Predictive Factors for the Progression of Diabetic Macular Ischemia

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• PURPOSE: To investigate the predictive factors for diabetic macular ischemia progression through the analysis of fluorescein angiography (FA) parameters.
• DESIGN: Retrospective, longitudinal study.
• METHODS: Data were collected from 79 eyes of 79 patients with type 2 diabetes mellitus. Macular ischemia severity was assessed using Early Treatment Diabetic Retinopathy Study (ETDRS) protocols and custom software used to quantify the foveal avascular zone (FAZ) area. Patients with ischemia grades "mild," "moderate," or "severe" and at least 2 macula-centered FA images over a minimum of 6 months were included. Main outcome measures were change in macular ischemia grades and FAZ enlargement rate (mm^2/year).
• RESULTS: The median FAZ areas in mild, moderate, and severe ischemia grades at baseline were 0.28, 0.37, and 0.73 mm^2, and significantly increased at the final FA (0.31, 0.41, and 1.23 mm^2) ($P = .001$). The median duration of follow-up was 27.5, 31.0, and 24.0 months, and was not significantly different between groups. FAZ enlargement rates were higher in the more advanced ischemia grades—"severe" (0.073 mm^2 [10.4%]/year) compared to "mild" (0.021 mm^2 [7.50%]/year) ($P = .02$) or "moderate" (0.019 [5.13%] mm^2/year) ($P = .03$). A greater ischemia severity grade was predictive for progression (odds ratio [OR] = 2.47, confidence interval [CI] = 1.21-5.05, $P = .02$). Macular ischemia progression itself was an independent predictive factor for visual acuity loss (OR = 4.60, CI = 1.54-13.7, $P = .03$).
• CONCLUSIONS: The rate of FAZ enlargement ranges from 5%-10% of baseline FAZ area per year in eyes with established ischemia. A greater macular ischemia grade was independently predictive for progression, and diabetic macular ischemia progression itself was predictive of the loss of visual function. (Am J Ophthalmol 2013;156:684–692. © 2013 by Elsevier Inc. All rights reserved.)

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DIABETIC MACULAR ISCHEMIA WAS FIRST ESTABlished using fluorescein angiography (FA) in the Early Treatment Diabetic Retinopathy Study (ETDRS).[1–3] Owing to the requirement of angiography for its evaluation, diabetic macular ischemia has not been studied in the pivotal epidemiologic studies of diabetic retinopathy, and is consequently not well understood.[4–6] Increasing our understanding of how quickly diabetic macular ischemia progresses, in whom it occurs, and its association with visual impairment is important in the clinical management of diabetic maculopathy. This may be of particular relevance because of emerging evidence for intravitreal pharmacotherapies, such as anti–vascular endothelial growth factor (VEGF), for the treatment of diabetic macular edema.[7–9]

The ongoing controversy regarding the potential adverse effects of anti-VEGF therapies on macular ischemia is largely based on case reports and noncomparative cases series—in patients receiving treatment for diabetic macular edema,[10–13] as an adjunctive treatment with pars plana vitrectomy in diabetic retinopathy,[14] and in eyes treated for exudative age-related macular degeneration.[15,16] These studies report that in the presence of macular ischemia, there is an adverse effect on outcomes, or a limit to the benefits of treatments. However, the deleterious effects of these intravitreal treatments on diabetic macular ischemia are far from clear. Firstly, larger prospective randomized trials, such as the Diabetic Retinopathy Clinical Research Network studies, did not address the potential effects of anti-VEGF therapy on ischemia.[7–9] Secondly, the Bevacizumab Or Laser Therapy (BOLT) trial, the only prospective study that examined macular perfusion, found no clear associations between intravitreal injections of bevacizumab and macular ischemia at 4 months.[17] In fact, a recent analysis of eyes with retinal vein occlusions has observed the opposite; that VEGF blockade with ranibizumab prevents, rather than worsens, "retinal nonperfusion."[18] Similarly, Neubauer and associates observed in eyes with diabetic macular edema an improvement in peripheral retinal ischemia after treatment with bevacizumab.[13]

In our previous cross-sectional study, we found that 41.3% of patients with diabetes had some form of macular ischemia.[19] However, a reduced visual acuity was only associated in those with moderate to severe disease (16.6%). It is not known if, or how quickly, diabetic macular ischemia progresses. Addressing the shortcomings in our knowledge

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of "diabetic macular ischemia progression" is likely to be of critical importance for a number of reasons. Firstly, the identification of those patients who are likely to progress may have considerable implications in those in a working age group. Secondly, it would aid in discerning between diabetic macular ischemia progression attributable to the natural history of the disease itself, or progression from the effects of treatments received, and may prevent the unnecessary exclusion of patients or untimely cessation of therapy.

In this report, we perform in-depth, longitudinal qualitative and quantitative analyses of the rate of progression for macular ischemia. We also examine clinical features at the baseline FA that may predict progression in an effort to identify parameters of interest for both clinical practice and future clinical trials.

PATIENTS AND METHODS

• **INCLUSION CRITERIA AND DATA COLLECTION:** In this retrospective cohort study, clinical and imaging data were collected from patients attending medical retinal clinics over a 6-month time period. Approval for data collection and analysis was obtained from the Institutional Review Board of Moorfields Eye Hospital, and adhered to the tenets set forth in the Declaration of Helsinki.

Patient demographic data, visual acuity, and retinopathy/maculopathy grades were obtained from standardized electronic reports in the United Kingdom National Screening Committee—Diabetic Eye Screening Programme, a grading system that has been described in more detail elsewhere.[20] Patients with a diagnosis of type 2 diabetes who underwent an FA within 6 months of the study period were included. FAs were graded according to ETDRS protocols (see below), and eyes with ETDRS-defined diabetic macular ischemia grades of "mild," "moderate," or "severe" and at least 2 macular centered FA images, separated by a minimum interval of 6 months, were identified.[2] Patients with a definite presence of macular ischemia—that is, those with "mild," "moderate," or "severe" macular ischemia grades—were included in order to assess the rate of progression and associations of this clinical entity. Exclusion criteria include ocular comorbidities such as retinal arterial or venous occlusion, epiretinal membrane, neovascular age-related macular degeneration, inherited macular disease, or macular scarring of any etiology. A total of 79 patients were identified; of these, 61 patients had both eyes meeting the criteria. From the remaining 18 patients, 1 eye was chosen from each patient using random block permutation and was included in the analysis. Clinical and imaging data from 2 time points were collected.

• **ACQUISITION AND ANALYSIS OF FLUORESCEIN ANGIOGRAMS:** *Grading methods for macular ischemia.* All angiographic images were acquired with a digital retinal camera system (Topcon TRC 50IX; Topcon Medical Systems Inc, Paramus, New Jersey, USA). One early-to-mid-phase image (at 20-40 seconds), centered on the macula, was chosen for analysis and no image manipulation was performed prior to grading. Figure 1 illustrates an example of FAs acquired over a period of 2 years. Macular ischemia was dual-graded by 2 masked assessors using protocols and standard photographs from ETDRS Report No. 11.[2,19] According to these criteria, diabetic macular ischemia was classified as none, questionable, mild, moderate, or severe. Substantial intergrader agreement was demonstrated, with a weighted kappa of 0.704 (standard error = 0.087, 95% confidence interval [CI] = 0.535-0.874). In the case of disagreement between graders, open adjudication was used to resolve the final grading decision.

Change in macular ischemia grades. The "baseline" FA was defined as the FA taken at the earlier time point and "final" FA and the later time point. A change in the macular ischemia grade, for example from "moderate" to "severe," was deemed as macular ischemia progression. FAs from both time points were graded in all eyes, and a change macular ischemia grade was defined as either "no change," "improvement," or "progression."

Quantification of the foveal avascular zone. Quantitative analysis of all images was performed using a validated image viewer and grading software package ("GRADOR"; Doheny Image Reading Center, Los Angeles, California, USA) that facilitates planimetric measurements.[19,21] Boundaries for the foveal avascular zone (FAZ) were manually delineated and area measurements calculated in square millimeters (mm^2), using a scale factor based on the camera's angle of view.

Quantification of the rate of foveal avascular zone enlargement. The "baseline" and "final" FAZ areas were quantified using the FA from the earlier and later time points, respectively. The rate of FAZ enlargement was calculated as the difference in area between the "baseline" and "final" FAs, expressed over the time interval between FAs (mm^2/year). The difference in area between the "baseline" and "final" FAs was also expressed as a percentage of the "baseline" FAZ size, in order to present the magnitude of change in FAZ size as a proportion of "baseline" measurements. This was similarly expressed over the time interval between FAs (%/year).

• **STATISTICAL ANALYSIS:** Clinical and imaging data were analyzed with frequency and descriptive statistics. Snellen visual acuities were converted to logMAR (logarithm of the minimal angle of resolution) visual acuity for the purposes of statistical analysis. The Wilcoxon rank-sum test was used for analysis of changes between baseline and final measurements in paired samples. The Mann-Whitney