The predictive value of serum *mannan-binding lectin* levels for diabetic control and renal complications in type 2 diabetic patients

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ABSTRACT

الأهداف: تقييم العلاقة بين تركيز الليكتين الرابط للمنان في مصل الدم والالتهابات الناتجة عن داء السكري من النمط الثاني، بالإضافة إلى تقييم علاقته بنسبة التحكم بمستوى السكر في الدم.

الطريقة: أُجريت هذه الدراسة المقطعية المقارنة في قسم أمراض الباطنة والباثولوجيا السريرية في كلية الطب التابعة لجامعة بنها، بنها، مصر، واستمرت خلال الفترة من أكتوبر 2009م إلى ديسمبر 2010م. شملت الدراسة 60 مريضاً مصاباً بداء السكري من النمط الثاني، وقد تم تقسيمهم إلى مجموعتي الدراسة وهما المجموعة ب وسي، بالإضافة إلى مجموعة الشاهد السليمة وهي المجموعة أ. لقد قمنا بعمل مجموعة من الاختبارات لكافة المشاركين في الدراسة وهي كالتالي: تقييم حساسية الجسم للأنسولين باستخدام مؤشر مقاومة الأنسولين بنموذج الاستتباب، ومستوى غلوكوز الدم أثناء الصيام، والهيموغلوبين السكري، والأنسولين، واليوريا، والكرياتينين، وبروتين سي التفاعلي، والليكتين الرابط للمنان.

النتائج: أشارت نتائج الدراسة إلى زيادة مستويات غلوكوز الدم أثناء الصيام، والأنسولين، ومؤشر مقاومة الأنسولين بنموذج الاستتباب، وبروتين سي التفاعلي، والليكتين الرابط للمنان لدى المرضى في مجموعتي الدراسة مقارنةً مع مجموعة الشاهد، مع ملاحظة زيادة ارتفاع هذه المستويات في المجموعة سي. ولقد كانت مستويات الهيموغلوبين السكري، واليوريا، والكرياتينين أعلى لدى المرضى منها لدى المشاركين في مجموعة الشاهد. وقد كان هناك علاقة طردية واضحة بين الليكتين الرابط للمنان ومستويات كلاً من: غلوكوز الدم أثناء الصيام، ومؤشر مقاومة الأنسولين بنموذج الاستتباب، واليوريا، والكرياتينين، وبروتين سي التفاعلي. وأشار منحنى خصائص تشغيل المتلقي لدى المرضى المصابين بالالتهابات إلى زيادة مستويات غلوكوز الدم أثناء الصيام، ومؤشر مقاومة الأنسولين بنموذج الاستتباب، وبروتين سي التفاعلي، والليكتين الرابط للمنان، فيما أثبت تحليل الانحدار إمكانية الاعتماد على زيادة مستويات الليكتين الرابط للمنان واعتبارها مؤشراً مستقلاً للاستدلال على ظهور الالتهابات المصاحبة لداء السكري.

خاتمة: أثبتت الدراسة أن ارتفاع مستويات الليكتين الرابط للمنان لدى المرضى المصابين بداء السكري من النمط الثاني قد يدل على ضعف نسبة التحكم بهذا المرض، بالإضافة إلى تفاقمه وتطوره إلى مضاعفات أخرى كأمراض الكلى وخصوصاً عند ارتباط ذلك بارتفاع مستويات بروتين سي التفاعلي.

Objectives: To evaluate the predictability of estimation of serum *mannan-binding lectin* (*MBL*) for the presence of infectious complications in type 2 diabetes mellitus (T2DM) and its relation to the extent of diabetes control.

Methods: A comparative cross-sectional study was conducted at the Departments of Clinical Pathology and Internal Medicine, Faculty of Medicine, Benha University, Benha, Egypt from October 2009 to December 2010. Sixty adult patients with T2DM were divided into 2 groups: Group B and Group C and Group A as the control group. All subjects evaluation of insulin sensitivity (Homeostasis Model Assessment of Insulin Resistance [HOMA-IR]), and blood samples for estimation of fasting blood glucose (FBG), glycosylated hemoglobin A1c (HbA1c) and serum insulin, urea, creatinine, C-reactive protein (CRP), and MBL.

Results: All patients had significantly increased FBG, serum insulin, HOMA-IR index, serum CRP and MBL levels compared with the control group, with significantly higher levels in Group C. Levels of HbA1c, serum urea, and creatinine were significantly higher in patients than controls. There was a positive significant correlation between serum MBL and FBG, HOMAIR index, serum urea, creatinine, and CRP levels. The receiver operating characteristics curve analysis in infectious cases revealed high FBG, HOMA-index and serum levels of HbA1c, CRP, and MBL, while regression analysis defined elevated serum MBL levels as a significant independent predictor for the presence of infection.

Conclusion: Elevated serum *MBL* in T2DM patients indicated a possible poor diabetic control and bad progression of the disease with possibility of the presence, or development of diabetic nephropathy especially in combination with elevated serum CRP.

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When endogenous insulin secretion is inhibited and high plasma glucose concentration is maintained, this ultimately causes profound proinflammatory condition, as glucose is known to be a proinflammatory substance.[1,2] Among the possibilities implicated in poor outcomes from hyperglycemic states are disruption of normal mitochondrial respiration, accumulation of asymmetric dimethyl arginine, impairment of immune function, and direct glucose toxicity.[3] The complement system has evolved as a central part of the innate immune defense against invading microorganisms. On activation, however, complement may cause damage to innocent by-stander cells through deposition of the membrane attack complex, and initiate inflammation via release of the anaphylatoxins C5a and C3a.[4] *Mannan-binding lectin* (*MBL*), a liver-derived protein, is a member of a family of Ca^{2+}-dependent collagenous lectins, and most of which are components of the innate immune system.[5] The *MBL* has a high affinity for N-acetyl glucosamine, a component of peptidoglycan, present on the surface of microbes, but not on human cells. Upon binding, *MBL* mediates deposition of complement factors using *MBL*-associated serine proteases for activation of the lectin pathway of the complement cascade.[6] The *MBL* gene coding region show some variant alleles, which results into low *MBL* serum concentration, and also impairment in the function, which is in turn associated with different diseases and complications.[7] Functioning as double-edged sword, functional *MBL* deficiency occurs in as many as 10% of the normal population, and these individuals may be at increased risk of infections.[8] However, high *MBL* serum levels and high *MBL* activity have been associated with inflammatory diseases, transplant rejection, and nephropathy in type I diabetics. Furthermore, both high and low serum *MBL* levels are associated with several aspects of autoimmune diseases.[9] Debatable results are gained when the role of *MBL* was studied in bacterial infections. Mutations in the *MBL* gene, has a direct effect on the susceptibility to infection in systemic lupus erythematosus and human immunodeficiency virus infection.[10] This is beside the fact that, with patients who are homozygotes for *MBL* variants, they are prone to invasive infections by *Streptococcus pneumoniae*.[11] Cui et al,[12] found increased C3 and *MBL* levels in serum might play a modulatory role in chronic rhinosinusitis development, while immunoglobulin and C4 *MBL* deficiency is not the main cause of chronic rhinosinusitis in adult patients. The present study aimed at evaluating the relation of serum *MBL* concentration to the extent of diabetic control, as well as the prediction of development of infectious and chronic inflammatory complications in patients with type 2 diabetes mellitus (T2DM) in order to be used as a marker for the occurrence, and progression of the diabetic inflammatory complications.

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Methods. This observational comparative cross-sectional study was conducted at the Departments of Clinical Pathology and Internal Medicine, Faculty of Medicine, Benha University, Egypt from October 2009 to December 2010, including 60 T2DM patients, and 30 age- and gender-matched healthy volunteers as a control group. The research ethical committee of our institution approved the conduction of this study. Patients and controls were informed of the study. They comprised information of the aims and the importance of the study, the voluntary nature of the study, and the procedures of the study (including the steps that the volunteers have to undergo, and the time they have to spend during the study). The T2DM patients, both male and female of any body mass index (BMI) were treated with diet control, oral hypoglycemic drugs, and/or insulin were included in this study, however, patients with type 1 diabetes, patients in whom secondary diabetes is suspected, women with gestational diabetes, and patients receiving drugs that might affect the blood sugar levels all were excluded from this study. The patients and control individuals were categorized into 3 groups: Group A - control group, includes 30 age- and gender-matched healthy volunteers chosen from those attending the hospital's blood bank, and passed the preliminary pre-donation investigations, and provided blood samples; Group B - includes T2DM patients who attended the outpatient clinic for follow-up, or for complaints of diabetic complications other than infections (n=30); and Group C - includes T2DM patients who attended the outpatient clinic complaining of infectious complications (n=30). After obtaining a written consent from patients and controls, patients were subjected to a full history taking and thorough physical examination. Insulin sensitivity of both control and study groups was evaluated using Homeostasis Model Assessment of Insulin Resistance (HOMA-IR)[13] test on the basis of fasting insulin and glucose levels, and according to the formula HOMA-IR= I x G/22.5, where I is fasting plasma insulin level (mcIU/ml), and G is fasting blood glucose in mg/dl divided by 18, considering an abnormal HOMA-index greater than 2.[14] Whole blood (10 ml) samples were obtained from patients and controls after at least 12 hours fasting. One ml blood was

collected on 50 ul of 3.8% ethylenediaminetetraacetic acid solution for glycosylated hemoglobin (HBA1c) determination (HBA1c was measured by cation exchange chromatographic/spectrophotometric method (Biosystems SA, Barcelona, Spain). Serum was separated by centrifugation and divided into 2 parts; the first part was used for determination of serum fasting blood glucose (FBG) level, serum urea, and serum creatinine (measured by Dimension ES clinical chemistry autoanalyzer (Dade Behring Inc, NE, USA). Serum insulin using an enzyme linked immunosorbent assay (ELISA)-kit supplied by INS-EASIA DIA SOURCE KAP 1251. This method is a solid phase enzyme amplified sensitivity immunoassay. The assay uses monoclonal antibodies directed against distinct epitopes of insulin. Calibrators and samples react with the capture monoclonal antibodies (MAP-1) coated on microtiter well, and with a monoclonal antibody (MAP-2) labeled with horseradish peroxidase (HRP). After an incubation period allowing formation of a sandwich, the microtiter plate is washed, then chromogenic solution (TMP) is added.The reaction is stopped by adding a stop solution, and the microtiter plate is read at 450 nm.[15] Serum C-reactive protein (CRP) level was estimated by nephelometry (BNAII, Dade Behring,® Marburg, Germany). The cut-off point used to detect abnormal values was more than 3 mg/dl, as suggested by the CRP kit manufacturer.[16] The second part of serum sample was placed in pyrogen-free Eppendorf tubes, and stored at -80°C until assayed for serum concentrations of *MBL* by ELISA using a commercial kit (oligomerized *MBL* [AntibodyShop,® Gentofte, Denmark]). The ELISA was performed in microwells coated with a monoclonal antibody against the MBL carbohydrate-binding domain in antibodies in coating buffer (100 mM Na_2CO_3/$NaHCO_3$, pH 9.6) for 16 hours at room temperature. After each step, plates were washed 3 times with phosphate-buffered saline (PBS) containing 0.05% Tween 20. Residual binding sites were blocked by incubation with PBS containing 1% bovine serum albumin (BSA). All subsequent steps were incubated for one hour at 37°C in PBS containing 0.05% Tween 20 and 1% BSA. Detection antibodies were conjugated to digoxigenin (Dig) using Dig-3-O-methylcarbonyl-ε-aminocaproic acid-N-hydroxysuccinimide ester (Boehringer, Mannheim, Ingelheim, Germany) according to instructions provided by the manufacturer. Detection of binding of antibodies conjugated to Dig was performed by horseradish peroxidase (HRP)-conjugated sheep anti-Dig antibodies (Fab, Boehringer Mannheim, Ingelheim, Germany). Enzyme activity of HRP was detected using 2,2'-azino-bis(3-ethylbenzthiazoline-6-sulphonic acid). The optical density (OD) at 415 nm was measured using a microplate biokinetics reader (EL312e; Biotek Instruments, Winooski, VT, USA). All incubation volumes were 100 mcl/well. All sera were analyzed in duplicates in at least 2 dilutions. The *MBL* concentrations in serum were expressed as ng/ml.[17]

Informed consent was obtained from all participants. Only individuals who accepted to participate were included in the study. The consent included data on the objective of the work, participants were informed that all data will be confidential, and are collected for the sake of scientific research only. No harmful techniques or interventions will be applied. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. This study was conducted according to the principles of Helsinki Declaration.

Obtained data were presented as mean ± standard deviation, ranges, numbers, and ratios. Results were analyzed using Wilcoxon Signed Ranks Test for comparisons between groups. The receiver operating characteristic (ROC) curve analysis judged by the area under the curve (AUC) was used to evaluate various parameters as predictors for the presence of infectious complications. All reported AUC were compared versus the null hypothesis (true area=0.5), and the evaluated parameter is proven to be diagnostic and specific if the AUC was significantly different compared to the true area. Regression analysis (stepwise method) was used for evaluation of the significant predictors. Data were analyzed using the Statistical Package for Social Sciences version 10 for Windows (SPSS Inc, Chicago, IL, USA). $P<0.05$ was considered statistically significant.

Results. The study enrolled 60 type 2 diabetic patients, and 30 volunteers of cross-matched age and gender as control group. There was no significant difference between patients and controls with regard to age, weight, and BMI. All studied T2DM patients had significantly higher FBG and serum insulin levels, and subsequently significantly higher HOMA-IR index compared to the control group. Group C patients also had significantly higher FBG and insulin levels compared to the Group B patients. The percentage of HbA1c was significantly higher in Groups B and C compared to the control group, but no significant differences could be observed regarding the HBA1c percentage in Group C compared to Group B patients. Also, mean serum urea and creatinine levels were significantly higher in Groups B and C compared to the control group with non-significantly higher levels in Group C compared to Group B patients. On the other hand, the mean serum CRP and *MBL* levels were significantly higher in Groups B and C compared to the control group

with significantly higher levels in Group C compared to Group B (**Table 1**). Fifteen patients in Group C had serum *MBL* level higher than the median value for the group, which is equal to 983.5 ng/ml, however, 8 patients had high serum *MBL,* but serum CRP was below the level of the median level for Group C, which is equal to 47.5 mg/dl, while the other 7 patients had serum level of both MBL and CRP higher than the corresponding median value. The other 15 patients of Group C had serum MBL level below than the median value, and 8 of them had serum CRP higher than its median level (**Table 2**). There was a positive significant correlation between serum MBL and FBG (r=0.438, p=0.001), HOMA-IR index, (r=0.287, p=0.026), serum urea (r=0.255, p=0.049), serum creatinine (r=0.389, p=0.002), and serum CRP (r=0.373, p=0.003).

Statistical analysis using the ROC curve analysis of clinical and laboratory data for the predictability for presence of infection anywhere in the body defined high FBG, HOMA-index, and serum levels of HbA1c, CRP, and MBL as specific predictors with AUC that was significant versus the null hypothesis that the true AUC=0.5, however these parameters showed the same significant value (p<0.001) (**Table 3, Figure 1**). Verification of the significant diagnostic yield of the studied clinical and laboratory data using the regression analysis (stepwise method) defined elevated serum MBL levels as a significant (p=0.0009, p=0.0007, p=0.0007, p=0.0003) independent predictor for the presence of infection elsewhere in the body, and its high significant predictability was evident in 4 models, followed by FBG in 3 models (p=0.006, p=0.005, p=0.0009), serum CRP in 2 models (p=0.007, p=0.009), and lastly serum creatinine in one model (p=0.026).

Discussion. Various functional disorders of the immune system reflect innate, genetically determined defects that lead to the temporary, or permanent impairment of the immunity. The *MBL* is considered to be particularly important for protection against infection, especially in patients with immuno-compromising diseases.[18] The *MBL* dysfunction has been associated with an increased susceptibility to numerous infectious diseases. Moreover, an association between *MBL* dysfunction and complications of infections including disseminated intravascular coagulopathy as a fatal sequelae for severe or uncontrollable infections.[19] The obtained results of the current study showed

Table 1 - Mean ± standard deviation levels of estimated parameters in studied groups.

Parameters	Control (Group A)	Non-infectious complications (Group B)	Infectious complications (Group C)	Significance of differences
Fasting blood glucose (mg/dl)	90.7 ± 8 (78-105)	257.1 ± 32.6 (195-325)	337.1 ± 67.7 (250-515)	P_1=0.0005 P_2=0.0003 P_3=0.0009
Serum insulin (mcIU/ml)	1.89 ± 0.45 (1.05-2.62)	4.85 ± 0.74 (3.2-5.8)	5.76 ± 1.67 (4.1-9.8)	P_1=0.0008 P_2=0.0006 P_3=0.002
HOMA-IR score	0.43 ± 0.13 (0.22-0.68)	3.08 ± 0.62 (2.09-4.57)	4.99 ± 2.49 (2.75-11.7)	P_1=0.0003 P_2=0.0001 P_3=0.0007
Glycosylated hemoglobin (%)	4.91 ± 0.37 (79-95)	8.39 ± 1.13 (6.2-9.9)	9.06 ± 1.21 (6.9-13.2)	P_1=0.0007 P_2=0.0005 P_3=0.073
Serum urea (mg/dl)	28.9 ± 2.6 (25-34)	38.6 ± 5.8 (30-52)	41.8 ± 7.6 (36-62)	P_1=0.0009 P_2=0.0007 P_3=0.084
Serum creatinine (mg/dl)	0.8 ± 0.14 (0.4-1)	1 ± 0.05 (0.9-1.08)	1.1 ± 0.11 (0.9-1.32)	P_1=0.028 P_2=0.026 P_3=0.088
Serum C-reactive protein (mg/dl)	4.4 ± 2.2 (1.9-8.6)	11.4 ± 7.3 (4.5-23.8)	57.3 ± 29.1 (23-135)	P_1=0.078 P_2=0.0009 P_3=0.007
Serum *mannan-binding lectin* (ng/ml)	215.6 ± 46.7 (135-295)	721 ± 174.9 (348-985)	1026 ± 201.7 (742-1650)	P_1=0.003 P_2=0.0009 P_3=0.017

Data are presented as mean ± standard deviation, ratios, and ranges in parenthesis, P_1 - significance of difference between Groups A and B, P_2 - significance of difference between groups A and C, P_3 - significance of difference between Groups B and C, HOMA-IR - Homeostasis Model Assessment of Insulin Resistance

Table 2 - Patients of infectious complicated group categorized according to median level of their serum *mannan-binding leptin* (*MBL*) level, and their corresponding serum CRP levels.

Category	Serum MBL	Serum CRP	*P*-value
Serum MBL more than median value (983.5 ng/ml)			0.0001
8	1229.1 ± 229.2 (985-1650)		
7	1092.4 ± 113 (996-1265)	75 ± 31.5 (48-128)	0.0002
Serum MBL less than median value (983.5 ng/ml)			0.00001
8	875.9 ± 83.3 (742-980)	34.8 ± 4.7 (29-42)	
7	898.9 ± 73.5 (785-982)	38.4 ± 9.7 (23-47)	0.0001

Table 3 - Receiver operating characteristics curve analysis data of certain variables for their predictability for the presence of infectious complications of type 2 diabetes mellitus as the constant variable.

Variable	Area under curve	Standard error	*P*-value	Asymptomatic 95% confidence interval	
				Lower bound	Upper bound
Age	0.539	0.075	0.075	0.392	0.686
Diabetic age	0.618	0.073	0.081	0.474	0.762
FBG	0.864	0.045	0.0009	0.775	0.953
HOMA index	0.620	0.063	0.001	0.626	0.873
HbA1c%	0.818	0.054	0.0008	0.712	0.923
Serum urea	0.620	0.072	0.08	0.478	0.762
Serum creatinine	0.638	0.073	0.084	0.494	0.782
Serum CRP	0.804	0.063	0.0011	0.681	0.927
Serum MBL	0.891	0.039	0.0009	0.814	0.968

FBG - fasting blood glucose, HOMA - Homeostasis Model Assessment, HbA1c - glycosylated hemoglobin, CRP - c- reactive protein, *MBL - mannan-binding leptin*

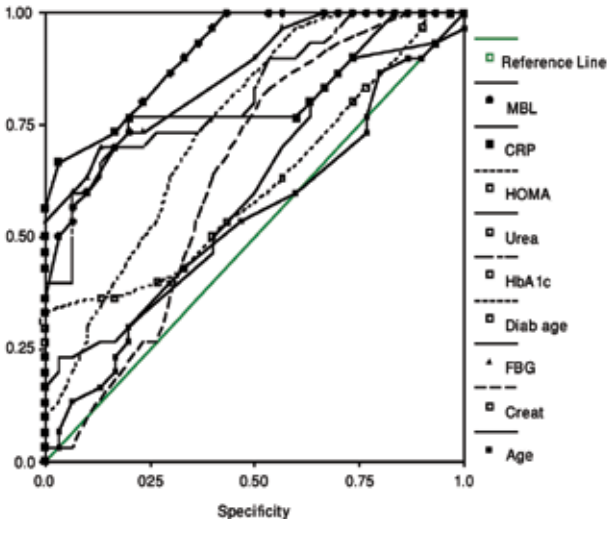

Figure 1 - The receiver operating characteristics curve analysis of estimated parameters as predictors of infectious complications of type 2 diabetes mellitus.

significantly higher serum levels of *MBL* in type 2 diabetics compared to controls, and in type 2 diabetics who had infectious complications compared to those free of infectious complications. The *MBL* serum level showed positive significant correlation with FBG and HOMA-IR index in type 2 diabetics, irrespective of the presence of infection. Despite the non-significant difference between Groups B and C as regards serum HbA1c levels that was significantly higher compared to controls, there was a positive significant correlation between the percentage of HbA1c and serum MBL levels. These data indicated an inverse correlation between serum MBL level and control of diabetes, and subsequently with its severity and liability for complications.

Fortpied et al[20] found using competition experiments, *MBL* had a similar affinity for mannose, fructose, and fructose lysine, and bound in a highly cooperative manner to fructose lysine-derivatized plates, and this

binding was associated with complement activation, and was much lower in serum from subjects with low-*MBL* genotypes, and concluded that *MBL* binding to fructoselysine and the ensuing complement activation, may provide a physiopathological link between enhanced glycation and complement activation in diabetes, and the cooperative character of this binding may explain the high sensitivity of diabetic complications to hyperglycemia. The reported higher levels of serum *MBL* in studied patients, irrespective of the presence of infectious complications, indicated a role for *MBL* in pathogenesis and/or aggravation of the diabetic status. These data supported that previously reported by Bouwman et al,[21] who found that *MBL* serum concentration and complex activity are increased in early-onset diabetic patients upon manifestation independently of genetic predisposition to high *MBL* production, indicating a possible role in the immunopathogenesis of type 1 diabetes, in addition to the adaptive islet autoimmunity. Serum levels of CRP and *MBL* were significantly higher in diabetics who had infectious complications compared to those free of infectious complications, a finding indicating that both parameters could be used for the evaluation of the presence of infection in diabetic patients. However, there was discrepancy between levels of both parameters in 16 patients.

These data point to a fact that *MBL* could not be considered as one of the primary phase reactants to infection unlike CRP, but illustrated the disturbed innate immune system, and go in hand with Siassi et al,[22] who analyzed the behavior of *MBL* in patients undergoing gastrointestinal resections for malignant disease, and reported that serum *MBL* levels did not rise immediately after surgery, and with Rau et al,[23] who reported that CRP is an acute-phase reactant with well-documented sensitivity that is commonly used to diagnose infectious and inflammatory conditions. In support of the obtained results, Perez-Castellano et al,[24] found no correlation between the levels of MBL and CRP in each phase, or with the pneumonia severity score, and concluded that *MBL* cannot act uniformly as an acute-phase reactant in pneumococcal pneumonia, and its levels do not correlate well with the severity of the pneumonia. Also, Louropoulou et al,[25] found *MBL* acts as a weak acute-phase protein in periodontitis.

The reported association between serum levels of *MBL*, CRP, and creatinine in association with FBG as significant predictors for inflammatory complications in one regression analysis model illustrated the closed circle of deterioration manifested as high FBG, disturbed immune, and kidney functions with release of primary phase reactant, similarly Hansen et al,[26,27] reported that in patients with type 2 diabetes, measurements of *MBL* alone, or in combination with CRP can provide prognostic information on mortality and the development of albuminuria. Also, Østergaard et al,[28] experimentally demonstrated that the degree of kidney alteration as a consequence of diabetes is modified by *MBL,* and these findings support a pivotal role of *MBL* in the development of diabetic kidney disease. Recently, Hansen et al[29] demonstrated that concentrations of both *MBL* and hsCRP are associated with the progression of renal disease in type 1 diabetes.

The major limitation of our study was the low number of samples tested. We strongly recommended that larger studies be performed in the future targeting different groups that allow a more detailed statistical analysis. Finally, the present results would suggest further studies to encourage the use of serum *MBL* as a marker for the occurrence and progression of the diabetic inflammatory complications.

In conclusion, our study shows that a relatively elevated serum *MBL* in type 2 diabetic patients indicated absent control and bad progression of the disease with possibility of presence, or development of diabetic nephropathy and elevated serum MBL levels, in combination with elevated serum CRP indicated concomitant infectious complications.

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