Vision Research xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Vision Research

journal homepage: www.elsevier.com/locate/visres

The role of dyslipidemia in diabetic retinopathy

Sandra S. Hammer, Julia V. Busik*

Department of Physiology, Michigan State University, East Lansing, MI, United States

ARTICLE INFO

Article history:
Received 1 February 2017
Received in revised form 6 April 2017
Accepted 13 April 2017
Available online xxxx

No of reviewers = 2

Keywords:
Dyslipidemia
Diabetic retinopathy
Inflammation
Cholesterol metabolism
Fatty acids
ASM
miR-15a
Liver X receptor
Bone marrow

ABSTRACT

Diabetic retinopathy (DR) affects over 93 million people worldwide and is the number one cause of blindness among working age adults. These indicators coupled with the projected rise of patients diagnosed with diabetes, makes DR a serious and prevalent vision threating disease. Data from recent clinical trials demonstrate that in addition to the well accepted role of hyperglycemia, dyslipidemia is an important, but often overlooked factor in the development of DR. The central aim of this review article is to showcase the critical role of dyslipidemia in DR progression as well as highlight novel therapeutic solutions that take advantage of the vital roles lipid metabolism plays in DR progression.

1. Diabetic dyslipidemia and DR progression

The role of lipids in the progression of DR can be documented back to the 1950s when Keiding et al. demonstrated a correlation between the formation of hard exudates and serum lipid levels (Keiding, Mann, Root, Lawry, & Marble, 1952). It was further confirmed by studies examining dietary lipid interventions (Houtsmuller, Zahn, & Henkes, 1980; Howard-Williams et al., 1985; King & Dobree, 1963). More recently, analysis of blood lipid profiles in Diabetes Control and Complications Trial (DCCT) samples established a tight association between the development of DR and dyslipidemia in type 1 diabetes, and several clinical trials using lipid lowering medications suggested a link between dyslipidemia and DR progression in type 2 diabetes (Action to Control Cardiovascular Risk in Diabetes Follow-On, 2016; Frank, 2014; Matthews, 2011; Wright & Dodson, 2011). Specifically, administration of peroxisome proliferator-activated receptor alpha (PPARα) activator, clofibrate (prototype of fenofibrate) found reductions in hard exudates (Cullen, Town, & Campbell, 1974; Duncan et al., 1968; Harrold, Marmion, & Gough, 1969), and the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study demonstrated that fenofibrate treatment resulted in a significant reduction in the need for laser therapy for DR at 5 years (Keech et al., 2007). The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye Study showed that patients with type 2 diabetes who received both fenofibrate and HMG-CoA reductase inhibitor simvastatin, to control triglyceride and cholesterol levels respectively, had less progression of DR at 4 years (Action to Control Cardiovascular Risk in Diabetes Follow-On, 2016).

Dyslipidemia is a complex disorder that involves both central, as well as organ-specific mechanisms (Chakravarthy et al., 2016; Chen, Esselman, Jump, & Busik, 2005; Tikhonenko et al., 2010; Yu & Lyons, 2005). These include abnormal levels of lipids in the plasma that arise from a disproportion in metabolism, release and/or uptake by the adipose tissue as well as inefficient lipid removal from blood circulation. In addition to central regulation, most cells in the body have tissue-specific control of lipid uptake, remodeling and elimination (Keller et al., 1993; Mast et al., 2011; Schultz et al., 2000; Tikhonenko et al., 2010; Wang et al., 2005; Zechner, 1997). Diabetes affects both central and retinal tissue-specific control of multiple lipid classes including fatty acids, triglycerides, cholesterol, and sphingolipids (Busik, Esselman, & Reid, 2012; Hazra et al., 2012; Tikhonenko et al., 2010). Moreover, insulin resistance has been shown to promote dyslipidemia by elevating LDL cholesterol, total cholesterol, free fatty acids and triglycerides as well as decreasing HDL cholesterol and inhibiting reverse cholesterol transport genes

* Corresponding author at: Department of Physiology, Michigan State University, 567 Wilson Rd, East Lansing, MI, United States.
E-mail address: busik@msu.edu (J.V. Busik).

http://dx.doi.org/10.1016/j.visres.2017.04.010
0042-6989/

(Ginsberg, Zhang, & Hernandez-Ono, 2005; Goff, D'Agostino, Haffner, & Otvos, 2005; Reaven & Chen, 1988). Patients with diabetic dyslipidemia were shown to have higher frequency of acquiring retinal irregularities (Cetin et al., 2013; Sacks et al., 2014). However, unlike macrovascular complications, where direct correlation between pathology and circulating lipid levels is well established (The ACCORD Study Group and ACCORD Eye Study Group, 2010), the role of circulating lipids in microvascular complications is still controversial. Indeed, Wisconsin Epidemiologic Study of Diabetic Retinopathy found no association between total cholesterol or high density lipoprotein (HDL) and incidence of DR or macular edema, while there was a modest association between higher levels of HDL and decreased prevalence of proliferative DR (Klein, Myers, Howard, & Klein, 2015). In the ACCORD follow-up study, ACCORD Follow-On Eye Study (ACCORDION), the beneficial effects of dual fenofibrate and simvastatin treatment disappeared 8 years after randomization in the original ACCORD study, although the effects of glycemic control persisted.

Thus, although there is an association between lipid control and the progression of retinopathy, the nature of this association is not well understood. In this review, we will discuss the effect of diabetes on systemic and retina-specific lipid changes as it relates to the pathogenesis of diabetic retinopathy.

1.1. Fatty acyls

Both systemic and retinal-specific fatty acid profiles are affected by diabetes and were suggested to contribute to the progression of DR. At the systemic level, diabetic patients have significantly elevated levels of triglyceride in skeletal muscle and blood when compared to non-diabetic patients (Sinha et al., 2002) with the severity of diabetes positively correlating with serum triglycerides (Cetin et al., 2013; Sacks et al., 2014). Specifically, in the liver under non-disease conditions, insulin promotes the conversion of fatty acids to triglycerides, followed by their secretion as very-low density lipoproteins (VLDL) Busik et al., 2012; Weinstock et al., 1997. However, during diabetic conditions where insulin levels are low or in cases of insulin resistance, plasma lipids levels as well as the composition of fatty acids, are dramatically altered (Goldberg, 1981, 2001; Goldberg & Capuzzi, 2001; Poisson, 1989; Vessby, 2000). Altered plasma fatty acid composition can contribute to both retinal, and bone-marrow-derived inflammatory as well as progenitor cell membrane composition and function (Lydic, Renis, Busik, & Reid, 2009; Opreanu et al., 2011; Tikhonenko et al., 2010, 2013).

In addition to the uptake from circulation, retina has very active lipid metabolism leading to remodeling of fatty acids (Tikhonenko et al., 2010). Therefore, retina has a fatty acid profile that is very distinct from that of blood plasma or liver, and retinal fatty acids are significantly altered by diabetes (Busik, Reid, & Lydic, 2009; Chakravarthy et al., 2016; Opreanu et al., 2011; Tikhonenko et al., 2010). Retinal saturated and unsaturated fatty acids are remodeled through a series of elongation and desaturation reactions (Tikhonenko et al., 2010). It has been demonstrated that diabetes can cause a significant reduction in levels of elongase enzymes (Tikhonenko et al., 2010; Wang et al., 2006). A decrease in retinal levels of one of the highest retinal n-3 polyunsaturated fatty acids (PUFA)-docosahexaenoic acid (DHA) is observed due to, at least in part, diabetes-induced alterations in fatty acid remodeling in the retina (Connor et al., 2007; Futterman & Kupfer, 1968; Tikhonenko et al., 2010).

1.2. Sterol lipids

In the retina, cholesterol levels are determined by several factors. These include systemic delivery, local production, as well as elimination of cholesterol (Fliesler, 2015; Fliesler & Bretillon, 2010; Fliesler, Florman, Rapp, Pittler, & Keller, 1993). Unlike the brain, which solely relies on local synthesis of cholesterol, the retina employs the Low-Density Lipoprotein Receptor (LDLR)-mediated pathway to deliver cholesterol obtained from diet or produced by the liver (Fliesler & Keller, 1995; Fliesler et al., 1993). Specifically, this blood-borne cholesterol is delivered to the retina predominantly via the retinal pigmented epithelium (RPE) layer Pikuleva & Curcio, 2014; Elner, 2002. Previous studies demonstrated that increased levels of LDL cholesterol pass through this retinal-blood barrier in the diabetic retina when compared to non-diabetic conditions (Du et al., 2013) Fliesler et al., 1993. In addition to increased LDL uptake through REP layer, increased permeability of retinal capillaries was shown to cause extravasation of plasma lipoproteins (Du et al., 2013; Wu & Lyons, 2011; Wu et al., 2008). Local synthesis of cholesterol has been shown to be primarily carried out by the Müller cells as well as photoreceptor inner segments (Mast et al., 2011; Pikuleva & Curcio, 2014; Zheng et al., 2012). Moreover, unlike other organs, the retina relies on active processes to remove cholesterol (Omarova et al., 2012; Pikuleva, 2008; Zheng, Mast, Saadane, & Pikuleva, 2015). Obstruction of pathways that control cholesterol metabolism can cause retinal cholesterol accumulation which can have detrimental effects on normal retinal function.

One of the mechanisms the retina employs to eliminate cholesterol involves the activation of the reverse cholesterol transport pathway (RCT) (Zheng et al., 2015). This pathway is actively used by the retina to transport cholesterol back to the liver in a multistep process (Mast et al., 2011). RCT-dependent removal of cholesterol is first controlled by ATP-binding cassette transporters ABCA1 and ABCG1 (Pikuleva & Curcio, 2014; Ye et al., 2011). These membrane-associated protein transporters are the major regulators of cellular cholesterol by acting as cholesterol efflux pumps that efflux cholesterol to lipid poor apolipoproteins (ApoA1 and ApoE) (Omarova et al., 2012). Genetic manipulation studies have demonstrated that downregulation of ABCA1 leads to pathologic vessel thickening and hardening (Sene et al., 2013). Additionally, patients with ABCA1 mutations are diagnosed with Tangier disease, a disease that is characterized by a severe reduction in HDL (Murano et al., 2016). Secondly, the retina relies on enzymatic elimination of cholesterol by cytochrome P450 enzymes (CYPs) (Zheng et al., 2015). CYPs metabolize cholesterol to more soluble oxysterols that rapidly diffuse to the systemic circulation. The three main CYPs involved in cholesterol metabolism are CYP46A1, CYP27A1 and CYP11A1. All three of these CYPs are present in retinal tissues (Pikuleva, 2008).

Abnormal cholesterol elimination in diabetic retina can lead to an increase in non-enzymatic oxidation and glycation. Oxidized and glycated LDL identified in the retina during diabetes were shown to induce retinal pericyte loss and oxidized LDL immunocomplexes and were implicated to play a role in diabetic retinopathy (Fu et al., 2014). Oxidized cholesterol, particularly 7-ketocholesterol (7kCh), is elevated in diabetes. 7kCh is a potent pro-apoptotic agent shown to activate caspases (Moreira, Larrayoz, Lee, & Rodriguez, 2009). Elevated levels of 7hCh were recently shown in photodamaged retina and are suggested to play a role in photoreceptor degeneration after exposure to constant light (Rodriguez & Fliesler, 2009).

1.3. Sphingolipids

Diabetes has been shown to alter sphingolipid metabolism (Fox et al., 2006; Maines, French, Wolpert, Antonetti, & Smith, 2006; Skoura et al., 2007). Sphingolipids are an important class of biologically active lipids that have critical roles in regulating cell growth, death, inflammation, adhesion and migration (Hannun & Bell, 1989). One of the main secondary messengers involved in

Please cite this article in press as: Hammer, S. S., & Busik, J. V. The role of dyslipidemia in diabetic retinopathy. *Vision Research* (2017), http://dx.doi.org/10.1016/j.visres.2017.04.010