TARGETING COMPLEMENT SYSTEM MANNOSE BINDING LECTIN (MBL) – IN DIABETIC NEPHROPATHY?

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ABSTRACT

Complement MBL and diabetes nephropathy are linked together, it is clear that complement system plays important role in pathogenesis of diabetic nephropathy. In the present article highlights the probable benefits by targeting MBL based on available study data and pathological role.

KEYWORDS:- MBL, MAC, DM, DN, DR.

INTRODUCTION

The development of type 1 and type 2 diabetes mellitus has a substantial negative impact on morbidity and mortality and is responsible for substantial individual and socioeconomic costs worldwide. One of the most serious consequences of diabetes mellitus is the development of diabetic angiopathy, which manifests clinically as microvascular and macrovascular complications. One microvascular complication, diabetic nephropathy, is the most common cause of end-stage renal disease in developed countries. Although several available therapeutic interventions can delay the onset and progression of diabetic nephropathy, morbidity associated with this disease remains high and new therapeutic approaches are needed. In addition, not all patients with diabetes mellitus will develop diabetic nephropathy and thus new biomarkers are needed to identify individuals who will develop this life-threatening disease. An increasing body of evidence points toward a role of the complement system in the pathogenesis of diabetic nephropathy.\[13]
**Diabetes induces changes in MBL**\[^{[1]}\]

The increase in MBL-Complement was associated with the increasing plasma glucose levels.\[^{[1]}\]

MBL levels increase after induction of diabetes and in parallel with increasing plasma glucose.\[^{[1]}\]

**Elevated MBL level in T1DM**

The hepatic protein mannan-binding lectin (MBL) activates the complement system on binding to carbohydrate patterns and is involved in first-line defence against invading microorganisms. Emerging evidence indicates that in some situations MBL may cause inexpedient complement activation and tissue injury through binding to endothelial glycosylations. MBL levels are suppressed by insulin treatment in critically ill patients and hypothetically, hepatic portal hypoinsulinemia could lead to increased levels of MBL in patients with type 1 diabetes.\[^{[2]}\]

MBL concentrations were positively correlated with urinary albumin excretion and increased with increasing urinary albumin excretion.\[^{[2]}\]

MBL concentrations are significantly elevated in patients with type 1 diabetes and suggest a possible role of MBL in the pathogenesis of renovascular complications in diabetes.\[^{[1,2]}\]

**MBL AND NEPHROPATHY IN T1DM**

Type 1 diabetic patient, evaluated serum levels of MBL can be seen as an independent marker of Diabetic nephropathy (DN) even after correcting for possible confounding factors.\[^{[3]}\]

**MBL AS BIOMAKER**

1) MBL is independent biomarker of DN.\[^{[3]}\]
2) MBL is strong Biomarker of Diabetic Retinopathy (DR).\[^{[5]}\]
3) MBL is a novel, independent diagnostic marker of DR in type 2 diabetic patients, suggesting that MBL may be involved in the pathogenesis of DR in diabetic patients.\[^{[6]}\]
4) In type 2 diabetic patients, evaluated serum levels of MBL can be seen as an independent marker of DR even after correcting for possible confounding factors.\[^{[7]}\]
MBL – IN PATHOGENESIS OF DN IN T2DM

MBL may be involved in the pathogenesis of DN in type 2 diabetes, and that determination of MBL status might be used to identify patients at increased risk of developing nephropathy complications.[4]

MBL, MEMBRANE ATTACK COMPLEX (MAC) AND NF-KAPPAB

MBL, MAC and NF-kappaB expression were significantly increased in glomerulus of diabetic nephropathy.[8]

ACTIVATION OF MBL PARTICIPATES IN DEVELOPMENT OF DN

The activation of mannose-binding lectin complement participates in the onset and development of DN.[8]

MBL AND hsCRP LEVEL

Concentrations of both MBL and hsCRP are associated with the progression of renal disease in type 1 diabetes.[9]

MBL HAS DIRECT EFFECTS AND ACTIVATES COMPLEMENT

1) MBL activates complement upon binding within the diabetic glomerulus.
2) Increased MBL auto-reactivity in the kidney and circulating C3a concentration.

HIGH LEVEL OF MBL AND VASCULAR COMPLICATION

High expression of MBL may be correlated with a significantly increased risk of vascular complications in diabetes. Thus MBL detection in diabetes is an effective and feasible method to predict vascular complications.[11]

Dysregulation of the complement system and of members of the tumor necrosis factor (TNF) superfamily may be involved in the development of diabetic vascular complications. The mannose-binding lectin pathway-an overall regulatory component of the complement system-is a particularly promising biomarker as it is directly involved in the development of diabetic angiopathy. In addition, two components of the TNF superfamily, namely TRAIL (tumor necrosis factor-related apoptosis-inducing ligand) and osteoprotegerin, may be involved in the pathogenesis of diabetic angiopathy.[12]
CONCLUSION FOR STUDY /REPORTS/EVIDENCES
Circulating levels of mannose-binding lectin (MBL), a pattern recognition molecule of the innate immune system, have emerged as a robust biomarker for the development and progression of this disease and evidence suggests that MBL, H-ficolin, complement component C3 and the membrane attack complex might contribute to renal injury in the hyperglycaemic milieu.[13]

Several ways of specifically manipulating the complement and TNF superfamily systems already exist, but whether or not these drugs provide new targets for intervention for late diabetic complications is still to be revealed.[12]

New approaches to modulate the complement system might lead to the development of new agents to prevent or slow the progression of diabetic nephropathy.[13]

TARGETING COMPLEMENT SYSTEM
1) MBL could be potential target in TYPE 1DM.[14]
2) Recent study on animal modem with AMI complement system can be targeted for therapeutic intervention thus this study gives insight that complement system could be targeted.[15]

Probable Benefits of Targeting MBL based on study till date.
1) Reduces albuminuria
2) Reduces renal injury and renovascular complication.
3) Delay the progression of diabetic nephropathy (DN)
4) Delays the development of diabetic retinopathy(DR)
5) Delay vascular complication in diabetic patient
6) Inhibit activation of complement

C1, MBL-MASPs and C1-inhibitor: novel approaches for targeting complement-mediated inflammation[16]
Complement activation is initiated by the pattern-recognition molecules complement component C1q, mannose-binding lectin (MBL) and ficolins (H-, L-, M-ficolin), which typically recognize antibody-antigen complexes or foreign polysaccharides. The associated proteases (C1r, C1s, MASP-1 and MASP-2) then activate the complement system. The serpin C1-inhibitor (C1-inh) blocks activity of all these complexes and has been successfully used in
models of disease. Many structures of these components became available recently, including that of C1-inh, facilitating the structure-guided design of drugs targeting complement activation.[16]

Unfortunately no such inhibitor till date is used in animal model study of diabetes and Diabetic nephropathy by targeting complement MBL.

MBL has promising target for diabetic nephropathy(DN) and retinopathy. (DR).

Conflict of Interest–Author declares there is no conflict of interest regarding the publication of these paper.

REFERENCE


