

**ASSOCIATION BETWEEN MANNOSE-BINDING
LECTIN and C-REACTIVE PROTEIN with
DIABETIC NEPHROPATHY IN TYPE 1-DIABETES**

Thesis

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SUMMARY

Type 1 diabetes mellitus is caused by deficiency of insulin secretion due to pancreatic β -cell damage. It is the most common endocrine-metabolic disorder of childhood and adolescence, with important consequences for physical and emotional development. Diabetes complications represent a huge burden for patient and health services. Diabetic nephropathy is one of the most devastating complications in patients with type 1 diabetes, being the most common cause of end-stage renal failure and the major predictor of premature death.

The fight against each single complication has led to significant improvement in diabetes care, especially for micro-vascular complications, yet, they remain a major source of morbidity and mortality. A common approach for the prevention and treatment of diabetes complications relies on the understanding of their complex pathophysiology.

It is generally believed that the pathogenesis of diabetic renal disease is multifactorial, and its progression may involve both low-grade inflammation and activation of the complement system. At present, microalbuminuria is considered the best available non-invasive marker for diabetic nephropathy risk. However, some studies have proved it has inadequate specificity and sensitivity. Thus, more investigations into new risk markers are needed.



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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

وَأَنْزَلَ اللَّهُ عَلَيْكَ
الْكِتَابَ وَالْحِكْمَةَ
وَعَلَّمَكَ مَا لَمْ
تَكُنْ تَعْلَمُ وَكَانَ
فَضْلُ اللَّهِ عَلَيْكَ
عَظِيمًا

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LIST OF CONTENTS

Title	Page No.
List of Tables	i
List of Figures	iii
List of Abbreviations	vi
Abstract	viii
Introduction.....	1
Aim of the Work.....	3
Review of Literature	
• Diabetes mellitus	4
• Diabetic nephropathy	34
• Mannose-binding lectin (MBL).....	75
Subjects and methods	101
Results.....	111
Discussion.....	140
Summary.....	160
Conclusion	168
Recommendations.....	169
References.....	170
Arabic summary.....	—

LIST OF TABLES

Tab. No.	Title	Page No.
Table (1):	Classification of types of DM.....	5
Table (2):	Types of insulin preparations and suggested action profiles	29
Table (3):	The stages of diabetic nephropathy	49
Table (4):	Clinical characteristics of diabetic patients and control group.....	113
Table (5):	Laboratory characteristics of diabetic patients and control group.....	114
Table (6):	Comparison of the clinicopathological characteristics between diabetic patients and control group	117
Table (7):	Comparison between non-complicated and complicated diabetic patients and control group in relation to clinical and laboratory variables.....	119
Table (8):	Comparison between normoalbuminuric and microalbuminuric diabetic patients and control group as regards clinical and laboratory variables.....	122
Table (9):	Comparison between progressors and non- progressors in normoalbuminuric and microalbuminuric diabetic groups as regards clinical and laboratory variables.....	126
Table (10):	Serum MBL levels in relation to clinicopathological characteristics of diabetic patients	130
Table (11):	Comparison between baseline and follow-up serum MBL levels in relation to diabetic complications and subgroups.....	130
Table (12):	Correlation between MBL levels and clinical and laboratory parameters of diabetic patients.....	131
Table (13):	Correlation between MBL levels and clinical and laboratory parameters of diabetic patients.....	132

LIST OF TABLES (Cont...)

Tab. No.	Title	Page No.
Table (14):	Multiple regression analysis of the relation of MBL to clinical and laboratory variables in type 1 diabetic patients	132
Table (15):	Comparison between baseline and follow-up hs-CRP levels in relation to diabetic complications and subgroups	138

LIST OF FIGURES

Fig. No.	Title	Page No.
Figure (1):	Possible mechanism for development of type 1 diabetes	8
Figure (2):	Cellular and molecular mechanisms in the development or prevention of type 1 diabetes	10
Figure (3):	Diagram of the effects of insulin deficiency	16
Figure (4):	Insulin activity profile of some available insulins	30
Figure (5):	Simple schema for the pathogenesis of diabetic nephropathy	37
Figure (6):	Hyperglycemia in Pathophysiology of diabetic nephropathy	39
Figure (7):	Histopathological finding in DN	44
Figure (8):	Algorithm for microalbuminuria screening.....	53
Figure (9):	Disease duration as risk factor DN	59
Figure (10):	Long-Term Monitoring of DN.....	73
Figure (11):	Genetic and functional buildup of MBL	77
Figure (12):	MBL subunit.....	78
Figure (13):	MBL trimer.....	78
Figure (14):	The Lectin Pathway of Complement Activation	83
Figure (15):	Function of complement system.....	85
Figure (16):	MBL recognizes bacterial surfaces by their particular spacing of carbohydrate residues	89
Figure (17):	Mechanism of complement activation in diabetic nephropathy	95
Figure (18):	Pie chart show the percentage of diabetic complications in the diabetic patients group.	112
Figure (19):	Baseline serum MBL levels in all diabetic patients compared with healthy controls.....	115

LIST OF FIGURES (Cont...)

Fig. No.	Title	Page No.
Figure (20):	Disease duration in complicated diabetic patient in comparison with non complicated.	120
Figure (21):	Baseline serum MBL levels in complicated and non-complicated diabetic patients compared with healthy controls.	120
Figure (22):	Box plot figure for baseline MBL levels among normo- and microalbuminuric diabetic patients and control.	123
Figure (23):	Baseline and follow-up serum MBL levels in normoalbuminuric and microalbuminuric diabetic groups.	124
Figure (24):	Blood pressure in normoalbuminuric group and microalbuminuric group in comparison with control group.	124
Figure (25):	Blood pressure in progressors and non progressors diabetic group.	127
Figure (26):	HbA1c in progressors and non progressors diabetic groups.	127
Figure (27):	Serum MBL levels in progressors and non progressors in Normoalbuminuric group and microalbuminuric diabetic group.	128
Figure (28):	Positive correlation between serum MBL levels and random blood glucose (RBG) in type 1 diabetic patients.	133
Figure (29):	Positive correlation between serum MBL levels and HbA1c in type 1 diabetic patients.	133
Figure (30):	Positive correlation between serum MBL levels and serum creatinine in type 1 diabetic patients.	134
Figure (31):	Positive correlation between serum MBL levels and urinary albumin creatinine rate (UACR) in type 1 diabetic patients.	134

LIST OF FIGURES (Cont...)

Fig. No.	Title	Page No.
Figure (32):	Positive correlation between serum MBL levels and high sensitivity C-reactive protein (hs-CRP) in type 1 diabetic patients.	135
Figure (33):	Receiver Operating Characteristic (ROC) curve analysis of MBL for detection of diabetic patients with micro-vascular complications.	136
Figure (34):	The cutoff value of MBL for detection of diabetic micro-vascular complications.	136
Figure (35):	Receiver Operating Characteristic (ROC) curve analysis of MBL for detection of progressors among normoalbuminuric diabetic group.	137
Figure (36):	The cutoff value of MBL for detection of progressors among normoalbuminuric diabetic group.	137
Figure (37):	Baseline and follow-up high sensitivity C-reactive protein (hs-CRP) as regard the progression in normoalbuminuric and microalbuminuric diabetic groups.	138
Figure (38):	Receiver Operating Characteristic (ROC) curve analysis of hs-CRP for detection of diabetic patients with micro-vascular complications.	139
Figure (39):	The cutoff value of hs-CRP for detection of diabetic micro-vascular complications.	139

LIST OF ABBREVIATIONS

Abbrev	Full term
ACE	Angiotensin-converting-enzyme
ACEI	Angiotensin-converting-enzyme inhibitor
ADA	American diabetes association
ADH	Anti-diuretic hormone
AER	Albumin excretion rate
ARBs	Angiotensin receptor blockers
BP	Blood pressure
CKD	Chronic kidney disease
COX-2	Cyclooxygenase 2
CRD	Carbohydrate recognition domain
CRP	C reactive protein
DCCT	The Diabetes Control and Complications Trial
DN	Diabetic nephropathy
EDIC	Diabetes Interventions and Complications
eGDR	Estimated glucose disposal rate
EPO	Erythropoietin
ESRD	End stage renal disease
ET-1	Endothelin-1
GBM	Glomerular basement membrane
GFR	Glomerular filtration rate
HMG-CoA	Hydroxy-3-methylglutaryl-coenzyme A
HRGECs	Human renal glomerular endothelial cells;
I/R	Ischaemia/reperfusion
IDDM	Insulin dependent diabetes mellitus
IgM	Immunoglobulin M
kDa	Unified atomic mass unit unit of atomic mass normally used for the molecular weight

LIST OF ABBREVIATIONS (Cont...)

Abbrev	Full term
KRT	Kidney replacement therapy
LCP	Lectin complement pathway;
LDL	Low density lipoprotein
MA	Microalbuminuria
MAC	Membrane attack complex
MASPs	MBL-associated serine proteases
MBL	Mannose-binding lectin;
mRNA	Messenger Ribonucleic Acid
NF-κB	Nuclear Factor Kappa Beta
NO	Nitrous oxide
NSAIDs	Nonsteroidal anti-inflammatory drugs
PDR	Proliferative diabetic retinopathy
PG2	Prostaglandins 2
PKC	Protein kinase C
PMN	Polymorphonuclear
PTH	Parathyroid hormone
RAAS	Renin-angiotensin-aldosterone system
RF	Rheumatoid factor
ROS	Reactive oxygen species
SLE	Systemic lupus erythematosus
T1DM	Type 1 diabetes mellitus
TGF-β1	Transforming growth factor beta
TNF-α	Tumor necrosis factor-alpha
UAE	Urinary albumin excretion
VEGF,	Vascular endothelial growth factor

ABSTRACT

Background: In diabetes, angiogenesis is disturbed, contributing to proliferative retinopathy, nephropathy and neuropathy. Diabetic nephropathy is one of the most serious complications in patients with type 1 diabetes, being the most common cause of end-stage renal failure and major predictor of premature death. The pathogenesis of diabetic renal disease is multifactorial, and its progression may involve both low-grade inflammation and activation of the complement system. Mannose-binding lectin (MBL) is a key molecule of the innate immune system and involves a pro-inflammatory component and complement activation at the vascular level.

Objectives: We determined the level of MBL in children and adolescents with type 1 diabetes mellitus as a potential marker for diabetic micro-vascular complications including diabetic nephropathy and assess its relation to the clinicopathological characteristics of patients, high sensitivity C-reactive protein (hs-CRP), glycemic control and progression of renal disease.

Materials and methods: *This* prospective study was carried out on 43 children and adolescents with type 1 diabetes compared with 30 age- and sex-matched healthy controls. Patients were subjected to detailed medical history with special emphasis on disease duration and insulin therapy, thorough clinical examination and laboratory assessment of hs-CRP, HbA1c and the presence of micro-vascular complications including nephropathy. All the patients were prospectively followed up for a mean period of 11 ± 4.3 months stressing on the progression in renal disease.

Results: Patients were divided according to the presence of micro-vascular complications into 2 groups. Baseline serum MBL levels were significantly elevated in all diabetic patients compared with controls ($p < 0.001$). MBL levels were also significantly increased in patients with micro-vascular complications (2054 ± 876 ng/mL) and non-complicated patients (1023 ± 462 ng/mL) compared with healthy controls (279 ± 120 ng/mL) with highest levels found in complicated patients ($p < 0.001$). Additionally, follow-up MBL levels were markedly elevated in patients with micro-vascular complications compared with non-complicated patients (3477 ± 1263 versus 1715 ± 799 ; $p < 0.001$) or baseline levels ($p < 0.001$). MBL levels were significantly increased in patients with retinopathy or peripheral neuropathy ($p < 0.001$). Diabetic patients were classified according to urinary albumin excretion (UAE) into 3 groups; normoalbuminuric, microalbuminuric or macroalbuminuric group. Baseline and

follow-up MBL levels were elevated in diabetic patients with or without microalbuminuria compared with control subjects ($p<0.001$). Type 1 diabetic patients progressed from normoalbuminuria or microalbuminuria to a higher albuminuria level had significantly higher baseline and follow-up MBL levels than non-progressors in each group and levels showed marked elevation in patients progressed from microalbuminuria to macroalbuminuria reaching a mean 4900 ± 675 ng/mL ($p<0.001$). Significant positive correlations were found between baseline MBL levels and disease duration, blood pressure, blood glucose, HbA1c, serum creatinine, triglycerides, total cholesterol, UAE and hs-CRP ($p<0.05$). Multiregression linear analysis showed that serum creatinine, UACR, and hs-CRP were independently related to baseline MBL levels in type 1 diabetic patients ($p<0.05$). ROC curve analysis revealed that the cutoff value of MBL at 1520 ng/mL could differentiate complicated from non-complicated cases with a sensitivity of 70.8%, specificity of 84.2%. As regards hs-CRP, levels were significantly higher in all diabetic patients and both diabetic groups than controls ($p<0.05$). Follow-up levels were significantly elevated than baseline hs-CRP levels in patients ($p<0.001$). Normo- or micro-albuminuric diabetic patients had also higher hs-CRP levels than controls ($p<0.05$), however, hs-CRP showed no significant difference between progressors or non-progressors and ROC curve showed a lower specificity of hs-CRP for detection of micro-vascular complications.

Conclusions: We suggest that serum MBL levels are elevated in type 1 diabetic patients, particularly those with micro-vascular complications and a significant correlation with HbA1c, UAE and hs-CRP exists. MBL can be considered a potential marker of progression of renal disease in type 1 diabetes that proved a better specificity than hs-CRP. Therefore, measurement of MBL levels in poorly controlled patients would help to identify those at high risk of developing micro-vascular complications who could benefit from intensive insulin therapy to achieve strict glycemic control.