patients with myocardial infarction. The normal level of MBL is about 400 – 800 ng / mL as given in the study done by Saevarsdottir et al. in normal healthy individuals (13) .The reference interval for MBL is not yet established due to genetic polymorphisms in the MBL2 gene. MBL levels vary depending on the individual & specific laboratory test used. The study by Pesonen et al. found "High MBL" genotypes more frequent in patients with acute myocardial infarction (14).Hamed Mehri et al also noted that serum levels of MBL were significantly increased in patients with coronary artery disease (22).

Keller et al. also noted that elevated serum concentrations of MBL are associated with an increased risk of future coronary artery disease(3). ROC is done to determine the sensitivity and specificity of the marker. And it has been determined that MBL has good sensitivity (93%) and specifity (96%) with a positive predictive value of 96.32 %

The limitations to the generalization of these results are it is a single center study and it lacks longitudinal follow up.

CONCLUSION:

The present study was done with an aim to find out the risk of coronary artery disease in recently diagnosed hypertensive individuals by estimating serum mannose binding lectin levels.

From this study we conclude that,

- MBL levels are significantly higher in hypertensive patients and in hypertensive patients with myocardial infarction
- MBL is an independent determinant of myocardial infarction in hypertensive patients.
- MBL is a marker of advanced subclinical atherosclerosis.

  Patients with myocardial infarction and have determined its significance as a marker to assess risk of myocardial infarction in hypertensive patients at an early stage and halt the progression of the disease.

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