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

Thesis

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العلاقة بين المانوزبيندنج لاكتين و البروتين التفاعلي سى والآعتلال الكلوي السكري بمرض البول السكرى النوع الاول

رسالة

توطئة للحصول على درجة الماجستير
في طب الاطفال

مقدمه من

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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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Sara Mohamed Fawzy


بسم الله الرحمن الرحيم
وَأَنْزَلَ اللهُ عَلَيْكَ
الْكِتَابَ وَالْحِكْمَةَ
وَعَلَّمَكَ مَا لَمْ
تَكُنْ تَعْلَمُ وَكَانَ
فَضْلُ اللهِ عَلَيْكَ
عَظِيمًا
صدق الله العظيم
سورة النساء آية (١١٣)

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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	Microalbumineria
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 1diabetes 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-progessors 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.