RECOMBINANT COMPLEMENT INHIBITOR CD59 – IN DIABETIC NEPHROPATHY.

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ABSTRACT
Article highlights the role of complement system and endogenous complement inhibitor in diabetes and its complication especially diabetic nephropathy. Recombinant CD59 can be used to treat diabetes nephropathy is not yet evaluated.

KEYWORD: CD59, MAC, COMPLEMENT SYSTEM.

INTRODUCTION
From available study, reports and evidences regarding the CD59 inhibitor complement. It is well established that the organ damage that complicates human diabetes is caused by prolonged hyperglycemia, but the cellular and molecular mechanisms by which high levels of glucose cause tissue damage in humans are still not fully understood. The prevalent hypothesis explaining the mechanisms that may underlie the pathogenesis of diabetes complications includes overproduction of reactive oxygen species, increased flux through the polyol pathway, overactivity of the hexosamine pathway causing intracellular formation of advanced glycation end products, and activation of protein kinase C isoforms.[2] 

COMPLEMENT SYSTEM AND DIABETIC COMPLICATION
In addition, experimental and clinical evidence reported in past decades supports a strong link between the complement system, complement regulatory proteins and the pathogenesis of diabetes complications.[2]
CD59 INACTIVATION
Role for the complement system and complement regulatory proteins in the pathogenesis of diabetic vascular complications, with specific emphasis on the role of the membrane attack complex (MAC) and of CD59, an extracellular cell membrane-anchored inhibitor of MAC formation that is inactivated by non enzymatic glycation.\[^{1,2}\]

EFFECT OF CD59 INACTIVATION
CD59 inactivation by glycation and hyperglycemia-induced complement activation increases MAC deposition, activates pathways of intracellular signaling and induces the release of proinflammatory, prothrombotic cytokines and growth factors. Combined, complement-dependent and complement-independent mechanisms induced by high glucose promote inflammation, proliferation and thrombosis as characteristically seen in the target organs of diabetes complications.\[^{2}\]

Glycation-inactivation of CD59 would cause increased MAC deposition and MAC-stimulated cell proliferation.\[^{1}\]

Evidences: CD59 glycation leads to vascular complication\[^{1,3}\]
Increased cell proliferation characterizes the major chronic vascular complications of human diabetes and because increased glucose levels in diabetes cause protein glycation and impairment of protein function
i) Human CD59 is glycated in vivo, (ii) glycated human CD59 loses its MAC-inhibitory function and (iii) inactivation of CD59 increases MAC-induced growth factor release from endothelial cells.\[^{1}\]
ii) The presence of this glycation motif in human CD59, but not in CD59 of other species, may help explain the distinct propensity of humans to develop vascular proliferative complications of diabetes.\[^{1}\]
iii) Activated terminal complement proteins C5b to C9 form the membrane attack complex (MAC) pore. Insertion of the MAC into endothelial cell membranes causes the release of growth factors that stimulate tissue growth and proliferation. The complement regulatory membrane protein CD59 restricts MAC formation.\[^{1}\]

DEFICIENCY OF CD 59/ MUTATION IN CD59 GENE\[^{4,5}\]
1] Paroxysmal nocturnal hemoglobinuria (PNH)\[^{4}\]
2] Chronic haemolysis\[^{5}\]
Eculizumab treatment in pediatric patients with recurrent acute predominantly motor, demyelinating neuropathy with conduction block, and chronic hemolysis attributed to p.Cys89Tyr mutation in the CD59 gene.\textsuperscript{[5]}

**MAC DEPOSIT CAUSES DAMAGES IN DIABETES**

CD59 is inhibitor of MAC, but hyperglycaemia and glycation of CD59 the inhibitory function is lost.

**EVIDENCE FROM DIABETIC PATIENT\textsuperscript{[6]}**

IDDM with varying degrees of mesangial expansion and glomerulosclerosis demonstrated a direct relationship between the degree of tissue damage and the amount of MAC deposited in the mesangium.\textsuperscript{[6]}

**IMPORTANT ROLE OF CD59**

1. Insulin Secretion.\textsuperscript{[7]}
2. Protects against atherosclerosis.\textsuperscript{[8]}

Thus from above discussion and study and evidence it is clear that complement system is linked with development of vascular complication also study suggest that glycation of complement inhibitor CD59 leads to deposition of MAC in mesangial cells leading to cell proliferation, glomerulosclerosis, activates pathways of intracellular signaling and induces the release of proinflammatory, prothrombotic cytokines and growth factors which contribute to development of nephropathy.

**Potential**

Use of recombinant complement inhibitor CD59 may be helpful and following benefits may occur with use of such recombinant preparation.

1. Release of insulin from pancreas\textsuperscript{[7]}
2. Will prevent atherosclerosis\textsuperscript{[8]}
3. Will prevent glomerulosclerosis
4. Reduce mesangial cell proliferation
5. Will inhibit downstream signalling preventing release of proinflammatory, prothrombotic, cytokines and growth factors\textsuperscript{[2]}
6. Delay the development of nephropathy
7. Recombinant complement inhibitor CD59 will delay vascular complication and also help in controlling glucose level since it release insulin\textsuperscript{[7]}

\textsuperscript{[2]}
Cost and availability of recombinant complement inhibitor CD59 for therapeutic purpose will matter. Also the pharmacokinetic data of such recombinant protein is unavailable. At present no animal study or trial till date is done with such recombinant CD59 is available. It is a promising area for research also the dose adverse effect of such inhibitor on various system especially Immune system is also area of interest. But data, study, report available till date suggest that CD 59 can be used to treat diabetic nephropathy.

Conflict of Interest: - Author declares there is no conflict of interest.

REFERENCES