Non-retinovascular leakage in diabetic maculopathy

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Abstract

Background—Diabetic macular oedema is the leading cause of vision deterioration in diabetic retinopathy. Extracellular fluid within the retina, which distorts the retinal architecture, was assumed to be strictly of retinal vasculature origin. However, there is some experimental evidence supporting clinical observations suggesting a possible role of the retinal pigment epithelium (RPE). An unusual form of diabetic maculopathy is presented in which the RPE and the subretinal space play the main role.

Methods—Fluorescein angiograms of 1850 non-proliferative diabetic retinopathy (NPDR) patients were examined. Nineteen eyes (14 patients, 1% of NPDR patients) met the criteria – mainly having minimal diabetic retinopathy with only a few microaneurysms and no clinically significant macular oedema (CSMO). Early phase angiograms were compared with late phase angiograms.

Results—It was found that in all 19 eyes the area of diffuse RPE late phase leakage was spread around the macular area. No cystic changes or cystoid macular oedema were present in any of the eyes and the visual acuity was 6/10 or better in all the eyes.

Conclusions—Possible changes occur in the RPE that may be responsible for the late leakage in NPDR patients – namely, diabetic retinal pigment epitheliopathy. These changes are associated with a breakdown of the outer blood-retinal barrier, consisting of leakage through RPE cells. No focal or diffuse leakage across the RPE has been reported in the literature related to the fluorescein angiograms in diffuse diabetic maculopathy.

(*Br J Ophthalmol* 1995; 79: 728-731)

Retinal ischaemia and oedema are the two major intraretinal components of diabetic maculopathy.¹ The variety of pathological changes that affect the macula, including capillary microaneurysms, capillary dilatation, and closure with areas of non-perfusion, focal or diffuse oedema, cystoid changes, and hard exudates, often make it difficult to relate abnormalities in visual function to a specific lesion.² However, it is known that diabetic macular oedema is the leading cause of decreased vision from diabetic retinopathy.³ Pathogenetically, the extracellular fluid within the retina increases, distorting the retinal architecture.^{1 3 4} Until recently it was assumed

that this fluid accumulation was strictly of retinal vasculature origin. However, some experimental evidence and clinical observations suggest a possible role for the retinal pigment epithelium (RPE).⁵⁻⁷ Macular oedema is one of the eligibility criteria for the early photocoagulation, as determined by the Early Treatment Diabetic Retinopathy Study Research (ETDRS) group.⁸ Fluorescein angiography is a necessary adjunct to treatment, serving as a guide by identifying sources of leakage.⁹

We present an unusual form of diabetic maculopathy in which the RPE and the subretinal space play the main role. Changes in the retinal capillary plane were absent or minimal; there was diffuse and extensive leakage from the RPE in the later phases of the angiogram. There was no clinically significant macular oedema (CSMO) as defined by the ETDRS or any cystoid changes in the macula, and visual acuity was good (6/10 or better).

Patients and methods

After our first observation of mild non-proliferative diabetic retinopathy (NPDR) with extensive leakage of fluorescein in the late phase, we analysed the fluorescein angiograms of 1850 NPDR patients taken between the years 1989 and 1993.

The patients were selected according to the following criteria:

- (1) Minimal diabetic changes in the retinal capillary plane at the macular area.
- (2) Impression of diffuse and extensive leakage in the subretinal space, as shown on stereoscopic view in the late phase of the angiogram.
- (3) Absence of CSMO (as defined by the ETDRS) in the colour photographs.
- (4) Absence of cystoid changes in the macular area.
- (5) Good visual acuity (6/10 or better).

Nineteen eyes of 14 patients met the above criteria. In five patients (10 eyes, 52.6%) the appearance in the two eyes was symmetrical; in the remaining nine patients (nine eyes, 47.4%), the appearance was unilateral, with minimal diabetic changes and a few microaneurysms without leakage in the other eye. Eyes with macular drusen or any signs of age-related macular degeneration (ARMD) were excluded from the study.

Analysis of the fluorescein angiograms was based on ETDRS report number 11.⁹

We analysed a 30° field (2F) of fluorescein angiographic negative slides, projected on a screen, extending along the horizontal meridian from about 5° temporal to the disc to about 20°

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Accepted for publication 8 March 1995

Figure 1 Grid dividing field 2F into nine subfields overlaid on a photograph of an early phase of fluorescein angiography. The radius of the innermost circle corresponds to 1/3 DD (considered to be 500 μ m) in the fundus of an average eye); the radii of the second and third circles correspond to 1 DD (1500 μ m) and 2 DD (3000 μ m), respectively.

temporal to the macula. The photographs of field 2F were taken at a rate of one frame per second, beginning 13 to 28 seconds after the fluorescein injection. Stereoscopic pairs of the 2F field were taken after the injection in a sequence of one pair per minute.

The grid, as suggested by the ETDRS,⁹ divided field 2F into nine subfields (Fig 1). The grid was projected together with the early and late negatives onto a screen. The radius of the innermost circle corresponded to the 1/3 disc diameter (DD) (considered to be 500 μ m), and the radius of the second and third circles was 1 and 2 DD, respectively. This division defined eight subfields around the foveal centre and one subfield in the macula including the foveal avascular zone (FAZ).

Using the early phase angiograms, we graded the patients according to the ETDRS report⁹ (Table 1):

- (1) Size of the FAZ.

Table 1 Classification of diabetic retinopathy from fluorescein angiography (EDTRS Report No 11)

Grading early phase photographs	
(1)	Size of the FAZ: Grade 0 = <300 μ m Grade 1 = 300 μ m Grade 2 = >500 μ m Grade 8 = Cannot grade
(2)	Outline of the FAZ: Grade 0 = Normal Grade 1 = Questionable Grade 2 = Destroyed less than one half of the circumference Grade 3 = Destroyed one half or more of the circumference Grade 4 = Outline completely destroyed Grade 8 = Cannot grade
(3)	Capillary loss: Step 0 = Absent (A) Step 1 = Questionable (Q) Step 2 = Definitely present (D) Step 3 = Moderate (M) Step 4 = Severe (S)
(4)	Arteriolar abnormalities: narrowing, staining and contour fuzziness
(5)	Capillary dilatation
(6)	Retinal pigment epithelial defects

FAZ=foveal avascular zone

- (2) FAZ outline: normal or qualified by damage to the surrounding capillary net.
- (3) Capillary loss: area of capillary non-perfusion.
- (4) Arteriolar abnormalities.
- (5) Capillary dilatation.
- (6) RPE defects.

On the late phase angiograms, we graded the patients according to the ETDRS report⁹ as well (Table 2):

- (1) Leakage from the centre of the macula.
- (2) Leakage source – if microaneurysms were found in one of the nine subfields, they were considered accountable for 11% of the leakage surrounding the fovea.
- (3) Cystoid changes in the retina in each of the subfields.
- (4) Diffuse RPE leakage without a retinal leakage source in each of the subfields.

Results

Of the 1850 eyes with NPDR, 19 eyes (1%) met the inclusion criteria. In the early phase of the angiograms, all 19 eyes were of normal foveal size ($\leq$ 300 μ m, grade 0 or 1).

In 17 eyes (89.4%) the FAZ outline was normal (grade 0), and in two (10.6%) there was minimal damage of the surrounding capillary net, affecting less than half a circle (grade 2).

One subfield (11% of the observed area) of capillary non-perfusion was definitely present in one eye (5.2%) (step 2), and one subfield was questionable in three eyes (15.7%) (step 1); in 15 eyes (78.9%) there was no sign of capillary non-perfusion (step 0).

Arteriolar abnormalities and capillary dilatation, as well as RPE defects, were absent in all eyes.

In the late phase of the angiograms, in 13 eyes (68%) no leakage was seen in the centre of the macula (grade 0). In two eyes (11%) a questionable leakage was seen in the macular circle (grade 1), and in four eyes (21%) the leakage covered the macular circle (grade 2). In four eyes one subfield (11%) of the leakage came from microaneurysms; in nine eyes two subfields (22%); and in six eyes three subfields (33%). Cystoid macular oedema or cystic changes were absent in all eyes. In all 19 eyes the area of diffuse RPE leakage was spread all over the eight fields surrounding the central macular circle (Fig 2).

Six patients (nine eyes) were followed for 1–3 years, and visual acuity of their affected eye was 6/10 or better, there was no change on

Table 2 Classification of diabetic retinopathy from fluorescein angiography (EDTRS Report No 11)

Grading late phase photographs	
(1)	Leakage at the centre of the macula: Grade 0 = No leakage Grade 1 = Questionable leakage Grade 2 = Definite leakage Grade 3 = Leakage from CMO Grade 8 = Cannot grade
(2)	Source of leakage (percentage from microaneurysms)
(3)	Cystoid changes
(4)	Other abnormalities: delay filling of retinal vasculature, choroidal leakage and macular hole

Fig 2A

Fig 2B

Fig 2C

Fig 2D

Figure 2 Early (A,B) and late (C,D) phase fluorescein angiograms of two representative cases. (A) and (B) present minimal diabetic changes, mainly microaneurysms. (C) and (D) present diffuse or focal leakage sites in and around the macular area.

the angiograms in the three patients (six eyes) with symmetrical angiogram appearance. In the other three patients with a non-symmetrical angiogram (three eyes), there was an increase in the number of microaneurysms, with pinpoint leakage around them.

Discussion

The two cell types responsible for the blood-retinal barrier, retinal pigment epithelial (RPE) cells and retinal capillary endothelial cells, are separated anatomically. Nevertheless, it is possible that an alteration in function in one cell type will lead to changes in the other.¹⁰ Until recently, the pathological changes in diabetic retinopathy were considered to be primarily of retinal vascular origin.^{11 12} These lesions are unique to the retinal circulation and include pericyte dropout, microaneurysm formation, and neovascularisation.^{13 14} Various studies,⁵⁻⁷ using fluorophotometric measurements, highlight the possible role of RPE dysfunction in the development of diabetic retinopathy, and especially diabetic maculopathy, by an early disruption of the blood-retinal barrier. Recently, Wong *et al*¹⁰ and Schweigerer *et al*¹⁵ found that RPE cells enhanced neovascularisation by producing basic fibroblast growth factor.

Glaser *et al*¹⁶ hypothesise that proliferating

RPE cells can inhibit retinal neovascularisation in diabetes.

Vinorez *et al*¹⁷ suggested that progressive damage to the RPE may occur during the course of diabetes. In an experimental study, the ultrastructural changes of the neural retina and RPE were examined in diabetic rats. Four types of changes occurred: (1) progressive thickening of the basal laminae of the RPE and the retinal capillaries; (2) progressive, often focal, thickening of the rest of Bruch's membrane; (3) marked dilatation of the basal infoldings of the RPE with formation of large vacuoles and cell swelling; (4) rare degenerative changes in the retinal capillary pericytes. Other studies¹⁸⁻²² also demonstrated similar structural RPE changes. According to one group,¹⁸ these changes are associated with a breakdown of the outer blood-retinal barrier, consisting of leakage through and staining of RPE cells by horseradish peroxidase; no leakage or staining was found by other groups.^{19 20} Under normal conditions, the RPE and Bruch's membrane are positioned as a barrier between the highly vascular choriocapillaris and the avascular outer retina.²² In general, RPE defects, through which fluorescence is transmitted from the choroidal circulation, appear early before the retinal vessels start to fluoresce.⁹ But what clinical evidence do we have of RPE dysfunction or breakdown of the

RPE barrier in diffuse diabetic macular oedema? To the best of our knowledge, no focal or diffuse leakage across the RPE has been reported in the literature related to the fluorescein angiograms either in diffuse diabetic maculopathy or in normal patients. However, subclinical focal or diffuse leakage through the RPE is a possibility that is difficult to prove.

The results of our study show angiographic findings which dispute the typical fluorescein picture of RPE defects, in that no early fluorescence was found in our patients. Likewise, one could expect to find capillary leakage in the early arteriovenous angiogram. It is possible that our group of patients, who constituted 1% of all NPDR patients observed at our centre, represent a subgroup of diabetic patients manifesting atypical diabetic retinal changes. This study raises many questions about the prognosis and progression of this form of diabetic retinopathy, such as why some patients presented with a non-symmetrical appearance, why visual acuity was not affected, and whether laser treatment is necessary in such cases? This study illuminates some different manifestations of diabetic retinal pigment epitheliopathy, which in our opinion should be noted and examined clinically, pathologically, and angiographically in larger series of patients.

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