Aim: To correlate change of an oedema index derived by scanning laser tomography with change of visual function in patients undergoing grid laser photocoagulation for clinically significant diabetic macular oedema (DMO).

Methods: The sample comprised 24 diabetic patients with retinal thickening within 500 µm of the fovea. Inclusion criteria included a logMAR visual acuity of 0.25, or better. Patients were assessed twice before a single session of grid laser treatment and within 1 week of, and at 1, 2, 4, and 12 weeks after, treatment. At each visit, patients underwent logMAR visual acuity, conventional and short wavelength automated perimetry (SWAP), and scanning laser tomography. Each visual function parameter was correlated with the mean oedema index. The mean oedema index represented the z-profile signal width divided by the maximum reflectance intensity (arbitrary units). A Pearson correlation coefficient (Bonferroni corrected) was undertaken on the data set at each time point.

Results: 13 patients exhibited significant correlation of the mean oedema index and at least one measure of visual function for the 10° × 10° scan field while 10 patients correlated for the 20° × 20° scan field. Seven patients demonstrated correlation for both scan fields. Laser photocoagulation typically resulted in an immediate loss of perimetric sensitivity whereas the oedema index changed over a period of weeks. Localised oedema did not impact upon visual acuity or letter contrast sensitivity when situated extrafoveally.

Conclusions: Correlation of change of the oedema index and of visual function following grid laser photocoagulation was not found in all patients. An absence of correlation can be explained by the localised distribution of DMO in this sample of patients, as well as by differences in the time course of change of the oedema index and visual function. The study has objectively documented change in the magnitude and distribution of DMO following grid laser treatment and has established the relation of this change to the change in visual function.
detailed explanation), oedema maps are generated which illustrate the extent and topographic magnitude of oedema across the SLT image. Note that the term “oedema” is used rather than “thickening” since the analysis incorporates two aspects of the effect of oedema on the z-profile. The oedema index analysis accentuates the presence of oedema rather than simply analysing the effect of retinal thickening. The oedema mapping technique is performed on an individualised basis and it has the advantage of being independent of a reference plane.14

The aim of the study was to determine correlation, if any, between change of the oedema index with change of visual function over the 3 month time course of the study for patients undergoing grid laser photocoagulation for clinically significant DMO. Elicitation of the relation between the oedema index and visual function will improve the understanding of the effects of laser photocoagulation on retinal morphology and vision.

**PATIENTS AND METHODS**

**Sample**
The sample comprised 24 patients (18 males and six females) with clinically significant DMO as defined by the Early Treatment Diabetic Retinopathy Study criteria.15 All diabetic patients exhibited oedematous maculopathy (with or without some non-circinate exudate) that was of non-uniform thickness across the macula. Two medical retina specialists independently confirmed the diagnosis of clinically significant DMO using stereo fundus biomicroscopy before inclusion of the patient into the study. The research followed the tenets of the Declaration of Helsinki. Informed consent was obtained from all subjects after explanation of the nature and possible consequences of the study. The study received approval from the Central Manchester research ethics committee. The mean age of the diabetic patients was 59.75 years (SD 8.05 years, range 45–75 years) and the mean time from diagnosis of diabetes was 8.39 years (SD 4.89 years, range 2–18 years). Three diabetic patients were insulin dependent and 21 patients were receiving oral hypoglycaemic medication. One eye was randomly assigned to the study if both eyes exhibited clinically significant DMO; 11 right eyes and 13 left eyes were assessed. A conservative standardised effect size of 1.0 (based upon the level of variance of the oedema mapping technique in diabetic subjects) was employed for the sample size estimation—that is, the standard deviation of the oedema index was assumed to be equal to the expected effect size. Using a two tailed $\alpha$ of 0.05 and a $\beta$ of 0.10 (that is, power = 90%), the minimum sample size for the diabetic patient group was calculated to be 21.

Inclusion criteria for all patients included a logMAR visual acuity of 0.25 or better using the 96% contrast Regan chart (that is, Snellen equivalent visual acuity of 20/30). Exclusion criteria comprised: (i) a distance refractive error greater than plus or minus 6.00 dioptres sphere and/or greater than plus or minus 1.50 dioptres cylinder; (ii) a family history of glaucoma in a first degree relative; (iii) an intraocular pressure minus 1.50 dioptres cylinder; (ii) a family history of glaucoma plus or minus 6.00 dioptres sphere and/or greater than plus or minus 21 mm Hg; (iv) any other eye disease or disorder (including significant lenticular opacity, see below); (v) any previous laser photocoagulation treatment; (vi) proliferative diabetic retinopathy and its sequelae—for example, vitreous haemorrhage and retinal detachment; (vii) central nervous system (CNS) disorders or psychiatric illness; and (viii) systemic medication with known CNS effects—for example, tranquillisers. Lenticular opacity was graded on the basis of slit lamp appearance and the Lens Opacities Classification System (LOCS) III.16

All eyes with the following LOCS III grades were excluded from the study: (i) nuclear colour > NC2; (ii) nuclear opalescence > NO2; (iii) cortical cataract > C2; and (iv) posterior subcapsular cataract $\geq$ P1.
Scanning laser derived oedema index and diabetic macular oedema

Scanning laser tomography

The Heidelberg retina tomograph (HRT) (Heidelberg Engineering, Heidelberg, Germany) was used to acquire topographic measurements of the macula of each patient. The HRT has been described in detail elsewhere. Single two dimensional section images, comprising 256 × 256 pixels (each with 8 bit intensity resolution), were recorded at a repetition rate of 20 Hz. Topographic fundus measurement was achieved by scanning 32 section images (termed a series image) along the optical axis over a period of 1.6 seconds. For each point, within the image, the resulting plot of reflectance intensity versus scan depth is termed a z-profile. The peak intensity of the z-profile is assumed to indicate the depth of the vitreous/internal limiting membrane interface.

The refractive error and corneal curvature of each patient was entered into the HRT database before image acquisition (and were unchanged over the period of the study). Steady fixation was achieved using a periscope and a 60 W light placed at a distance of 3 metres that was viewed with the fellow eye—that is, the periscope allowed patients to see around the HRT during the acquisition of macular images. The monitor aiming cross was employed to centre the image frame on the fovea. Seven HRT images were acquired both for the 10° × 10° and the 20° × 20° scan fields at each visit. Scan depth remained constant throughout repeated HRT image acquisition of a given eye both within and between visits.

Analysis

Automated perimetry data

Automated perimetry printouts that exhibited false positive or false negative catch trial response rates greater than 33%, and those that exhibited fixation loss greater than 20%, were excluded from the analysis. The respective perimeter results from the diabetic patients were compared to databases of normal fields. For conventional automated perimetry, the established STATPAC II normal database of HFA program 10-2 was utilised. For SWAP, normal HFA program 10-2 sensitivity values were derived from the results of 400 normal subjects between the ages of 18 and 84 years (mean age 48 years, SD 17 years) who had undergone SWAP using program 30-2. The details of the derived program 10-2 normal database have been described in detail elsewhere. In brief, a weighted linear interpolation procedure, based upon the angular distance between each 10° × 10° stimulus location and the four surrounding 30-2 locations, was used to derive normal program 10-2 short wavelength perimetric thresholds. The short wavelength sensitivity of a given stimulus location for each diabetic patient was then compared to the mirror image location in the opposite horizontal hemifield of the same eye. Those stimulus locations that exhibited negative asymmetries greater than the confidence limits of the normal database were recorded. This analysis was developed in order to negate the effect of pre-receptor absorption and light scatter on short wavelength sensitivity—that is, it was sensitive to defects in the shape of the SWAP “hill of vision” rather than being dependent upon absolute sensitivity. The area (degrees2) of clusters (that is, three, or more, contiguous stimulus locations) of stimulus locations with negative asymmetries reaching statistical probability levels of p < 0.05 and p < 0.005 was calculated.

Scanning laser tomography data

The SLT images were analysed with the aid of custom software provided by Heidelberg Engineering (Heidelberg, Germany). The custom software produced image files of maximum reflectance intensity and of z-profile signal width. “Super pixel” values were averaged from each set of 4 × 4 pixels; the resulting resolution of the maximum reflectance intensity and the z-profile signal width image files was 64 × 64 super pixels. The z-profile signal width was measured at 50% of the maximum reflectance intensity following fitting of the z-profile with a 16th order polynomial. The data files were subsequently downloaded for custom analysis using the oedema mapping software utility (TView J Cassidy, JG Flanagan, and C Hudson). The maximum reflectance intensity maps were normalised in order to express reflectance intensity as a function of the range of intensity values within a given image. The normalisation procedure reduced the influence of variation in reflectance intensity between successive SLT images. The oedema index was then calculated for each pixel, such that:

Oedema index = SW/NI

where SW is the signal width (µm) of the z-profile and NI is the normalised maximum reflectance intensity (arbitrary units), at a given pixel. Consequently, the determination of the oedema index is a relative measurement and the derived values are in arbitrary units.

The mean oedema index provided a global summary that averaged the oedema index values of every pixel within the scan field. Manual alignment algorithms (TView) were used to establish the area of the oedema map that was common to each of the constituent SLT images; the common area was then used to calculate the mean oedema index for each visit and to analyse change in the oedema index between visits.

A Pearson correlation coefficient was undertaken on the data set of each diabetic patient to establish the correlation between change of visual function and change of the mean oedema index over the time course of the study. The following visual function parameters were used: (i) Regan logMAR visual acuity at 96%, 25%, and 11% contrasts; (ii) mean deviation (MD) and corrected pattern standard deviation (CPSD) of conventional automated perimetry; and (iii) SWAP cluster area of stimulus locations reaching statistical probability levels of p < 0.05 and p < 0.005. Correlation over the time course of the study resulted when the oedema index reduced and visual function improved, and/or when the oedema index increased and visual function deteriorated. Visual function was correlated with the mean oedema index derived for the 10° × 10° and 20° × 20° scan fields. A Bonferroni correction was applied to the correlations to correct for type I experimental error (since multiple comparisons were undertaken on the mean oedema index to establish any significant correlation with the various parameters of visual function). Consequently, p < 0.001 was taken to indicate significant correlation.

RESULTS

Correlation of change of the mean oedema index and change of visual function over the time course of the study was found in 16 of the eligible 22 diabetic patients. One diabetic patient withdrew from the study after visit 3 and another patient was excluded from the correlation analysis owing to unreliable automated perimetry results. Thirteen diabetic patients exhibited significant correlation of the mean oedema index and at least one measure of visual function for the 10° × 10° scan field and 10 patients showed correlation for the 20° × 20° scan field. Seven patients demonstrated correlation for both scan fields. For the 10° × 10° scan field, four patients exhibited correlation with visual acuity (for one, or more, of the three Regan charts). Four patients exhibited correlation with SWAP (for one, or both, of the cluster area statistical levels), two of which also correlated with visual acuity. In addition, six patients exhibited correlation with MD. Six patients correlated with CPSD of conventional perimetry, four of which also correlated with MD. A single patient exhibited correlation with all visual function parameters—that is, visual acuity, MD, CPSD, and SWAP.

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For the 20° × 20° scan field, six patients exhibited correlation with visual acuity. Six patients correlated with SWAP, two of which also exhibited correlation with visual acuity. Three patients exhibited correlation with CPSD; all three of these patients also exhibited correlation with SWAP. In addition, two patients correlated with MD, both of which also correlated with CPSD and SWAP. A single patient exhibited correlation with all visual function parameters.

Two of the patients were selected for detailed description to illustrate a situation in which no correlation occurred (patient 1) and a situation in which significant correlation occurred with visual function (patient 23). The oedema maps (10° × 10° scan field) for diabetic patient 1 are shown in Figure 1. The corresponding time courses of change in the mean oedema index and visual function are shown in Figure 2. Patient 1 exhibited no correlation of the mean oedema index and any measure of visual function for either of the scan fields. The mean oedema index of patient 1 reduced 3 days after laser treatment, despite a localised increase of the oedema index involving the fovea (Fig 1) and then progressively increased to reach a maximum at week 4 (Fig 2). The mean oedema index subsequently returned to approximately baseline values at 12 weeks after laser treatment. The measures of visual function all showed an initial deterioration that reached a maximum at 1–2 weeks after laser treatment and then subsequently improved. Conventional perimetry and SWAP had deteriorated at 12 weeks after laser treatment relative to baseline. Visual acuity deteriorated 3 days after laser treatment, consistent with the localised change in the oedema index involving the fovea, before eventual recovery (from week 2 onwards).

Figure 1  Oedema maps for diabetic patient 1 (left eye, 10° × 10° scan field). The whiter the pixel the greater the magnitude of the oedema index [A; baseline. B, C, D, E, and F; 3 days, 1, 2, 4, and 12 weeks post-treatment, respectively]. The fovea is located approximately in the centre of each scan.

Figure 2  Time course of change in the mean oedema index value (upper left) for the 10° × 10° and 20° × 20° scan fields and the various parameters of visual function for diabetic patient 1 (left eye). Upper right: Regan logMAR visual acuity (at 96%, 25%, and 11% Weber contrasts). Lower left: MD and CPSD of conventional perimetry. Lower right: SWAP cluster volume (at statistical probability levels of p<0.05 and p<0.005).
The oedema maps (20°×20° scan field) for the baseline and subsequent visits of diabetic patient 23 are shown in Figure 3. The corresponding time courses of change in the mean oedema index (10°×10° and 20°×20° scan fields) and the various parameters of visual function are shown in Figure 4. Patient 23 exhibited significant correlation of change of the mean oedema index for the 10°×10° scan field and SWAP cluster area (p<0.005). Patient 23 also exhibited significant correlation of the mean oedema index for the 20°×20° scan field and visual acuity (at 25% contrast), MD, and CPSD of conventional perimetry and SWAP cluster area (p<0.005). The mean oedema index increased 3 days after laser treatment (Fig 4) and subsequently reduced relative to baseline. Those visual function parameters that demonstrated significant correlation deteriorated 3 days after laser treatment and/or improved relative to baseline.

**DISCUSSION**

The group mean oedema index for all pixels within 10°×10° and 20°×20° scan fields for a group of 56 elderly normal subjects has previously been reported to be 1.21 (SE 0.04) and 1.57 (SE 0.06) (arbitrary units) respectively.

The corresponding values for a group of 24 age matched patients with clinically significant DMO were found to be significantly higher—that is, 1.57 (SE 0.10) and 1.97 (SE 0.11) respectively. The group mean coefficient of repeatability, which defines the 95% confidence limits for repeatability, when expressed as a function of the group mean oedema index was found to be approximately 25%. Change of the mean oedema index over the time course of the study correlated with at least one of the three functional outcome measures (that is, logMAR visual acuity, conventional perimetry, and SWAP) in 16 of 22 eligible diabetic patients.
patients. Thirteen patients correlated for the 10° × 10° scan field and 10 patients for the 20° × 20° scan field; seven patients demonstrated correlation for both scan fields. Correlation of the mean oedema index and of visual function, however, was not found for every combination of parameters, or for every diabetic patient. This finding is consistent with the localised distribution of DMO and obvious differences in the time course of change of the various parameters.

The mean oedema index represents the average of the oedema index of every pixel within the scan field. All of the diabetic patients in this study exhibited localised areas of DMO. In some cases, localised change of the oedema index, although clearly visible on the oedema maps, could be observed in the lack of change within the complete scan field (analogous to relying upon the MD index of automated perimetry to detect a focal relative visual field defect). Deterioration in visual acuity can result if a localised increase in the oedema index involves the fovea; such effects can occur alongside minimal change, or even a reduction, of the global mean oedema index (for example, patient 1). These findings emphasise the value of the oedema mapping technique. Reliance upon a global measure of retinal oedema in some situations will fail to detect subtle localised change. Similarly, techniques that rely upon a high level of interpolation (that is, previous values are inferred from closest nearby measured points rather than measured directly) to produce topographic maps of retinal thickening, such as optical coherence tomography and the retinal thickness analyser,15 will also fail to detect the true extent and magnitude of subtle localised change.

Obvious differences were also apparent in the time course of change of the various parameters. Grid laser photocoagulation typically resulted in an immediate localised sensitivity loss for conventional and short wavelength perimetric sensitivity11 whereas the resulting change of the mean oedema index occurred over a period of weeks (for example, patients 1 and 23). In addition, SWAP typically showed extensive and deep localised visual field loss in the diabetic patients before treatment16 and, consequently, was unable to reflect post-laser change of DMO because of dynamic range limitations imposed by the design of the perimetric stimulus. Interestingly, no relation was found between the photocoagulation treatment parameters and the various outcome measures—the sample size was too small, however, for such a relation to be revealed.

To the best of our knowledge, no other study that has utilised an objective measure of retinal oedema has detected a transient increase of DMO following laser treatment (for example, patients 1 and 23). This can frequently be explained by an insufficient frequency of follow up. A transient increase of DMO involving the fovea is often clinically suspected following grid laser photocoagulation and is usually associated with a concomitant temporary reduction of visual acuity. Patients who exhibited an obvious post-laser reduction in visual acuity (for example, patient 1) showed an increase in localised oedema situated at the fovea (Fig 1). Resolution of the post-laser increase of the oedema index (for example, patient 23) was associated with a relative recovery of perimetric sensitivity and visual acuity (Fig 4). Indeed, we have previously reported a general recovery of perimetric sensitivity and visual acuity 3 months post-laser (relative to 3 days post-laser) in the same cohort of patients.11 The finding of a transient increase of DMO following treatment objectively documents the initial response of the retina to grid laser photocoagulation. By the same token, panretinal (or peripheral scatter) photocoagulation can result in a more obvious transient reduction of visual acuity that is associated with the spontaneous development of macular oedema or the worsening of pre-existing DMO.17 Uncorrected refractive error can result in broadening of the z-profile18 and, consequently, artefactual increase of the oedema index. The spherical refractive error component was corrected for every patient by appropriate adjustment of the refraction on the HRT control panel. Cylindrical refractive error was not corrected; however, only one diabetic patient had astigmatism greater than 0.75 dioptres and the study essentially measured change in the oedema index over time. Consequently, the impact of astigmatism on the outcome of the study was minimal.

In summary, this study has objectively and non-invasively documented change in the magnitude and distribution of DMO for patients undergoing grid laser treatment and has established the relationship of this change to that of visual function. Correlation of change over time in the two main parameters of the study—that is, visual function and the SLT derived oedema index, occurred in 16 patients. Significant correlation did not occur in all possible situations because, first, grid laser photocoagulation typically resulted in an immediate loss of perimetric sensitivity whereas the oedema index changed over a period of weeks. Secondly, localised oedema failed to impact upon visual acuity or letter contrast sensitivity when situated extrafoveally. Thirdly, localised change of the oedema index was often obscured by the lack of change within the rest of the scan field. Furthermore, the study has revealed new information about the progress of DMO following laser treatment. The finding of a transient increase of DMO objectively documents the initial response of the retina to grid laser photocoagulation. In addition, the protocol described in the paper can be used in the future to effectively evaluate new treatment strategies for the amelioration of DMO.

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