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Editorial

Dyslipidemia and Diabetic Retinopathy

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Diabetic Retinopathy (DR) is one of the most common microvascular complications of Diabetes Mellitus (DM) and is the most common cause of preventable legal blindness in persons aged 25-74 years [1]. Despite the advances in the field of metabolic control of diabetic patients, the prevalence of DR remains high. Nearly all patients with type 1 diabetes and >60% of patients with type 2 diabetes have retinopathy during the first two decades of disease [2]. Hyperglycemia triggers retinal endothelial cell activation and increases leukocyte/endothelial interaction leading to breakdown of the Blood Retinal Barrier (BRB) and vascular hyper permeability. This leakage results in diabetic macular edema, the most common cause of decreased visual acuity in diabetic patients. Later, capillary degeneration and ischemia develop which lead to uncontrolled neovascularization in an attempt to compensate for the lack of blood flow [3,4]. The current therapeutic intervention including timely laser photocoagulation, vitrectomy and repeated intravitreal injections of anti-VEGF or steroids, are invasive and limited by significant side effects. Furthermore, they may be effective for preservation of sight in proliferative diabetic retinopathy and macular edema but their ability to reverse visual loss is poor. Many patients have evidence of retinal subclinical inflammation at the time they are diagnosed with diabetes [5]. This means that pro-DR mechanisms arise early during the course of diabetes, although the nature of these mechanisms is not clearly evident. Hence, shifting investigative efforts to elucidate the mechanisms initiating and promoting the early changes in retinal function is important to develop effective therapeutic approaches with the goal of preventing (or at least minimizing) the development/progression of DR.

The early inflammatory response in retina has been proposed to be the result of persistent hyperglycemia as well as of dyslipidemia [6-8]. The role of dyslipidemia in the development of DR has not yet been studied in details despite the clinical evidences that dyslipidemia may contribute to the pathogenesis of DR [9,10]. Dysregulation of lipid signaling has been reported in a variety of retinal diseases including DR, retinopathy of prematurity, and age-related macular degeneration[11]. This dysregulation is characterized by an increase in n6 Polyunsaturated Fatty Acids (PUFA), such as AA, while the n3 PUFA, such as Docosahexaenoic Acid (DHA) [9,12-14]significantly decreased. DHA is known to elicit beneficial effect against microvascular complications of diabetes [15,16]via its lipid products such as neuroprotectin D1, resolvins and lipoxins. Interestingly, activation of $cPLA_2$ was reported in experimental models of ischemic retinopathy [17,18]. Activation of cytosolic phospholipase A_2 ($cPLA_2$) generates freeAA which in turn via different enzymatic pathways including cycloxygenase (COX2), lipoxygenase (LOX), and cytochrome P450 (CYP) is converted to pro-inflammatory mediators such as hydroxyeciosatetreanoic acids (HETEs), leukotrienes and prostaglandins.

Our previous studies demonstrated for the first time that 12/15-lipoxygenase-derived lipid metabolites 12- and 15-HETEs are implicated in the pathogenesis of microvascular dysfunction during DR [19,20]. This includes pathological retinal neovascularization via disrupting the delicate balance in the levels of Vascular Endothelial Growth Factor (VEGF) and the Pigment Epithelium Derived Factor (PEDF). Furthermore, these lipid metabolites via activation of NADPH oxidase, a known source of reactive oxygen species during DR modulate endothelial cell barrier function and induce hyperpermeability. Effect of 12/15-LOX-derived HETES on retinal endothelial cell barrier was associated with activation of VEGF receptor2 (KDR) through oxidation of the Protein Tyrosine Phosphatase (PTP). Our findings suggest that these lipid metabolites derived from endothelial 12/15LOX are implicated in DR via both paracrine and autocrine loop. The paracrine loop involves activation of retinal Muller cells to produce VEGF and down regulate PEDF. On the other hand the autocrine loop involves activation of VEGFR2 (KDR) signaling pathway in REC via oxidation of the PTP. Interestingly, enriching the retina with n3 PUFA such as DHA diverts the activity of 12/15-LOX from generating the pro-inflammatory and pro-angiogenic lipid metabolites (HETEs) to generate anti-inflammatory and angiostatic metabolites such as neuroprotectin D1, lipoxins and resolvins. Therefore, we suggest 12/15-LOX as an endogenous double-edged sword depending on the type of substrate available for its activity.This means that inhibition of 12/15-LOX or dietary supplement with ω-3 Polyunsaturated Fatty Acids (PUFAs) may be used either as an alternative or supplement to the current therapeutic strategies for the DR.

In addition to dyslipidemia, oxidative stress is a key factor in mediating both hyperglycemia and dyslipidemia-induced retinal vascular injury. Our previous studies highlighted the NADPH oxidase as a major source of ROS generation in rodent retina of experimental diabetes and oxygen-induced retinopathy model as well as in retinal endothelial cells treated with high glucose or hypoxia [21-24]. We also found that effects of HETEs on retinal endothelial cells are linked to NADPH oxidase activity suggesting that dysregulation of

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lipid metabolism in diabetic retina contributes to the change in redox status of retina during DR. Despite the experimental evidence which suggest oxidative stress as a mediator of the neurovascular damage during DR, the efficacy of antioxidant in treatment of DR is still questionable. A 5 year follow-up of antioxidant supplementation in type 2 diabetes showed no change in the best-corrected visual acuity during the follow-up. However, there was remarkable retardation in the progression of retinopathy to advanced stage in the patients received antioxidant supplementation in comparison to patients without supplementation [25]. This suggests that oral antioxidant supplementation might be useful in prevention of progression of DR and in turn saving sight in diabetic patients.

In summary optimum control of blood glucose and possibly lipid and oxidative stress signaling are the foundation to reduce the risk of retinopathy development and progression by reducing the early inflammatory response in retina of diabetic patients.

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