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Visual fields correlate better than visual acuity to severity of diabetic retinopathy

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Abstract *Aims/hypothesis:* We compared the outcomes of perimetric and visual acuity tests in patients with diabetic retinopathy. *Methods:* We examined 59 diabetic patients with different degrees of retinopathy using stereo fundus photography in accordance with the Early Treatment of Diabetic Retinopathy Study (ETDRS) and fluorescein angiography. Conventional white-on-white perimetry (WWP) and short wavelength automated perimetry (SWAP) were performed and analysed with reference to normal values. Visual acuity was measured with ETDRS charts. *Results:* Regression analysis revealed that visual acuity was significantly associated with increasing severity of retinopathy according to the ETDRS scale when visual acuity was estimated by counting logarithm of minimum angle of resolution (LogMar) scores, but not when visual acuity was measured by the conventional reading of the smallest line that could be seen. Visual acuity decreased by 0.02 LogMar per ETDRS step ($p=0.03$). The degree of visual field loss was significantly associated with increasing severity of retinopathy according to the ETDRS scale, perimetric sensitivity decreasing by 0.44 dB per ETDRS step ($p=0.0001$) using WWP, and by 0.40 dB per ETDRS step ($p=0.04$) with SWAP. The size of the area of the foveal avascular zone and adjacent perifoveal intercapillary areas (PIAs) also affected the central visual field as obtained both by WWP (-2.6 dB/mm², $p=0.03$), and by SWAP (-7.9 dB/mm², $p=0.002$), but did not affect visual acuity. The regression model fit for peripheral retinopathy according to the ETDRS scale was better using WWP than SWAP or visual acuity, while SWAP testing was superior to both WWP and visual acuity when measuring effects caused by enlarged foveal

avascular zones and PIAs. *Conclusions/interpretation:* Perimetry can provide more useful information than visual acuity on functional loss in diabetic retinopathy, particularly when the perifoveal capillary network is damaged.

Keywords Diabetic retinopathy · Foveal avascular zone · Perimetry · Visual acuity · Visual fields

Abbreviations dB: decibel · ETDRS: Early Treatment Diabetic Retinopathy Study · FAZ: foveal avascular zone · LogMar: logarithm of minimum angle of resolution · MD: mean deviation · PIA: perifoveal intercapillary area · r^2 : coefficient of determination · SITA: Swedish Interactive Threshold Algorithms · SWAP: short wavelength automated perimetry · WWP: white-on-white perimetry

Introduction

Diabetic retinopathy is a major cause of acquired blindness before 65 years of age in the industrialised countries in the Western world, but is also a rapidly increasing problem in urban areas in developing countries [1]. Once sight-threatening vascular changes have developed, laser therapy can substantially reduce the risk of vision loss [2], but to prevent or delay progression of vascular abnormalities, it is necessary to regulate the hyperglycaemic and related metabolic disturbances by systemic drug therapy [3]. The effects of drug therapy have been and still are monitored using photographic assessment of morphological vascular changes in the retina, based on findings from seven stereo fundus photographs of specified retinal fields. Of the severity scales used for this assessment, that presented by the ETDRS group is probably one of the most widely accepted and used [4]. However, it would be extremely useful to be able to assess the course of diabetic retinopathy not only by morphology but also by monitoring visual function.

Conventional white-on-white perimetry (WWP) has been reported to enable identification of retinal changes

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caused by diabetes in their early stages [5–6], and selective loss of short wavelength sensitivity has been reported in diabetic patients with no or minimal retinopathy [7–8]. Blue-on-yellow, or short wavelength automated perimetry (SWAP), has been suggested to be more sensitive to early retinal changes than WWP. A number of studies have compared SWAP and WWP in patients with diabetes [9–13], but the results are not conclusive regarding the relative usefulness of these two tests. Few studies have assessed to what extent the perimetry can document functional loss due to diabetes-induced damage of the perifoveal capillary network [10].

In the present study, we explored visual field defects in diabetic patients and compared related WWP and SWAP test modalities, using the Statpac mean deviation (MD) and pattern deviation probability map concept to analyse all perimetric test results [14]. Our primary aim was to assess visual field defects using the specified methods in patients with different degrees of diabetic retinopathy according to the ETDRS severity scale. The secondary aim was to correlate visual field data to vascular occlusion in the foveal region, i.e. the size of the foveal avascular zone (FAZ) and the most adjacent perifoveal intercapillary areas (PIAs) as visualised by fluorescein angiography.

Subjects, methods and materials

Subjects

Patients with different degrees of diabetic retinopathy, and who regularly attended the outpatient clinic at the Department of Ophthalmology, Malmö University Hospital, gave their informed consent to participate in the present study, which was approved by the Ethics Committee of Lund/Malmö. Inclusion criteria were: age less than 70 years, no ocular disease that could impact visual function apart from diabetic retinopathy and minimal to mild cataract, and no previous laser treatment of the examined eye. One eye of each patient was included. If both eyes were eligible and had different visual acuity, the eye with the best visual acuity was selected. Data on age at diagnosis, and duration of diabetes were collected.

Characterisation of vascular changes and cataract

Fundus photography and grading of retinopathy

After dilatation of the pupil, stereo fundus photographs of seven 35° standard fields of the retina [4] were taken using a retinal camera (TRC 50 IX; Topcon, Tokyo, Japan) and colour slide film (Kodachrome 64). Grading of retinopathy was performed in a masked fashion using the 11 steps of the ETDRS severity scale [4]. Macular oedema was defined as any thickening of the retina within the vessel arcades.

Fluorescein angiography

Fluorescein (25%) angiography was performed after dilatation of the pupil. Digital images were taken using a retinal camera (Topcon) in one 35° field, centred on the fovea, and processed in the commercially available Image Net 2000 system, version 2.55 (Topcon). The borders of the FAZ and each PIA adjacent to the avascular zone were marked as described by Sleightholm et al. [15] (Fig. 1), and the areas were calculated using Topcon Image Net 2000 system software. The FAZ borders were defined on two different occasions 1 week apart. The concordance between the two independent measurements was high; the correlation coefficient was 0.99 when including all subjects with measurable FAZ. After excluding one outlier, which had a

Fig. 1 The FAZ (marked zone in middle) and adjacent PIA (marked zones surrounding the middle zone) in a 30-year-old patient with type 1 diabetes (a). Corresponding visual field defects in WWP (b) and SWAP (c). Grey-scale representations are based on differential light sensitivity values expressed in dB. Probability maps show the statistical significance of test point locations with sub-normal sensitivity values after eliminating effects of cataract

very large FAZ of 3.9 mm², the correlation coefficient was 0.93.

Cataract

The presence of lens opacities was graded using a slit lamp microscope and the Lens Opacities Classification System II [16].

Characterisation of visual function

Visual acuity

The ETDRS charts [17] were used when measuring visual acuity. Best corrected visual acuity was estimated in two ways: (1) by the smallest line on the chart where the individual could read all letters; (2) by counting logarithm of minimum angle of resolution (LogMar) scores [18], i.e. a threshold estimate of visual acuity.

Visual field tests

All visual fields were tested using the Humphrey field analyser 750 (Carl Zeiss Meditec, Dublin, CA, USA). To minimise perimetric learning effects, a training session was performed for both WWP and SWAP procedures on a first visit. On the second visit, patients underwent four different perimetric examinations, two with SWAP and two with WWP. For each test modality we obtained one 24-2 field including 54 test point locations within the central 24° of the visual field, and one high-resolution 10-2 field with 68 test points covering the central 10°. All subjects were tested in the same order: 24-2 Swedish Interactive Threshold Algorithms (SITA) SWAP [19], 10-2 Full Threshold SWAP, SITA Standard 24-2 WWP, and a 10-2 SITA Standard WWP. In general, the different tests lasted 3 min for SITA SWAP 24-2, 12 min for Full Threshold SWAP, and 4 to 5 min for both 10-2 and 24-2 SITA Standard WWP. Despite the short test times for most perimetric programmes, all patients were required to rest between the visual field tests to avoid fatigue effects. The Statpac program implemented in the Humphrey field analyser [20] was used to interpret the results of the WWP, while a preliminary Statpac was used to interpret 24-2 SITA SWAP [21]. Reliability parameters, e.g. frequencies of fixation losses, false negative and false positive answers, were used without set criteria. The reasons for this are that fixation loss monitoring using the blind spot method does not perform well in SWAP, since in SWAP a Goldmann stimulus size V is used. A large percentage of subjects report seeing the large bright stimulus when it is exposed in the blind spot, even when fixation is perfect according to the screen monitor. High frequencies of false answers can seriously affect test results, but were not used as an exclusion criterion in this study. The purpose was to test the applicability of perimetry in an ordinary clinical setting of

patients at different stages of diabetic retinopathy, and not in elite observers.

No Statpac limits were available for the 10-2 Full Threshold SWAP test. To analyse these visual field tests using the same parameters as those applied in the other tests, we collected a normal database including 180 eyes of 90 healthy subjects and calculated a new Statpac for 10-2 SWAP. The mean age of these healthy subjects was 45 years (range 20 to 79). They had no or very limited experience of perimetry, and therefore all underwent training for WWP and SWAP prior to inclusion. The 10-2 SWAP normal database was then processed in a way that was almost identical to that of the original Statpac for WWP [14] (Fig. 2). Thus, MD values and pattern deviation probabilities maps, which are both part of the Statpac interpretation tool, were also made available for the 10-2 Full Threshold SWAP.

Statistical methods

Visual function and retinopathy according to the ETDRS scale

The 24-2 pattern, which examines a larger area, was used when correlating the degree of retinopathy according to the ETDRS scale [4] to visual field loss. The 10-2 pattern, which tests inside the central 10° of the visual field, was used when comparing the size of the FAZ and PIA with visual function.

The correlations between WWP or SWAP and the 11 steps of the ETDRS retinopathy scale were analysed by linear regression. Two visual field parameters were included in the analyses, MD values and number of significantly depressed test points in the pattern deviation probability maps at the $p < 0.01$ level.

Fig. 2 Profile of the hill of vision along the horizontal meridian for a right eye. **a** WWP age-corrected normal values; **b** WWP depression needed to reach $p < 0.01$ limit; **c** SWAP age-corrected normal values; **d** lower SWAP sensitivities needed to reach $p < 0.01$ limit

The effects of retinopathy on visual acuity were also analysed by linear regression.

Visual function and FAZ+PIAs

The effects of the size of the FAZ and PIAs on the central and paracentral visual field were analysed using multivariate linear regression models. To avoid dilution of the effects caused by more peripheral retinal damage, new MD values (6° MD) were calculated based on the 16 test points inside the central 6°. The 10° field including 68 test points covers approximately 6.25 mm² on the retina, while the 6° field covers approximately 2.25 mm². The maximum FAZ area among our patients was 1.47 mm² after exclusion of one extreme outlier with an FAZ area of 3.9 mm². The number of significantly depressed points at the $p<0.01$ level inside the same central 6° area was compared with the size of the FAZ and PIAs, and also to the number of PIAs.

To avoid confounding effects, the presence or absence (20/38) of macular oedema was also included. The association between FAZ+PIAs and visual acuity was estimated by linear regression.

Results

General

Of the 63 patients included, 59 completed all examinations. Thus, most analyses are based on 59 patients. Twenty-three patients on insulin treatment who were younger than 30 years of age at diabetes diagnosis were considered as having type 1 diabetes, and the remaining 36 as having type 2 diabetes. Mean age at time of this study was 50.6 years, ranging from 20 to 69. The age at diabetes diagnosis was 35.0 years, ranging from 2 to 62, and diabetes duration was 15.8 years ranging from 0 to 57 years.

Visual function in patients with different degrees of diabetic retinopathy according to the ETDRS severity scale

All patients performed perimetry well according to the reliability indices false positive and false negative responses. The frequency of false positive answers ranged from 0 to 28%, the median was 7%, and the mode value was 0%. Only two subjects had frequencies of false positive answers larger than 15%. Frequencies of false negative response ranged from 0 to 16%, with a median and mode value of 0%.

Both WWP and SWAP correlated significantly to the level of diabetic retinopathy when considering total loss as expressed by MD values, $p=0.0001$ and $p=0.04$ respectively (Fig. 3). The regression model fit was better for WWP ($r^2=0.23$) than for SWAP ($r^2=0.07$). As expected, MD values were worse (more negative) in eyes with more advanced retinopathy.

Localised visual field loss, as measured by the number of significantly depressed points at the $p<0.01$ level in pattern deviation maps, increased by 0.67 points per ETDRS step ($p=0.002$) with WWP. With SWAP the increase was 0.41 abnormal points per ETDRS step, but this was not significant ($p=0.26$).

There was no significant association between visual acuity, as estimated by the conventional smallest line that could be read, and diabetic retinopathy as graded by the ETDRS scale ($p=0.17$). We found a significant correlation, however, when estimating visual acuity by counting LogMar scores. Visual acuity decreased by 0.02 LogMar per ETDRS step ($p=0.03$), but the r^2 was only 0.08.

Influence of cataract

Most subjects had no or only mild cataract. Forty-two eyes had no nuclear cataract (N0), while 16 eyes had mild nuclear cataract (N1). Cortical cataract was absent (C0) in 43 eyes, minimal (C1) in 13 and mild (C2) in 13 eyes. Forty-eight eyes had posterior subcapsular cataract (PS0), nine had minimal posterior subcapsular cataract (PS1) and one eye had mild posterior subcapsular cataract (PS2). The effect of cataract on the visual field was negligible or small. When adding the individual Lens Opacities Classification System II grading as an explanatory variable to the regression model there were no or minimal effects of cataract on the visual field ($p=0.95$). Similarly, the effects of cataract on the SWAP fields also failed to reach statistical significance ($p=0.14$).

Visual function vs FAZ and PIAs

Of the 59 subjects who underwent perimetry, 46 had high-quality angiograms enabling accurate outlining of the FAZ and PIAs and subsequent measurement of the areas. When estimating the effects of FAZ size on visual function, one outlier with an FAZ area of 3.9 mm² was excluded. The FAZ area for the other subjects ranged from 0.22 to 1.47 mm². The central 10-2 visual field of this outlier was considerably more damaged than those of the other subjects: WWP MD 10-2 was -9.3 decibels (dB) (mean MD in the group: -1.2 dB) and the SWAP MD 10-2 was -14.8 dB (group mean: -2.67 dB). The number of significantly depressed points in the pattern deviation maps was also much higher than in the rest of the group. Inclusion of this outlier would have yielded a number of highly significant results and improved the p values of our analyses. As regression analysis is very sensitive to outliers, this person was excluded from analyses. Thus, 45 subjects were included in the FAZ and PIA vs degree of retinopathy, visual field and visual acuity analyses.

There was poor correlation between the FAZ area alone and degree of retinopathy ($p=0.38$). However, when PIAs were included, the correlation was very clear ($p=0.0007$). The number of PIAs represents a measure of the branching of the retinal perifoveal intercapillary network, and the

Fig 3 Using WWP (a), the MD decreased by 0.44 dB for each ETDRS step ($p=0.0001$). With SWAP (b) the slope was 0.40 dB per ETDRS step ($p=0.04$)

fewer the number, the more severe the damage. Accordingly, the number of zones was inversely correlated to the degree of retinopathy ($p=0.03$).

The size of the FAZ alone was not enough to explain the 6° MD, but on adding the size of PIAs to the FAZ and also including the number of PIAs in a multivariate regression analysis, the regression models improved meaningfully, as estimated by r^2 , namely from 0.01 to 0.22 with WWP, and 0.03 to 0.35 with SWAP. Thus, larger FAZ and PIAs reduced perimetric threshold sensitivity; at the same time, an increased number of PIAs improved threshold sensitivity.

In WWP the 6° MD decreased significantly ($p=0.03$), namely by 2.6 dB per mm^2 increase of FAZ and PIAs. More pronounced effects and higher significances were seen in SWAP, in which the 6° MD decreased 7.9 dB per mm^2 increase of FAZ and PIAs ($p=0.002$). In SWAP the number of depressed test points increased significantly ($p=0.03$) with a 4.4 points per mm^2 increase of FAZ and PIA. No significant increase of such points was seen in WWP ($p=0.48$). The presence of macular oedema did not affect the central 6° field in SWAP ($p=0.11$) when size of FAZ and PIAs was included in the same regression model.

Regression analyses did not reveal any significant correlation between the size of the FAZ or of the PIAs and FAZ together and visual acuity, neither when estimating visual acuity by the smallest line that could be read ($p=0.23$), nor when counting LogMar scores ($p=0.08$).

Discussion

In this study comparing visual acuity and perimetric tests for functional loss in patients with diabetic retinopathy, we found that the regression model fit for peripheral retinopathy according to the ETDRS scale was better with WWP testing than with SWAP or visual acuity testing, while SWAP testing was superior to both WWP and visual acuity testing when measuring effects caused by enlarged FAZ and PIAs.

SWAP has been suggested as a useful tool for defining visual function loss in diabetic patients with early ischaemic damage of the macula [10] or clinically significant macular oedema [9]. Decreased blue-on-yellow sensitivity has even been demonstrated in diabetic children without clinically detectable retinopathy [12]. Our results suggest that WWP might be better than SWAP in separating groups with different levels of retinopathy, while central SWAP appears

superior to WWP in identifying more localised field loss caused by macular damage.

Since the results of SWAP testing are considerably more affected by cataract than WWP, the interpretation of SWAP fields using raw threshold sensitivity values, age-corrected threshold values or global indices such as mean sensitivity or MD could be misleading. The pattern deviation concept aims at eliminating the effects of cataract on the visual field [22–23]. To our knowledge, this study is the first to compare SWAP and WWP using empirically derived pattern deviation probability maps for SWAP 10-2 in diabetic patients. The use of this concept when interpreting test results of diabetic patients could be extremely useful, particularly as they tend to develop cataract earlier than healthy subjects [24]. Indeed, it is possible that previous comparisons between WWP and SWAP testing in patients with diabetes were affected by cataract, even when age-matched control groups were included.

It was interesting to note the difference between the two ways of estimating visual acuity. The threshold approach [18] correlated better with severity of diabetic retinopathy than the conventional method based on the smallest line that could be read. This indicates that LogMar scores are more sensitive and should be preferred when assessing visual function with visual acuity testing.

In non-diabetic subjects, the size of the FAZ has been reported to be between 0.2 and 0.4 mm^2 [6, 10, 25–27]. In diabetic patients with retinopathy, the FAZ is enlarged [26], particularly in patients with reduced visual acuity [28]. We found no significant relation between visual acuity and FAZ, and no clear correlation between FAZ size and retinopathy level as graded by the ETDRS scale. However, when the size of PIAs was added to the FAZ size, there was a significant correlation in agreement with a previous study [29], indicating damage to the macular capillary network in line with the development of diabetic retinopathy. Such damage correlated better with SWAP testing than with WWP or visual acuity testing. SWAP has also been reported to be more sensitive for macular oedema than WWP [9]. However, in our analysis the presence or absence of macular oedema did not influence the correlation between the FAZ and PIA size and SWAP sensitivities. Thus, the inclusion of presence of macular oedema in the same regression model had no effect on the slope or p value for FAZ and PIAs.

Had we included the outlier in which the FAZ extended to the periphery of the macula, we could have demonstrated

highly significant effects of FAZ, both on general and localised field loss ($p < 0.0001$ in both cases and with both methods). We believe, however, that an excessive impact from one single outlier should be interpreted with great caution, and therefore excluded this subject from the analyses of FAZ and PIAs.

Some of our results are in conflict with those reported by Henricsson and Heijl in 1994 [30]. They found that diabetic retinopathy had no significant influence on WWP results in eyes with mild retinopathy, but that clear evidence of this influence existed at more advanced stages (ETDRS 43 or higher). In our sample, 24% of the subjects with mild to moderate retinopathy, defined as ETDRS levels below 43, had significantly depressed fields as measured by MD values, and 46% of our patients had more than twice as many abnormal points as expected in a normal eye. There is no obvious explanation for the different results of the two studies, apart from improvements in diagnostic techniques.

In summary, visual function as measured by perimetry, correlated with the degree of diabetic retinopathy according to the ETDRS scale, as well as with the size of the FAZ and adjacent PIAs. Conventional WWP was at least as sensitive as SWAP for the various ETDRS steps, but SWAP was more sensitive to abnormalities in the foveal capillary network. Angiographically visualised FAZ and PIAs represent measures of central vascular damage, but since they did not correlate well with visual acuity impairment, perimetry seemed more useful when monitoring visual function as a measure of the size of the FAZ and PIAs. Thus, our results suggest that perimetry testing matches, and can also provide additional useful information to conventional photographic documentation, when monitoring patients with diabetic retinopathy. To conclusively prove the value of perimetry in the monitoring of such patients, longitudinal studies should be conducted.

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