Proceedings S.Z.M.C. Vol: 37(2): pp. 01-08, 2023. PSZMC-878-37-2-2023

Characterization of Mannose Binding Lectin (MBL) Levels in Type-2 Diabetes Mellitus Patients Amongst Pakistani Population

[1]Hijab Batool ,[1]Muhammad Dilawar Khan,[2]Omar Rasheed Chughtai,[1]Sana Rafaqat,[3]Fouzia Sadiq,[1]Hafiz Muhammad Bilal

[1]Department of Clinical Chemistry and Immunology, Chughtai Institute of Pathology.
[2]Department of Histopathology, Chughtai Institute of Pathology.
[3]Research Director, Shifa Tameer-e-Millat University, Pitras Bukhari Road, Islamabad, Pakistan.

ABSTRACT

Introduction: Mannose Binding Lectin (MBL) is a pattern recognizing molecule in the Lectin complement pathway and acts by activating the complement cascade via binding with ligands. There is evidence of increased autoreactivity of Mannose Binding Lectin in various diseases especially diabetes. MBL deficiency can reduce pathogen clearance and impair atherogenic lipoprotein removal whereas higher levels are associated with exaggerated immune response due to complement activation in the presence of hyperglycemia.

Aims & Objectives: This study aims to find out the association of MBL (Mannose Binding Lectin) with different clinical parameters in healthy controls and type 2 DM patients to predict disease outcome in type 2 diabetics. Mean level of MBL in type 2 diabetics and healthy population will be compared to characterize MBL levels amongst diabetics helping the clinicians to stratify patients according to disease severity.

Place and duration of study: It was a cross sectional analytical study conducted at Chughtai Institute of Pathology from July 2019 to January 2020 on samples collected nationwide at Chughtai Lab collection centres.

Material & Methods: We selected 300 adult male and females in this study after taking informed consent based on strict inclusion and exclusion criteria. Of these 200 were known cases of type 2 diabetes mellitus and 100 healthy controls. .Fasting blood samples were drawn from both groups were analyzed for hs-CRP, HbA1c, creatinine, Total Cholesterol, Alanine amino transfer as (ALT), HDL-Cholesterol, LDL-Cholesterol, Glucose, Triglyceride, and Mannose Binding lectin. eGFR (Estimated Glomerular Filtration rate) was calculated for each patient and control. Data was analyzed via Graph Pad Prism 5 and SPSS version 23.0, p value ≤ 0.05 was taken as significant.

Results: Mean age of the participants was 47.9 years in diabetic group and 39.3 years in healthy controls. The healthy population had a mean MBL level of 110.1 (SD±3.94) pg/ml and mean MBL level of diabetic group was 197.9 (SD±12.84) pg/ml ($p<0.05$). No differences in MBL levels were detected based on gender distribution. There was a significant difference among HbA1c, LDL-C, HDL-C, Fasting Glucose, TG, creatinine and eGFR amongst the diabetic and the healthy group ($p<0.05$). There was a negative correlation between MBL levels and plasma glucose and a positive correlation between the former and HDL-C in the healthy controls. In diabetic patients having MBL above 178pg/ml, a positive correlation of HbA1C with MBL was found. CRP in the healthy population resembled levels in patients with elevated MBL and the ratio Trig/HDL was higher in this subgroup having a positive correlation with MBL.

Conclusion: MBL plays a role in pathophysiology of diabetes mellitus and elevated MBL having positive correlation with HbA1c might show association of glycemic control with the biomarker levels. A direct relationship of MBL with development of cardiovascular complications in type 2 diabetics was suggested by a positive association of MBL with TG to HDL-C ratio.

Keywords: Type 2 Diabetes Mellitus, HbA1c, Triglyceride to HDL ratio, Mannose Binding Lectin.

INTRODUCTION

Our complement system is grouped into three pathways which are interconnected: the classical pathway, the lectin pathway, and the alternative pathway [1]. All these convey into common lytic pathway. This cascade is an immediate response to the invading microorganisms resulting in lysis and inflammation [2]. Mannose Binding Lectin (MBL) is one of the four pattern recognizing molecules in the Lectin complement pathway. MBL acts by activating the complement cascade via binding with ligands which are sugar specific and present on microorganisms and dead tissue in a calcium dependent mechanism[2]. MBL is primarily synthesized by the hepatocytes and belongs to C type lectin family[3]. Individuals with MBL deficiency are at increased risk of infections and there is evidence that MBL inhibition improves

clinical outcome in cases of acute myocardial infarction[4].

There is evidence of increased autoreactivity of Mannose Binding Lectin in various diseases especially diabetes. Hyperglycemia associated with diabetes mellitus results in glycation of proteins, cells and endothelial surface with an increased activity of MBL resulting in complement activation contributing towards sustained chronic inflammation[5]. A study conducted on European population has documented an elevation of mannose binding lectin, also called mannose binding protein in type 1 Diabetes Mellitus leading to an increased risk of diabetic nephropathy and cardiac disease but not enough data is available for type 2 Diabetes Mellitus[6]. Elevated C-reactive protein (CRP) is associated with chronic inflammation and increased mortality in patients with Type 2 diabetes[7]. An increased expression of MBL genotype has been found in patients with diabetic nephropathy indicating that high levels of MBL might be a risk of developing nephropathy by aggravating complement activation. Also, MBL mediated complement activation has been linked with pathogenesis of renal diseases[6]. The disease outcome can be improved by invasive treatment but only once the disease course is accurately predicted.

There is mixed association of MBL with cardiovascular disease (CVD) and poor outcome in diabetics. Some of the studies demonstrated higher MBL levels whereas others reported low levels linked with increased number of episodes of cardiac events and increased mortality in diabetics and healthy population [8,9]. Abnormal MBL levels have been correlated with increased intima media thickness of carotid artery. Activation of lectin complement pathway through MBL may activate the coagulation cascade leading to thrombosis which could increase the risk of myocardial infarction. Studies have supported the fact that MBL has central role in reperfusion injury, and this can even blur its cardioprotective actions[8]. MBL deficiency can reduce pathogen clearance and impair atherogenic lipoprotein removal whereas higher levels are associated with exaggerated immune response due to complement activation in the presence of hyperglycemia[10]. All the above stated studies have been conducted on different populations around the world, but no study has been conducted on Pakistani population.

The association of MBL with biomarkers like CRP, Lipid profile, Creatinine, eGFR and HbA1c in type 2 diabetes largely remains unknown amongst our population. We designed this study to characterize MBL levels amongst the diabetic population and comparing it to healthy controls. We also aimed to find out the mean level of MBL in type 2 diabetics and healthy population. MBL levels can thus be used to stratify patients according to disease severity and make therapeutic decisions easier for the physicians. Ratio of Triglyceride to HDL-Cholesterol which has been linked with CVD will also be compared with MBL levels to predict disease outcome in type 2 diabetics. Association of MBL with glycemic control, kidney functions and lipid profile parameters can help to identify high risk patients at a much earlier stage.

MATERIAL AND METHODS

This study was conducted at Chughtai Institute of Pathology from July 2019 to January 2020 after approval from Institutional Review Board of CIP under letter number CIP/IRB/1004. Sample size was calculated by using the formula n = [DEFF*Np(1-p)]/ [(d2/Z21-α/2*(N-1)+p*(1-p)]from Open Epi, Version 3, open source calculator with 95%CI.This was a cross sectional study . Two hundred subjects with type 2 Diabetes Mellitus diagnosed according to the criteria laid by American Diabetes Association along with one hundred healthy controls were included in the study[11] after explaining the nature of the study to them and taking informed consent. Diabetic patients with kidney diseases other than diabetic nephropathy, malignancy, familial hyperlipidemias and active infections were excluded from the study. Fasting blood sample was drawn from both groups and was immediately brought to the laboratory for analysis or stored at -20^0 C if early analysis was not possible. Blood samples were analyzed for hs-CRP, HbA1c, creatinine, Total Cholesterol, Alanine amino transferase (ALT), HDL-C (HDL-Cholesterol), LDL-C (LDL-Cholesterol), Glucose, Triglyceride, and Mannose Binding lectin. All analytes except MBL were measured at fully automated chemistry analyzer (Abbott Alinity ci and Roche Cobas 6000). Serum levels of MBL were measured using ELISA (Enzyme linked immunoassay). Estimated Glomerular Filtration rate (eGFR) was the calculated parameter. Data was analyzed via Graph Pad Prism 5 and SPSS version 23.0.

RESULTS

Clinical And Demographic Features Of Both Study Groups:

The diabetic group consisted of 200 cases including 80 females and 120 males and 100 healthy controls consisted of 51 females and 49 males. Mean age of the participants was 47.9 years (SEM 0.793) in

diabetic group and 39.3 years (SEM 1.348) in healthy controls. There was a significant difference among the levels of HbA1c,Fasting Glucose, LDL-C, TG, HDL-C, creatinine and eGFR the healthy and diseased group.Mean Triglycerides/HDL ratio in Diabetes group was 5.28 ± 0.325 compared to control 3.23 ± 0.189. Gender frequency is given in Fig-1 and Clinical variables in terms of means and standard deviation (SD) in both study groups are given in Table-1.

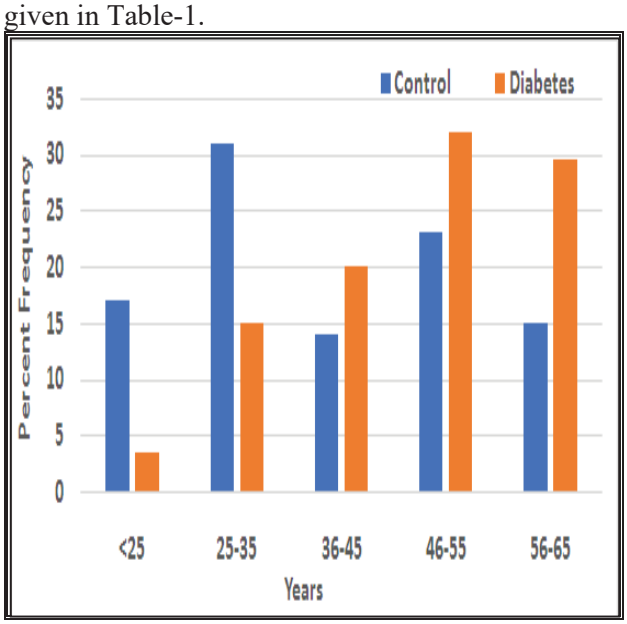


Fig-1: Age frequency in the Study Groups (percentage frequency of age in years)

Clinical Variable	Control (Mean & SD)	Diabetes (Mean & SD)	P – value
Fasting glucose mg/dl	89.7± 1.088	149.9± 4.331	0.000
HbA1c	5.2± 0.030	7.9± 0.137	0.000
Mannose Binding Lectin pg/ml	110.1± 3.944	197.9± 12.840	0.000
Total cholesterol mg/dl	172.7± 3.369	180.2± 3.171	NS
LDL mg/dl	117.7± 3.420	121.0± 2.860	NS
HDL mg/dl	41.5± 0.834	38.3± 0.680	0.005
Non-HDL mg/dl	132.8± 3.719	141.7± 3.049	NS
Triglycerides mg/dl	123.3± 5.424	181.0± 8.218	0.000
eGFR m/min/1.73m 2	108.5± 2.008	99.0± 1.403	0.000
CRP mg/dl	0.6± 0.061	0.8± 0.085	NS
Creatinine mg/dl	0.8± 0.023	0.8± 0.170	0.032
ALT U/L	30.9± 1.728	36.5± 1.982	NS

Table-1: Clinical Variables in Type 2 Diabetics and Healthy Controls

Mannose Binding Lectin In Study Groups And Diabetic Sub Groups:

In our study baseline serum Mannose Binding Lectin in healthy control group ranged between 43 and 178pg/ml whereas in Diabetes group it ranged between 78 and 1291pg/ml (Mean values and SDs are given in Table 1). Mann Whitney test showed that MBL was significantly elevated in diabetic group as compared to healthy controls. Distribution of MBL on the basis of age and gender is given in Figure 2. The onset of pre-diabetes and diabetes among Pakistan population has been reported around 40 years[30]. Hence, we used 40 years as the cut-off age to further analyze the concentration of MBL among the diabetics (Fig-2 C).

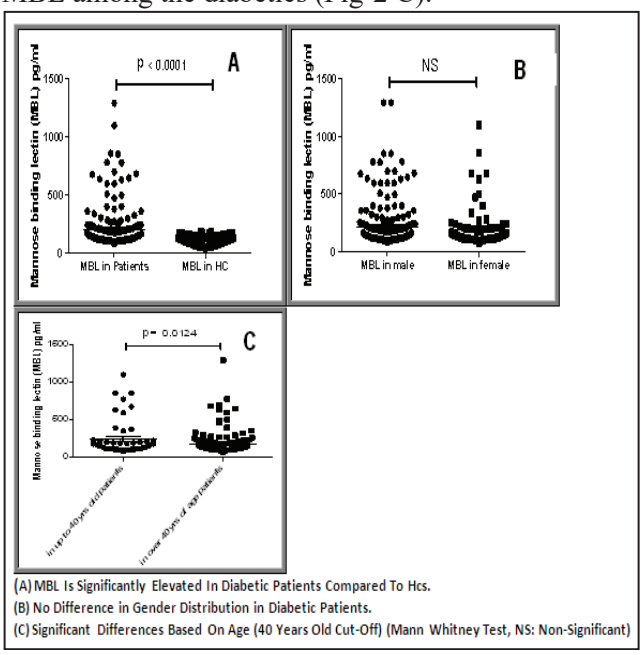


Fig-2: Distribution of Mannose Binding Lectin in study population.

(A) MBL Is Significantly Elevated In Diabetic Patients Compared To Healthy Controls.

(B) No Difference in Gender Distribution in Diabetic Patients.

(C) Significant Differences Based On Age (40 Years Old Cut-Off) (Mann Whitney Test, NS: Non-Significant)

Correlation of MBL with Age and Clinical Parameters amongst Study Groups:

Correlation between the study groups was found with the help of Spearman non parametric correlation coefficient. In healthy controls, MBL was negatively correlated with age (A), plasma glucose (B) and positively correlated with HDL-Cholesterol (C) (Fig-3). Except correlation with plasma glucose which was highly significant, all other correlations were modest but still significant (Fig-3).

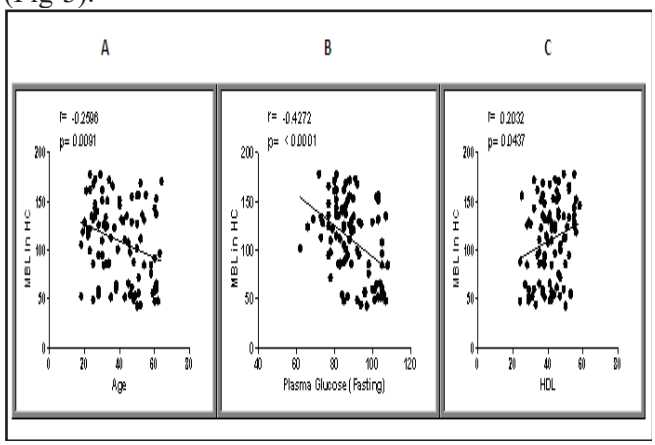


Fig-3: Correlation of Mannose Binding Lectin with Age, Glucose and HDL-C in Healthy controls

Albeit weak, sera levels of MBL significantly **inversely** correlate with HbA1c, plasma glucose, triglycerides and Triglyceride/HDL ratio in diabetic patients (Figure 4). There was no correlation of MBL with other clinical parameters like ALT, creatinine, eGFR, Total cholesterol and LDL in both healthy and diseased population.

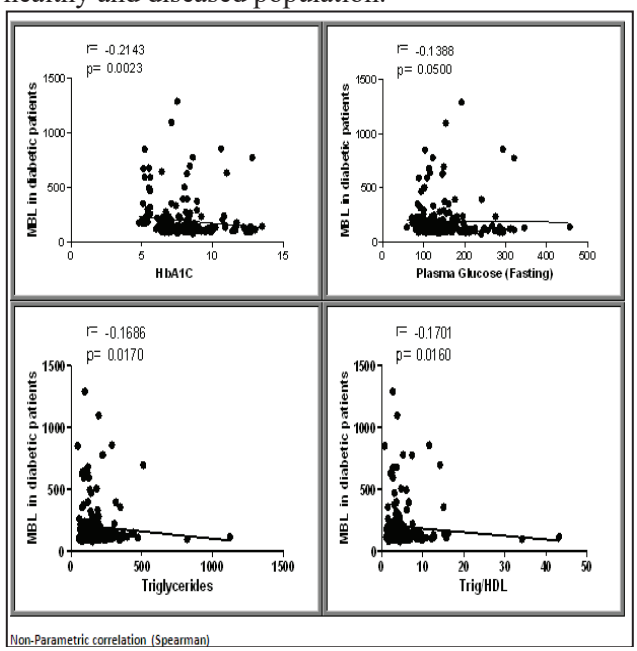
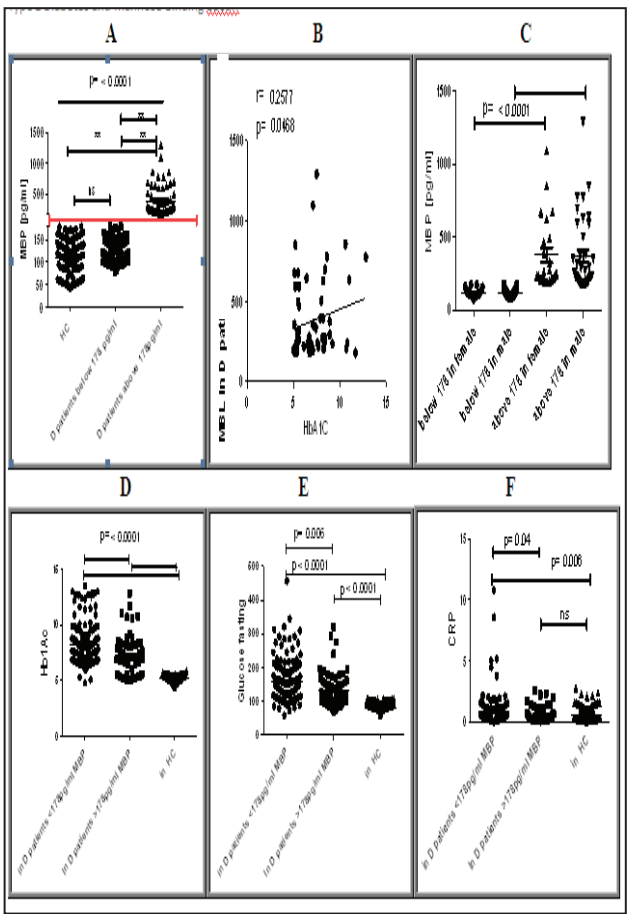


Fig-4: MBL correlation with clinical variables in diabetic group

We further divided the diabetics into two sub groups on the basis of a cut off level of MBL of 178 pg/ml i.e. Diabetic patients with MBL less than 178pg/ml (D1) and Diabetic patients with MBL more than 178pg/ml (D2) as there was no overlap of MBL values above 178pg/ml in both study groups. We then compared the clinical parameters between the divided diabetic group and healthy controls. There was a positive correlation of HbA1C with MBL in diabetic patients having MBL above 178pg/ml and there was a significant difference between the MBL levels of the male and females using 178pg/ml as the cut off. Also, there was a significant difference in the fasting Plasma Glucose, Triglyceride and HbA1c levels between the healthy controls and two diabetes subgroups, within the subgroups, with D1 having higher HbA1c as compared to D2. CRP was significantly higher in D1 as compared to D2 and healthy controls but no significant difference was found between the CRP levels of D2 and controls i.e. CRP in the healthy population resembles levels in patients with elevated MBL. Only the ratio Trig/HDL is higher in the above 178pg/ml (D2) compared to the below 178 pg/ml group (D1) (Fig-5)



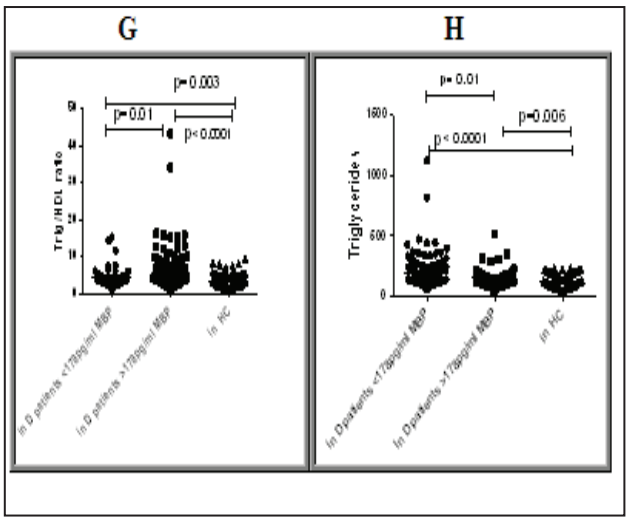


Fig-5: Comparison of clinical parameters between healthy controls and diabetes subgroups on the basis of MBL levels.

(*MBP {Mannose Binding Protein} can be used interchangeably with MBL

***In this figure Group labelling has not been used. Group description of D1 and D2 has been given instead)**

DISCUSSION

Number of adult individuals with type 2 Diabetes mellitus is increasing day by day in Pakistan with a pooled prevalence of 13.7%[12]. Diabetes affects the quantity and quality of patient's lives along with a financial burden on the families. IDF Diabetes Atlas 2017 (International Diabetes Federation) ranks Pakistan at 10th position out of 221 countries of the world with 7.5 million cases affected by Diabetes[13]. The total number of diabetes cases is projected to substantially surge in the coming years with associated rise in CVD and kidney failure. All this will produce substantial financial and monetary burden on the community particularly in the developing countries like Pakistan. There is an utmost need to find a biomarker having a direct role in the pathogenesis of DM and which can identify patients at increased risk of developing complications as a result of diabetes.

In our study we determined the serum MBL levels in type 2 diabetes patients and healthy controls and found a significant statistical difference between the values of the two groups. This is in accordance with the findings of Guan and his colleagues who stated that there was a significant difference between the MBL values of diabetic patients with nephropathy as compared to healthy group[14]. Another study mentioned that the serum MBL levels were more elevated in diabetes patients with complications suggesting that pathogenesis of diabetes related complications have a direct relation with MBL[15]. Hansen with his colleagues followed diabetes patients for 15 years and suggested that serum MBL can prove to be a prognostic marker and provide valuable information regarding development of complications[16].

We also compared MBL levels in healthy controls with CRP, HbA1c, creatinine and parameters of lipid profile in which MBL showed negative correlation with glucose and positive correlation with HDL-C in healthy population. In our study a positive correlation was seen between HbA1c and serum MBL in diabetic group (cut off was 178pg/ml serum MBL) which is similar to the findings given by Guan et al who demonstrated a positive correlation between HbA1c and MBL[14]. The researchers in this study mentioned that there was a significant statistical difference between the clinical variables in the diabetic group and healthy controls which is similar to the present study. Another study shows parallel results with positive correlation of MBL with HbA1c levels in diabetic patients[15]. This was further elaborated in our study by comparing the subgroups of diabetes with healthy controls showing significant differences. We demonstrated that patients with MBL>178pg/ml had CRP levels similar to healthy controls. This is similar to the findings of Hansen et al who reported that there was no correlation of CRP levels with MBL among the diabetics[16]. A recent study showed that elevated MBL depicts poor glycemic control and increased risk of development of complications especially in the presence of high levels of CRP[17].

Serum MBL levels can induce the release of inflammatory mediators cytokines like TNF-alpha along with IL-1 and IL-6[18]. Decreased MBL levels are associated with insulin resistance, increased body weight and can have a modifying effect on inflammatory response[19,20].

We demonstrated a significantly higher triglyceride to HDL ratio in the diabetic population having MBL above 178pg/ml. Studies reveal that Trig/HDL-C ratio has a strong association with extent of coronary artery disease and is proved to be an independent predictor of myocardial injury[21]. This ratio has also been evaluated to predict glycemic control among type 2 diabetes patients and was found to be significantly positively correlated with HbA1c levels higher than 7% [22]. The findings of our study with positive correlation of higher MBL levels with HbA1c and Trig/HDL ratio may point towards the association of MBL with increasing risk of cardiovascular disease amongst diabetics with higher MBL levels. This has been postulated in other studies as well in which a higher MBL has been reported in type 1 diabetic patients with history

of cardiovascular disease and higher MBL levels have been associated with greater risk of development of atherosclerosis[16,23]. There is also evidence that MBL has a major contributing role in reperfusion injury in type 2 cardiac pathology with reports of decreased myocardial infarct size when treatment with complement inhibitors was initiated[24]. A recent study investigated the association between MBL and CVD among diabetic population and found that both elevated serum MBL levels and increased expression of MBL genotype are an independent risk factor for development of CVD in type 2 diabetes patients[25].

Biological linkage between MBL and pathogenesis of diabetes is still unclear; complement activation can play a protective role and MBL can promote anti-inflammatory actions in association with apoptotic cell clearance [26]. On the other hand, it can exacerbate inflammatory tissue damage which its activity is not regulated [27]. Not all the patients with diabetes develop complications suggesting that factors other than glycemic control are required for the development of complications. In our study there was a significant distinct difference in the serum MBL levels of healthy population and type 2 diabetics which might suggest differences in MBL genotype distribution. We demonstrated a negative correlation of blood glucose levels with MBL suggesting that in healthy controls MBL remains at a lower level with tight glycemic control. In diabetic group, patients with MBL greater than 178pg/ml had a significant positive correlation with HbA1c which shows that poor glycemic control can be associated with increased MBL. Studies report that carbohydrate recognition domains of MBL may show less efficiency with poor glycemic control and there is compromised complement activation [28]. In our study CRP levels were mimicking healthy population in diabetic group with higher MBL levels which is similar to the findings of a recent study in which the authors stated that MBL and CRP may carry out different type of roles in inflammatory activity[14]. Complement activation in diabetes contribute to increased risk of complications in diabetes and MBL can exacerbate this effect by playing major role in complement regulation and initiation of oxidative stress. Also, MBL related enzymes can have a triggering effect on coagulation cascade and this result in increased risk of complications[29]. MBL can identify patients who are at a greater risk of developing nephropathy. MBL estimation can be an important addition to the currently available tests for diabetes. Studies have shown that elevated MBL levels had a greater discriminatory ability than CRP, HbA1c and creatinine to predict diabetic nephropathy with an AUC of 0.809 (95%CI, 0.769–0.848) [14] . Hansen et al reported that MBL alone can provide valuable prognostic information on mortality and development of nephropathy [17]. MBL levels depend predominantly on genotype and this can be used to stratify patients by simply analyzing genotypes of patients at an earlier stage. It has been found that renal functions deteriorate more rapidly in patients with high MBL genotype expression and thus an estimation of genotype and be used to stratify diabetics into high risk and low risk cases [30]

Our study had some limitations also. The medical history of patients was not collected related to past medical events, family history, medication history and all these can alter MBL levels among patients. We suggest serial measurement of MBL which can help in risk stratification of type 2 diabetes patients. Further studies in our population can help health care physicians to predict risk of complications in diabetic population and whether changes in treatment can alter MBL levels indirectly denoting a better patient outcome. MBL values given in the study needs to be confirmed by further studies because the MBL levels, although high, are not the same in different populations of the world. Reasons might be the different kits used, study conducted on different set of population, different environmental and genetic factors, all of which have to be further elaborated.

CONCLUSION

Both increased and decreased MBL levels have a role in pathophysiology of diabetes mellitus. We found that serum MBL was significantly higher in the diabetic group as compared to healthy controls and diabetic patients with elevated MBL having positive correlation with HbA1c showing association of glycemic control with MBL levels. A direct relationship of MBL with development of cardiovascular complications in type 2 diabetics was suggested by a positive association of MBL with TG to HDL-C ratio. High risk groups can be identified by analyzing MBL in laboratory as MBL levels vary significantly based on glycemic control and lipid profile parameters.

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The Authors:

Dr. Hijab Batool,
Consultant Pathologist,
Department of Clinical Chemistry and Immunology,
Chughtai Institute of Pathology,

Dr. Muhammad Dilawar Khan,
Professor of Chemical Pathology,
Department of Clinical Chemistry and Immunology,
Chughtai Institute of Pathology,

Dr. Omar Rasheed Chughtai,
Assistant Professor of Histopathology,
Director Operations,
Chughtai Institute of Pathology,

Sana Rafaqat,
Medical Technologist,
Department of Clinical Chemistry and Immunology,
Chughtai Institute of Pathology,

Dr. Fouzia Sadiq,
Research Director,
Shifa Tameer-e-Millat University,
Pitras Bukhari Road, Islamabad, Pakistan,

Dr. Hafiz Muhammad Bilal,
Resident Pathologist,
Department of Clinical Chemistry and Immunology,
Chughtai Institute of Pathology,

Corresponding Author:
Dr. Hijab Batool,
Consultant Pathologist,
Department of Clinical Chemistry and Immunology,
Chughtai Institute of Pathology.
Email: dr.hijabbatool@cll.edu.pk