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Diabetic complications in the cornea

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ABSTRACT

Diabetic corneal alterations, such as delayed epithelial wound healing, edema, recurrent erosions, neuropathy/loss of sensitivity, and tear film changes are frequent but underdiagnosed complications of both type 1 (insulin-dependent) and type 2 (non-insulin-dependent) diabetes mellitus. The disease affects corneal epithelium, corneal nerves, tear film, and to a lesser extent, endothelium, and also conjunctiva. These abnormalities may appear or become exacerbated following trauma, as well as various surgeries including retinal, cataract or refractive. The focus of the review is on mechanisms of diabetic corneal abnormalities, available animal, tissue and organ culture models, and emerging treatments. Changes of basement membrane structure and wound healing rates, the role of various proteinases, advanced glycation end products (AGEs), abnormal growth and motility factors (including opioid, epidermal, and hepatocyte growth factors) are analyzed. Experimental therapeutics under development, including topical naltrexone, insulin, inhibitors of aldose reductase, and AGEs, as well as emerging gene and cell therapies are discussed in detail.

1. Introduction

Diabetes mellitus is currently the leading cause of legal blindness in the working age adults worldwide. Diabetic retinopathy (DR) is a major and the most severe ocular complication of diabetes mellitus (Aiello et al., 1998). DR is the leading cause of new blindness in persons 25 to 74 years of age in the United States, accounting for about 8000 new blindness cases each year (Aiello et al., 1998; Negi & Vernon, 2003). Patients with insulin-dependent diabetes (type 1, IDDM) will develop DR in more than 90% of cases, and proliferative DR (PDR), in up to 50% of cases after 20 years of disease; patients with non-insulin-dependent diabetes (type 2, NIDDM) also frequently develop DR (Aiello et al., 1998; Klein, 2008; Negi & Vernon, 2003). Overall, 43% of type 1 and 60% of type 2 diabetics lose vision within 5 years of the onset of PDR.

Diabetic eye disease is typically considered as a retinal microvascular disorder and is thus generally called diabetic retinopathy. Nonproliferative DR (NPDR) is associated with retinal ischemia, pericyte loss, capillary closure, retinal hemorrhages, microaneurysms, and macular edema. PDR is associated with intravitreal hemorrhages, optic disc or peripheral neovascularization, preretinal fibrovascular membranes, and vitreoretinal traction with retinal detachments (Yam & Kwok, 2007). DR is mainly treated with tight blood glucose control that is more effective in IDDM and laser surgery [panretinal laser photocoagulation (PRP)], (Aiello et al., 1998; Henricsson, Nilsson, Janzon, & Groop, 1997; Negi & Vernon, 2003; Yam & Kwok, 2007). Eyes with non-clearing vitreous hemorrhage are treated with vitrectomy followed by PRP (Aiello et al., 1998). DR and/or PDR progression may be slowed down by treatment with steroids, somatostatin analogs, and antagonists of vascular endothelial growth factor (Dhoot & Avery, 2016; Jonas, 2007; Lang, 2007; Ljubimov, Boulton, Caballero, & Grant, 2008). Results from animal models suggest that combination therapy may be the most promising future approach to PDR treatment (Dorrell, Aguilar, Scheppke, Barnett, & Friedlander, 2007; Jo et al., 2006; Kramerov et al., 2006).

Given its major impact on vision, retinal disease in diabetes remains the primary concern of physicians. At the same time, other parts of the eye (e.g., iris, lens, optic nerve) also suffer from diabetic complications, although they are encountered in less than 30% of diabetic patients (Blum et al., 2007; Ducrey, 1996; Helbig, 2007; Murtha & Cavallerano, 2007; Nakamura, Kanamori, & Negi, 2005). Corneal problems seem to be more frequent affecting up to 70% of examined diabetic patients (Abdelkader, Patel, McGhee, &

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Alany, 2011; Didenko, Smoliakova, Sorokin, & Egorov, 1999; Schultz, Van Horn, Peters, Klewin, & Schutten, 1981; Vieira-Potter, Karamichos, & Lee, 2016). However, these changes are rarely diagnosed (Herse, 1988; Wylegała, Moćko, Woyna-Orlewicz, Teper, & Orzhechowska-Wylegała, 2006). Major attention is paid to the retina despite the proposed inclusion of ocular surface assessment during eye examination in diabetic patients (Aiello et al., 1998; Ben Osman et al., 1995; DeMill, Hussain, Pop-Busui, & Shtein, 2016). Currently, 18% of corneas transplanted in the United States come from diabetic donors (Lass et al., 2015), which may not be beneficial for recipients due to lasting epigenetic changes in these corneas. The present review will attempt at bridging this gap and presenting a comprehensive analysis of corneal diabetic complications. Earlier reviews on diabetic corneal disease focused primarily on clinical problems (Cisarik-Fredenburg, 2001; Kaji, 2005; Sánchez-Thorin, 1998). More recently, appropriate attention was given to the mechanisms of disease and available therapies (Bikbova, Oshitari, Tawada, & Yamamoto, 2012; Calvo-Maroto, Perez-Cambrodí, Albarán-Diego, Pons, & Cerviño, 2014; Misra, Braatvedt, & Patel, 2016; Shih, Lam, & Tong, 2017; Vieira-Potter et al., 2016). This review provides recent updates in this rapidly developing field and analyzes in more detail the latest therapeutic candidates. Emphasis is also given to molecular events and mechanisms underlying this disease, which need to be understood in more detail in order to develop new effective treatments (Karamichos, 2015).

2. General manifestations of diabetes in the cornea

Clinically observed corneal diabetic alterations include increased corneal thickness, epithelial defects, epithelial fragility and recurrent erosions, ulcers, edema, superficial punctate keratitis, delayed and incomplete wound repair, endothelial changes, and neuropathy exemplified by reduced corneal sensitivity (Bikbova et al., 2012; Cavallerano, 1992; Gekka et al., 2004; Herse, 1988; Malik et al., 2003; Módis et al., 2010; Negi & Vernon, 2003; Saini & Khandalavla, 1995; Saito et al., 2003; Shih et al., 2017; Su et al., 2008; Sánchez-Thorin, 1998; Vieira-Potter et al., 2016; Wylegała et al., 2006). Diabetic corneal neuropathy, corneal autofluorescence [possibly due to the accumulation of advanced glycation end products (AGEs)], and epithelial fragility are all augmented in patients with DR (Chang, Hsu, Hu, & Chen, 1995; Janiec et al., 1995; Saini & Mittal, 1996a; Van Schaik et al., 1999; Bikbova et al., 2012; Calvo-Maroto, Perez-Cambrodi, Garcia-Lazaro, Ferrer-Blasco, & Cerviño, 2016; DeMill et al., 2016). Diabetics often have low tear secretion and dry eye syndrome (Beckman, 2014; Cousen, Cackett, Bennett, Swa, & Dhillon, 2007; Inoue et al., 2001; Manaviat, Rashidi, Afkhami-Ardekani, & Shoja, 2008; Yoon, Im, & Seo, 2004). Similar to diabetic retina, diabetic corneas are also affected by dyslipidemia with increased content of sphingosines and ceramides (Priyadarsini, Sarker-Nag, Allegood, Chalfant, & Karamichos, 2015; Priyadarsini, McKay et al., 2016). Major changes in human and animal diabetic corneas are listed in Table 1.

2.1. Epithelial abnormalities

Diabetic epithelial problems are often summarily referred to as diabetic keratopathy emphasizing the major impact on corneal epithelium. Signs of diabetic keratopathy include epithelial fragility, defects and recurrent erosions, non-healing ulcers, corneal edema due to altered epithelial barrier function, superficial punctate keratitis, abnormally slow and often incomplete wound healing, lower cell density especially in the basal layer, and increased susceptibility to injury (Ben Osman et al., 1995; Cavallerano, 1992; Gekka et al., 2004; Inoue et al., 2001; Ohashi, 1997; Quadrado, Popper, Morgado, Murta, & Van Best, 2006; Saini & Khandalavla, 1995; Sánchez-Thorin, 1998; Szalai et al., 2016; Vieira-Potter et al., 2016; Wylegała et al., 2006). The data on the prevalence of diabetic keratopathy depending on the type of diabetes remain inconsistent and need to be revisited (Didenko et al., 1999; Schultz et al., 1981). Women with poor glycemic control have a higher diabetic keratopathy incidence than men, especially with IDDM (up to 90%) (Schultz et al., 1981).

It has been long suggested that diabetic keratopathy is a sign of peripheral neuropathy (Schultz, Peters, Sobocinski, Nassif, & Schultz, 1983). This idea was substantiated by later findings of frequent association between corneal epithelial changes and manifestations of diabetic neuropathy (Bikbova, Oshitari, Baba, & Yamamoto, 2016; Didenko et al., 1999; Mocan, Durukan, Irkec, & Orhan, 2006). At the same time, neurotrophic keratopathy is reportedly a rare event in diabetics (Lockwood, Hope-Ross, & Chell, 2006). Moreover, direct structural and functional changes

Table 1
Manifestations of corneal diabetes.

Abnormality	Manifestation	Reference
Neuropathy (nerves)	Decreased sensitivity	Saini & Mittal, 1996a
	Decreased subbasal nerve fiber and branch density	Rosenberg et al., 2000
	Delayed nerve regeneration after injury	Gao et al., 2016
	Increased stromal nerve thickness and tortuosity	Mocan et al., 2006
Keratopathy (epithelium)	Delayed wound healing	Chen et al., 2009
	Compromised barrier function	Chang et al., 1995
	Persistent epithelial defects	Herse, 1988
	Recurrent erosions	Herse, 1988
	Epithelial fragility	Saini & Khandalavla, 1995
	Edema	Cisarik-Fredenburg, 2001
	Ulceration	Herse, 1988
	Low cell density	Szalai et al., 2016
	Stem cell dysfunction	Saghizadeh et al., 2011
	Increased autofluorescence	Chang et al., 1995
Immune cell alterations	Dendritic cell accumulation	Leppin et al., 2014
Stromal changes	Abnormal collagen bundles	Zou et al., 2012
	Stromal edema	Gül et al., 2008
Endothelial changes	Decreased cell density	Szalai et al., 2016
	Cell pleomorphism	Matsuda et al., 1990
Tear film changes	Low tear secretion	Cousen et al., 2007
	Increased tear osmolarity	Beckman, 2014
Biomechanics problems	Increased corneal response factor	Kotecha et al., 2010

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