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Diabetic retinopathy, an overview

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ABSTRACT

This overview introduces contributions to a special issue on causes of vision loss from diabetes mellitus, focusing on the retina and also the cornea. Diabetic retinopathy is the most common and leading cause of vision loss among people with diabetes. Research to detect early symptoms, understand mechanisms leading to diabetic eye disease, and the development of treatments is a highly active research area, with currently about 2000 scientific publication per year. We provide a series of 27 comprehensive reviews and research articles from leading experts in the field.

Diabetes mellitus (DM) affects about 400 million adults worldwide (Lee, Wong, & Sabanayagam, 2015; Rowley, Bezold, Arikan, Byrne, & Krohe, 2017) a number that is anticipated to double by 2030 according to the World Health Organization (WHO, global report on diabetes 2016; accessed Feb 4, 2017). Diabetic eye disease is a major complication of DM and causes visual impairment and blindness, with diabetic retinopathy being a leading cause of vision loss among working-age adults. Even with mild to moderate vision loss, nonproliferative diabetic retinopathy (Fig. 1) and diabetic macular edema (Fig. 2) are associated with reduced quality of life (Mazhar et al., 2011). In the 1980's, epidemiologic studies focused on diabetes mellitus in North America, but it is now recognized that diabetes is a global concern. From 1990 to 2010, blindness increased by 27% and visual impairment by 64% (Leasher et al., 2016). Although proliferative diabetic retinopathy (Fig. 3) is the most common form of vision threatening diabetic retinopathy in patients with type 1 DM, diabetic macular edema accounts for most of the vision loss in DM, because it is more common in the more prevalent type 2 DM (Lightman & Towler, 2003).

Despite the growth of DM and diabetic retinopathy globally, our understanding and ability to successfully treat patients with DM have changed dramatically over the last few decades. For example, laser photocoagulation was the standard care for diabetic macular edema (DME) and was beneficial in maintaining visual acuity level in about a third of patients with DME compared to patients without treatment based on the multicenter (Early Treatment Diabetic Retinopathy Study Research Group, 1991). Panretinal photocoagulation was the standard for high-risk proliferative diabetic retinopathy (PDR) based on the earlier diabetic retinopathy study (Rand, Prud'homme, Ederer, & Canner, 1985). With the development of agents that block the bioactivity of vascular endothelial growth factor (VEGF), visual acuity has been shown to be improved in about 40% of patients with DME with anti-VEGF medications and is considered a standard treatment for many patients with DME given compliant follow up (Elman et al., 2010; Nguyen et al., 2012). The Diabetic Retinopathy Clinical Research Network (DRCR.net) funded by National Eye Institute found comparable outcomes for patients who had DME and visual acuity of 20/40 or better with monthly bevacizumab (1.25 mg), ranibizumab (0.3 mg), or aflibercept (2 mg), reported in Protocol T (Wells et al., 2015). Patients with $\leq$20/50 visual acuity had improved visual acuity and reduced number of injections with aflibercept treatment. Other multicenter clinical trials (VISTA and VIVID) found intravitreal aflibercept 2 mg monthly had equivalent outcomes to intravitreal aflibercept administered every two months (Brown et al., 2015; Heier et al., 2016).

Corticosteroid formulations are also used to treat DME as it is recognized that inflammation plays a role in complications of DR, including DME. In addition, corticosteroids can affect angiogenic pathways. Formulations, such as triamcinolone (4 mg) (Elman et al., 2010), dexamethasone (0.7 mg) Boyer et al., 2014 or fluocinolone acetonide (0.2 μg) Campochiaro et al., 2012 improved vision and reduced macular thickness in multicenter clinical trials for DME. Triamcinolone is a suspension and causes floaters, whereas dexamethasone and fluocinolone are inserts causing usually one floater when the intravitreal insert is symptomatically visible to the patient.

The reduced burden of injections is important for patient care and to reduce the risk of endophthalmitis. Triamcinolone and dexamethasone last about 3 months, whereas fluocinolone acetonide lasts up to 36 months. Bevacizumab and ranibizumab require monthly injections, whereas aflibercept is effective when delivered every two months. anti-VEGF treatments have been associated with increased intraocular pressure (IOP) Bressler et al., 2015 and increased need for glaucoma surgery (Eadie, Etminan, Carleton, Maberley, & Mikelberg, 2017), but the risk for glaucoma following anti-VEGF treatment is not as apparent as with corticosteroids (Maturi et al., 2016). Before fluocinolone acetonide is offered for

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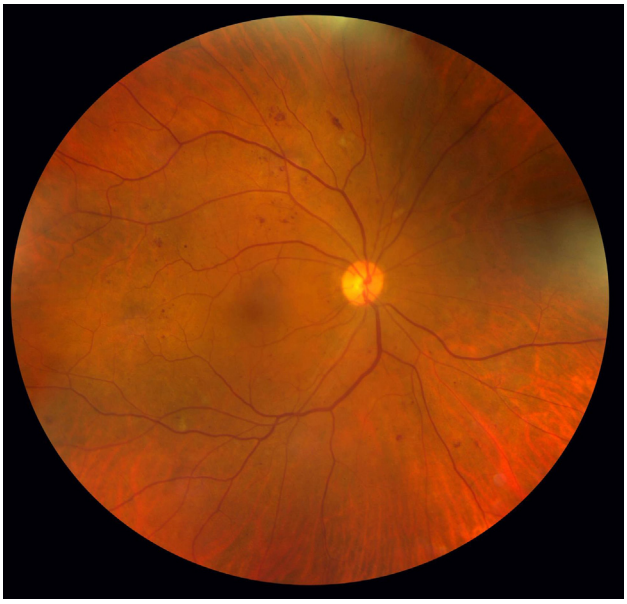
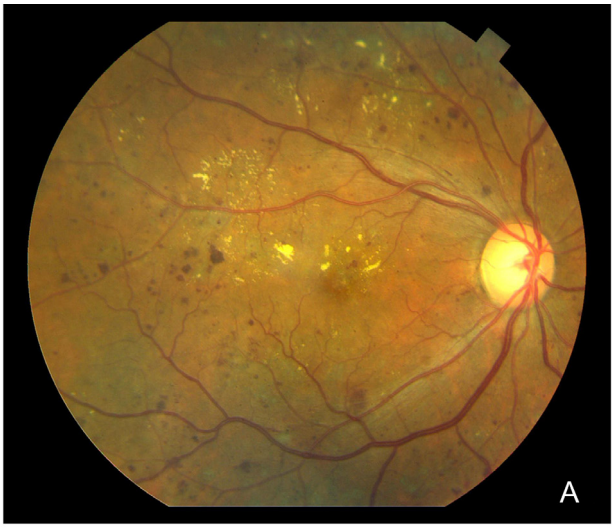


Fig. 1. Image of right eye showing scattered hemorrhage and microaneurysms. In the inferonasal quadrant there is subtle venous beading of a vein and some intraretinal microvascular abnormalities (IRMA). These are all characteristics of nonproliferative diabetic retinopathy (NPDR). *(Courtesy of Danielle Princiotta, COA).*

DME, it is recommended that the patient receive a month trial of corticosteroids, such as prednisolone acetate 1% eye drops four times daily, to check for an increase in IOP in response to steroid treatment. Steroids also increase the risk of cataract formation progressing in almost all patients who received the fluocinolone acetonide and, in theory, may have increased risk of endophthalmitis. Imposed monthly injections of ranibizumab were reported to be associated with increased risks of a broad definition of cardiovascular risks (hypertension, vascular death, non-fatal myocardial infarction, stroke) in 17–19% (Bressler et al., 2014; Brown et al., 2013; Domalpally, Ip, & Ehrlich, 2015). In part, this may be due to reduced serum VEGF levels associated with intravitreal anti-VEGF treatment. However, currently many physicians base whether to administer treatment with an anti-VEGF treatment on the finding of macular thickening and cysts on optical coherence tomography (OCT). If response does not occur following a number of treatments, e.g., 4 monthly injections, there are other medications including steroid formulations that can be considered.

Besides the benefit to DME, studies have also demonstrated that anti-VEGF treatment and some steroid formulations, e.g. fluocinolone acetonide, not only reduced progression of non-proliferative diabetic retinopathy but also reduced the severity of DR (Wykoff et al., 2016).

Other aspects of glycemic and lipid control have been evaluated for general diabetic care. Good glycemic control and use of fenofibrate were associated with slowed progression of diabetic



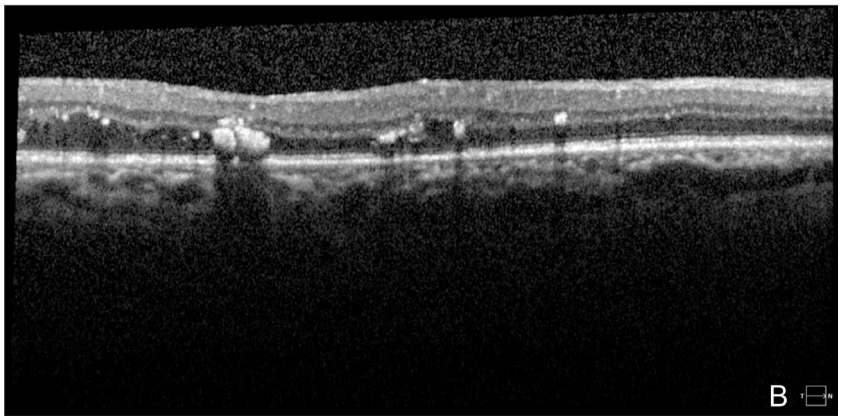


Fig. 2. A. Image of right eye with scattered yellow exudates, blot hemorrhages and microaneurysms in macula. B. Accompanying scan from a spectral domain optical coherence tomogram (OCT) showing cysts and highly reflective material in the inner and outer nuclear and plexiform layers.

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