

Glycosylation Enzyme Inhibition May Provide Novel Rationale for Diabetic Retinopathy Treatment

Subclinical inflammation plays an important role in the pathogenesis of diabetic retinopathy, evidence reveals.

REVIEWED BY RAKESH CHIBBER, PhD

A specific novel treatment of diabetic retinopathy may be possible based on the inhibition of a glycosylating enzyme, according to research published in *Diabetologia*.

The authors, from King's College London, GKT School of Biomedical and Health Sciences, wrote that increasing evidence suggests that chronic subclinical inflammation plays an important role in the pathogenesis of diabetic retinopathy (DR). "We recently reported that a glycosylating enzyme, core 2 beta-1, 6-N-acetylglucosaminyl-transferase (core 2 GlcNAc-T), is implicated in increased leukocyte-endothelial cell adhesion in [DR] via an upregulation mechanism controlled by [tumor necrosis factor-alpha] TNF-alpha."

BACKGROUND

Fluorescein angiography shows that an early clinical feature of DR is capillary occlusion. Retinopathy is associated with increased leukocyte entrapment in retinal capillaries and areas of capillary nonperfusion followed by endothelial cell damage, Rakesh Chibber, PhD, and colleagues wrote. Earlier studies have demonstrated that structural changes in O-linked carbohydrates expressed on the surface of leukocytes play a prominent role in controlling adhesion to endothelial cells. Therefore, Dr. Chibber's group described how the plasma of diabetic

patients with retinopathy causes a catalytic upregulation of core 2 GlcNAc-T, leading to a comparable increase in cell adhesion properties.

Dr. Chibber's group reported that this activity is higher in type 1 and 2 diabetic patients with DR, and that TNF-alpha modulates core 2 GlcNAc-T activity via protein phosphorylation mediated by serine/threonine protein kinase C-beta2.

The group designed the present study to clinically validate the association between plasma levels of TNF-alpha, phosphorylation of leukocytic core 2 GlcNAc-T and corresponding enzyme activity at different stages of DR in patients with diabetes.

An early clinical feature of diabetic retinopathy is capillary occlusion.

PATIENTS, MATERIALS AND METHODS

Dr. Chibber and colleagues included 25 patients with type 1 diabetes and 41 with type 2 diabetes from the Diabetes Outpatient Clinic and the Eye Unit at St.



Figure 1. Fundus photo of a 25-year-old patient with 15-year duration of diabetes. Image shows early conversion to proliferative diabetic retinopathy with a marked cotton wool spot and venous engorgement.

Thomas' Hospital in London. They found 15 age-matched nondiabetic healthy controls from the patients' relatives and hospital employees. Patients with type 1 diabetes had the condition for an average of 18.9 ± 2.2 years, and type 2 patients had the disease for 9.2 ± 1.8 years. Investigators determined the level of DR severity as absent, nonproliferative DR (NPDR) or proliferative DR (PDR) (Figure 1).

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The activity of core 2 GlcNAc-T was severalfold higher in polymorphonuclear (PMN) leukocytes of patients with diabetes than in those of healthy controls ($P < .0001$), the investigators found. "We observed a close relationship between enzyme activity in PMN leukocytes and severity of [DR]. PMN leukocytes of diabetic patients with PDR ($n=18$) exhibited core 2 GlcNAc-T activity that was approximately 2.6-fold higher than that from patients with NPDR ($n=23$)

($P < .0001$)," Dr. Chibber wrote.

Circulating TNF-alpha values were significantly higher in diabetic patients than in healthy patients, although there was no evidence of differential TNF-alpha levels in plasma from patients with type 1 and type 2 diabetes. The authors also wrote that there was a positive correlation between plasma levels of C-reactive protein and TNF-alpha. There was a significant positive correlation between TNF-alpha and the severity of DR. "In this regard, plasma levels of TNF-alpha in diabetic patients with PDR ($n=16$) were significantly higher than in subjects affected by NPDR ($n=23$)," they wrote.

IMPLICATIONS

This study validates the pivotal role of circulating plasma TNF-alpha in the induction of core 2 GlcNAc-T, which is associated with the biosynthesis of carbohy-

drate moieties affecting cell adhesion events, Dr. Chibber and colleagues wrote. "The central and causal role of leukocytes in vasoocclusive processes and endothelial cell injury leading to the pathogenesis of [DR] suggests a pathophysiological significance of the enzyme in diabetes, probably through P-selectin glycoprotein ligand-1-mediated adhesion events."

Higher levels of glucose and/or TNF-alpha may upregulate the expression of adhesion molecules on the surface of endothelial cells and cause leukocyte adhesion to the diabetic retinal vasculature. The contribution of TNF-alpha to the onset and progression of DR is supported by previous studies, the investigators said. "Given the wide spectrum of biological activities shown by TNF-alpha, and in particular its important role in the general responses of the immune system, our results reveal a novel rationale for a specific treatment of diabetic retinopathy," Dr. Chibber and colleagues concluded. ■

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Ben-Mahmud BM, Chan WH, Abdulahad RM, et al. Clinical validation of a link between TNF-alpha and the glycosylation enzyme core 2 GlcNAc-T and the relationship of this link to diabetic retinopathy. *Diabetologia*. 2006;49:2185-2191.