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Diabetic choroidopathy

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ABSTRACT

Early histopathological studies of diabetic choroids demonstrated loss of choriocapillaris (CC), tortuous blood vessels, microaneurysms, drusenoid deposits on Bruchs membrane, and choroidal neovascularization. The preponderance of histopathological changes were at and beyond equator. Studies from my lab suggest that diabetic choroidopathy is an inflammatory disease in that leukocyte adhesion molecules are elevated in the choroidal vasculature and polymorphonuclear neutrophils are often associated with sites of vascular loss. Modern imaging techniques demonstrate that blood flow is reduced in subfoveal choroidal vasculature. Angiography has shown areas of hypofluorescence and late filling that probably represent areas of vascular loss and/or compromise. Perhaps, as a result of vascular insufficiency, the choroid appears to thin in DC unless macular edema is present. Enhanced depth imaging (EDI-SD) OCT and swept source (SS) OCT have documented the tortuosity and loss in intermediate and large blood vessels in Sattler's and Haller's layer seen previously with histological techniques. The risk factors for DC include diabetic retinopathy, degree of diabetic control, and the treatment regimen. In the future, OCT angiography could be used to document loss of CC. Because most of the measurement and imaging are in the posterior pole, the severity of DC may be underappreciated in the published accounts of DC assessed with imaging techniques. However, it is now possible to document DC and quantify these changes clinically. This suggests that DC should be evaluated in future clinical trials of drugs targeting DR because vascular changes similar to those in DR are occurring in DC.

1. Introduction

Diabetes mellitus (DM) affects all small and large blood vessels in the body. Vascular dysfunction eventually results in tissue injury and degeneration. In the eye, the focus has always been the retinal changes that result in diabetic retinopathy (DR). However, it would seem logical that the choroidal vasculature would also be affected in DM and the choroid itself would degenerate resulting in diabetic choroidopathy.

The first report on diabetic choroidopathy, technically a diabetes-induced non-inflammatory degeneration of choroid, was from Hidayat and Fine (1985) in a small cohort of endstage, blind and painful diabetic eyes (Hidayat & Fine, 1985). In this cohort, there was choriocapillaris (CC) dropout, luminal narrowing, and thickening of basement membranes with arteriosclerotic changes in some arteries. Fryczkowski performed vascular casts of a small cohort of diabetic eyes and analysed the choroidal vasculature with scanning electron microscopy (SEM) (Fryczkowski, 1988; Fryczkowski, Hodes, & Walker, 1989). Loss of CC, large and intermediate blood vessel tortuosity, vascular hypercellularity and microaneurysms were documented with SEM in the human diabetic choroids.

2. Choroidal vascular loss

We documented the loss of functional CC in diabetic choroid using endogenous alkaline phosphatase (APase) enzyme histochemical activity. APase stains the entire choroidal vasculature; when enzyme activity is not present, there are no viable endothelial cells (Fig. 1) (Lutty & McLeod, 2005; McLeod & Lutty, 1994). Furthermore, choroidal neovascularization (CNV) has the greatest enzyme activity (Fig. 2). Large fields of CC were dysfunctional in flat mount preparations of diabetic choroids using this histochemical analysis and the subjects were not endstage but rather represented all stages and types of diabetics, many without retinopathy (Lutty & McLeod, 2005; McLeod & Lutty, 1994). The loss of functional choroidal blood vessels could be quantified using this method and image analysis. There were two types of loss: diffuse and focal or complete. Diffuse loss had capillary segments missing but no defined areas of absolute CC loss, whereas focal or complete

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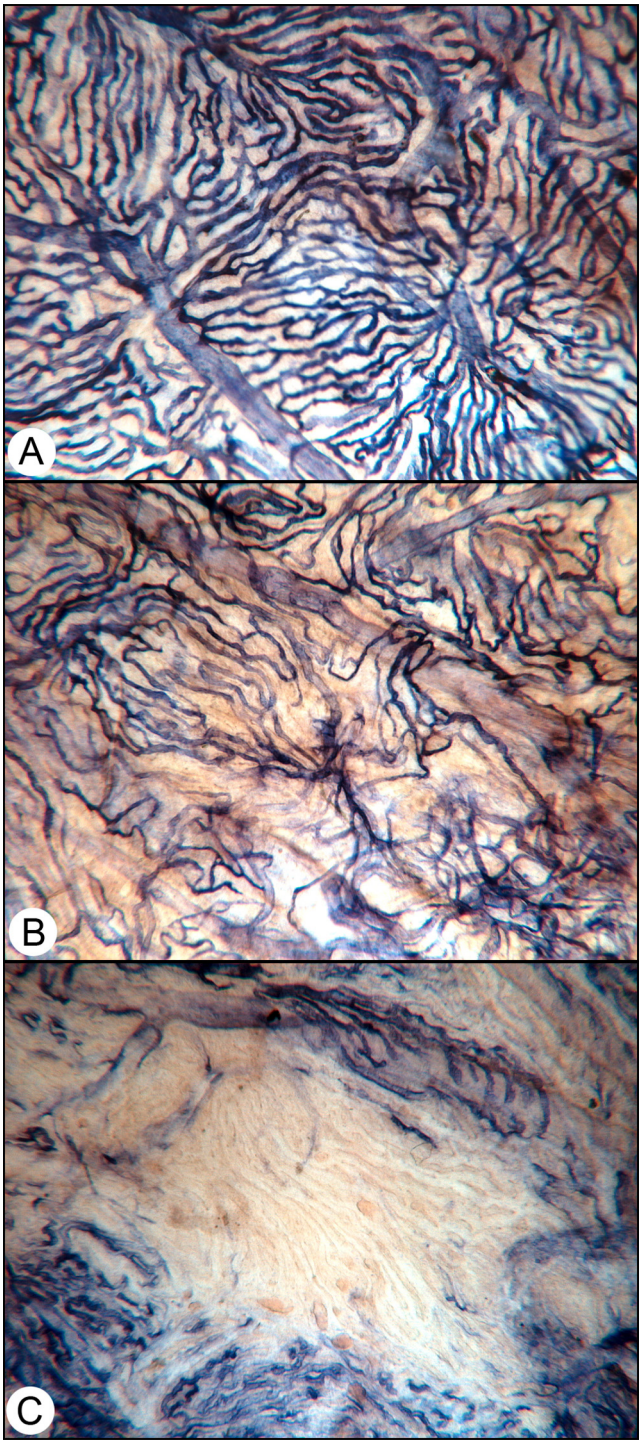

Fig. 1. Alkaline phosphatase-incubated choroid from a 50 year-old type 1 diabetic subject. (A) A normal area of choroid where all choriocapillaris are viable, i.e. are APase^{+}. Organized lobules are apparent in this area. (B) Area in the same choroid that has diffuse choriocapillaris loss. (C) An area of complete focal loss of choriocapillaris (Lutty, 2000, 2013) (With permission Fig. 2 in Lutty, *Invest. Ophthalmol. Vis. Sci.* 2013; 54: ORSF81-7. doi: 10.1167/iovs.13-12979).

loss had a defined border of atrophy with CC segments being APase^{-} (Fig. 1). The latter loss was able to be mapped and quantified and it was determined that there was four times more CC loss in diabetics than in older control, nondiabetic subjects (Cao, McLeod, Merges, & Lutty, 1998). We hypothesize that loss in viable vasculature resulted in hypoxic RPE and outer retina, for which the CC is the sole source of oxygen and nutrients.

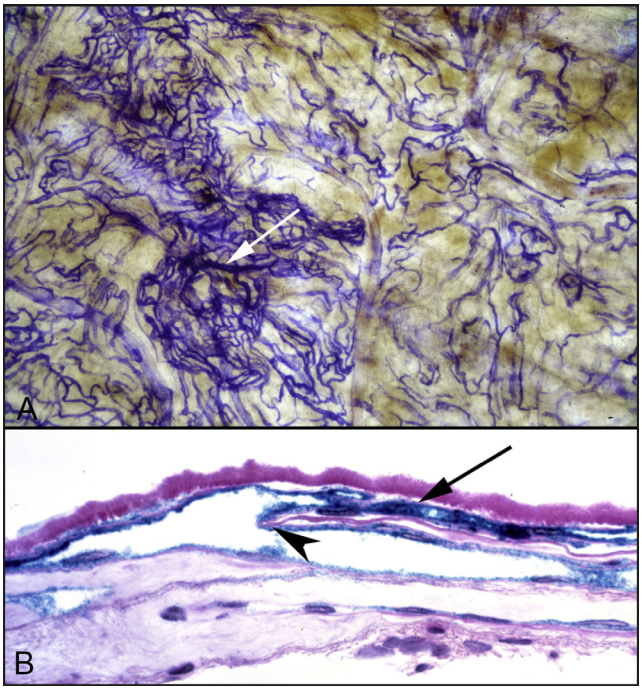

Fig. 2. Choroidal neovascularization (CNV) in diabetic choroid. (A) Alkaline phosphatase incubated choroid from an 74 year old type 2 diabetic that has a large CNV formation (arrow). The yellow material is basal laminar deposit which accumulates non-reduced formazan reaction product. The CNV formation is surrounded by areas with severe CC loss. (B) A section through the CNV that was stained with PAS (pink) and hematoxylin (purple) demonstrates a pink basal laminar deposit ocer the CNV (arrow, intense blue APase activity) which has grown through a break in Bruchs membrane (arrowhead) (McLeod & Lutty, 1994).

After the analysis of the vasculature in the flat perspective, the choroids were flat-embedded in glycol methacrylate, a transparent polymer from which two micron sections could be cut and then stained with tradition histochemical stains. Using PAS and hematoxylin staining, we observed accumulation of debris (PAS^{+}) on Bruchs membrane (BrMb) that was similar to basal laminar deposits (BLD) seen in age-related macular degeneration (AMD). The height of these deposits was quantified and related to the complete focal choriocapillaris degeneration (CCD) and choroidal neovascularization (CNV) (Fig. 3). The more severe the diabetic choroidopathy the greater the deposit height (Cao et al., 1998), suggesting that vascular insufficiency resulted in accumulation of debris on and in BrMb.

3. Etiology of choriocapillaris loss in diabetes

Diabetes is an inflammatory disease (Adamis, 2002). Elevated levels of TNFα and IL1β had been measured in diabetic sera compared to sera from control subjects, reinforcing DM as an inflammatory disease (Lampeter et al., 1992). Also, there are more activated leukocytes, especially polymorphonuclear neutrophils (PMNs), circulating in diabetics than in nondiabetics (Wierusz-Wysocki et al., 1987). It seemed logical that inflammation and inflammatory cells might contribute to loss of choroidal vasculature because Schmid-Schonbein had demonstrated accumulation of macrophages and PMNs in the retinas of diabetic rats (Schröder, Palinski, & Schmid-Schönbein, 1991). In addition, the choroid is the site of many inflammatory pathologies like multifocal and serpiginous choroiditis, bird-shot choroidopathy, uveitis, and Vogt–Koyanagi–Harada disease.

Our focus was on PMNs because, once firmly adherent, they can undergo an oxidative burst that can damage endothelial cells