Quantification of Cystoid Changes in Diabetic Maculopathy

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Purpose. In patients with diabetic macular edema and cysts, quantification of the extent of the cystoid formation has been difficult. This study was performed to introduce reliable measurements of cysts, the quantification of the extent, and its relation to visual acuity.

Methods. Fluorescein angiography generated with a scanning laser ophthalmoscope provided detailed recognition not only of the foveal microvasculature, but also of well-demarcated cystoid formations in the early phases. The sampling area included the central 2.5° of the fovea. Using digital image analysis, two independent observers estimated the area covered by cysts, the number of cysts, and the foveal avascular zone (FAZ).

Results. Twenty-three subjects with diabetes and macular cysts were enrolled in the current study. The mean area of the cysts was \(0.315 \pm 0.241 \text{ mm}^2\) (0.05 mm\(^2\) to 0.9 mm\(^2\)), and the number of cysts ranged from 1 to 7. Both parameters, area of cysts \((r^2 = 0.61)\), and number of cysts \((r^2 = 0.48)\) showed a significant correlation with visual acuity \((P < 0.01)\), whereas FAZ \((0.08 \text{ to } 0.58 \text{ mm}^2)\) showed no significant correlation with visual acuity.

Conclusion. Fluorescein angiography allows a reproducible quantification of the extent of macular cysts. The relation of visual acuity to the number of cysts and to the area covered by the cystoid formation is highly significant. Thus, both these measures can provide an objective criterion for the estimation of visual prognosis and an outcome for evaluation therapy techniques.

Macular edema is a frequent cause of visual disability and continues to be a major problem in patients with diabetes.\(^1,2\) The formation of cysts in the central macula is particularly important because it can result in severe visual consequences.\(^3,4\) Cystoid formations result from either edematous Müller cells or from expansion of fluid in extracellular spaces in the inner retina.\(^5\) Clinical investigators have reported the appearance of cystoid macular edema (CME) in a variety of disease conditions, as documented by fluorescein angiography or microscopic studies.\(^6,7\)

Quantitative measurements have focused on the impact of disorders of the blood–retina barrier in patients with diabetes and for semiquantitative evaluation of the extent of the edema.\(^8\) Most of these studies have been based on photoangiography, which provides excellent spatial resolution. Recently, the contrast and temporal resolution of video fluorescein angiography has been further improved with the introduction of the scanning laser ophthalmoscope.\(^9\) This technique provides detailed visualization of the perifoveal capillary network\(^10,14\) and even visualizes formations of lower contrast, such as cystoid formations. Thus, it is possible to quantify the area of the cystoid formation more precisely than was possible before.

In this article, we describe the methodology of the assessment of the cystoid component of diabetic maculopathy, with first measurements of cystoid formations and their relation to visual acuity in 23 patients with diabetic macular edema and central cysts.

MATERIALS AND METHODS

Subjects

Twenty-three patients with diffuse diabetic macular edema and central cysts\(^4\) were recruited in the current study. Informed consent was obtained from each sub-
ject, including detailed explanations of all procedures before participation in this study. The protocol for this study was reviewed and approved by the RWTH University Institutional Review Board for the use of human subjects. This study was conducted in agreement with the principles of the Declaration of Helsinki. The group of patients with diabetes consisted of 17 men and 6 women ranging in age from 26 to 67 years (12 [52%] with insulin-dependent diabetes mellitus; 11 [48%] with noninsulin-dependent diabetes mellitus). Best-corrected visual acuity was determined by an ophthalmologist using objective refractometry and with the lighting conditions and standardized charts as described by DIN 58220.14 For statistical analysis, all visual acuity scores were converted to logarithmic equivalents (logMAR). Visual acuity ranged from 20/20 to 20/800 (mean, 20/50), and the duration of diabetes ranged from 4 to 31 years (mean, 17 years). Glucose metabolism was assessed by the blood level of hemoglobin A1c (HbA1c; normal laboratory range, 4.3% to 6.0%), which in the study group averaged 7.2% (standard deviation, 1.4%). Retinopathy level was classified by means of fundus photography according to ETDRS criteria, scaling diabetic retinopathy into 13 levels ranging from no retinopathy to severe vitreous hemorrhages.16 Stages of diabetic retinopathy included 6 patients with microaneurysms only or with mild, nonproliferative diabetic retinopathy (level 29 to 45), 11 patients with moderate to moderately severe nonproliferative diabetic retinopathy (level 47 to 53), and 6 patients with mild to moderate proliferative retinopathy (level 61 to 65). In none of the patients, a laser treatment (grid or focal) of the posterior pole was performed before participation in the study.

**Angiographic Procedure**

In all subjects, fluorescein angiographic studies were performed with a scanning laser ophthalmoscope (SLO-101 Rodenstock Institute, Germany). For each series of angiograms, the eye for study was selected randomly.

Total preparation time and angiographic procedure took approximately 20 to 30 minutes for each patient, including detailed recordings of the macula (20°) and peripheral retina. Preangiographic preparation included one syringe with sodium fluorescein (10%, 2.5 ml) and one with saline (10 ml). The routinely used injection device included a 50 to 50 cm of tubing (volume, 2.5 ml) leading to a three-way valve. The first fluorescein syringe (2.5 ml) was connected to the three-way valve and injected to fill the tubing. For each series of angiograms, a 20-gauge microcatheter was inserted into an antecubital vein. The end of the microcatheter was connected to the tubing. This setup allowed patient mobility and provided quick access for intravenous injections in case of emergency. After aligning the patient’s eye to the illumination beam of the instrument, the patient practiced the eye positions needed to obtain the standard views in the angiogram.

**Data Collection**

The first red-free images of the posterior pole were captured in both the 20° and the 40° field. While in the 20° mode, the nerve fiber layer and arterioles were brought into best focus, and the barrier filter for fluorescein angiography was inserted into the detection pathway. In this mode, the large retinal vessels were still visible enough (black vessels on a gray background) to permit monitoring the patient’s eye position. Next, the three-way valve was opened and the fluorescein in the tubing, followed immediately by a column of saline, was injected. Within 10 to 20 seconds, the dye arrived at the eye and provided visualization of the capillary network. After the initial recordings (20 to 50 seconds), the magnification was changed to 40°, providing recordings of the entire posterior pole and periphery. Figure 1 illustrates the early angiographic phase of a patient with cystoid formations in the 20° and 40° magnifications. Throughout the entire recording, the video gain was fixed (gain 2) to avoid changing signal-to-noise ratio, which could interfere with the interpretation of the amount of hyperfluorescence over time.

**Data Evaluation**

Parts of the methodology used in this study have been described in detail elsewhere.14 The scanning laser ophthalmoscope is connected to both a computer-based image sequence storage unit and a video recorder (U-matic). Direct on-line digitization and storage (50 images per second, 256 X 256 pixel) of 2 to 5 seconds of the early phase are adequate for analysis purposes. The digital recordings of the perifoveal capillary network are then accessible for detailed off-line evaluation.14 In each angiogram, the area of interest was defined by determining the center of the FAF and superimposing the 2.5° measuring circle. The foveal avascular zone (FAZ) was computed as previously described,17 and each cyst was marked. The area in mm² was calculated from the pixel size (10 X 10 μm) times the number of pixels within the boundary drawn by the cursor. The area covered by cysts was calculated from the single readings. The measurements procedure was standardized to avoid fluorescein leakage affecting the area of interest; therefore, readings were performed approximately in the middle of a range from 20 to 50 seconds (mean measurement time 34 seconds) after fluorescein injection.
FIGURE 1. (A) Fluorescein angiogram of a 47-year-old woman with diabetes (12 years' duration; severe, nonproliferative diabetic retinopathy) with CME. This 40° view of the posterior pole is in the early venous phase (17 seconds), which already shows the cystoid changes in the macula. (B) Fluorescein angiogram of the macular region in the 20° magnification (same patient as in Fig. 1A). This image clearly reveals the macular cysts accompanied by moderate capillary dropout.

Measurement Parameters

Measurements were performed for each test eye in an area of 2.5° diameter around the center of the FAZ. Within this region, the highest contrast in an image is possible because the capillaries were in a single layer and macular pigment blocked choroidal fluorescence. A measurement area of 2.5° diameter (2.5° = 1.7 mm²) was chosen, including the region of highest visual acuity (approximate diameter, 350 µm) and the surrounding capillary microvasculature to measure the cystoid changes.

The macular cyst measurements (number and area covered by cysts) and FAZ measurements were made by two independent observers (OA and AR) in a masked fashion. For the cyst count, in one patient disagreement in the count of cysts occurred and was discussed until agreement was reached (interobserver agreement, 96%). The area of cysts and FAZ differed between the two observers by less than 5%, and the presented results represent the average of both readings. Figure 2A shows the angiographic pictures of a patient with diabetes and macular cysts and unaffected visual acuity (20/20), whereas Figure 3 shows a patient with diabetic maculopathy and cystoid formations and impaired vision (20/200). Figure 2B illustrates the interactively marked cysts.
Macular Cysts in Diabetic Retinopathy

The mean value and standard deviation are given for all samples with normal distributions. Pearson correlation coefficients were calculated to evaluate the relation between the parameters. Statistical significance was computed after carrying out Fisher’s $r$ to $z$ transform with $n - 2$ of freedom. For statistical analysis, all visual acuity scores were converted into logarithmic equivalents (logMAR) when calculating acuity values or computing correlation coefficients.

RESULTS

For patients with diabetes, central cysts were readily seen and demarcated 20 to 50 seconds after fluorescein injection. All single cyst measurements ranged from 0.012 mm$^2$ to 0.441 mm$^2$ (mean ± SD, 0.096 ± 0.079 mm$^2$), and in all subjects at least one cyst overlapped the central avascular arcade forming the FAZ. Figure 4 provides a histogram of the distribution of the single size of cysts. The cysts are much larger than the resolution limits of the system because the average cyst represents nearly 1000 pixels. The mean area of cysts for each patient was 0.315 ± 0.241 mm$^2$, ranging from 0.076 mm$^2$ to 0.580 mm$^2$.

Visual acuity is correlated with measured parameters of cysts (Fig. 5). There is a significantly negative correlation between visual acuity (logMar) and number of cysts ($r = -0.69; P < 0.01$) and between area of cysts and visual acuity ($r = -0.78; P < 0.01$). In other words, patients with diabetes with a larger number of cysts and/or area of cysts showed more visual impairment. In contrast, the area of the FAZ was not significantly correlated to visual acuity in patients with diabetes with cysts ($P = 0.33$). Small FAZ could be

![Figure 3. Fluorescein angiogram (20° observation field) of the left eye of a 65-year-old patient with diabetes (17 years' duration; mild, proliferative diabetic retinopathy) with CME and impaired visual acuity (20/200). The angiogram shows the cystoid changes (seven cysts; 0.424 mm$^2$ area) associated with moderate capillary drop out and microvascular abnormalities, especially temporoinferior. The FAZ surrounding capillary arcade is not yet enlarged by capillary closure.](image)

![Figure 4. Histogram of the distribution of all measured areas of macular cysts.](image)

![Figure 5. (top) Scatterplot and the regression line of visual acuity and the number of cysts in patients with diabetes ($P < 0.01$). (bottom) Scatterplot and the regression line of visual acuity and the area of cysts in the studied patient group ($P < 0.01$).](image)
found over the full span of visual acuity. Comparing FAZ with the parameters of cyst measurements, no significant correlation to any of them was found (FAZ versus number of cysts, \( P = 0.91 \); area of cysts, \( P = 0.24 \)).

Furthermore, visual acuity and age, stage of diabetic retinopathy (Spearman rank correlation), duration of diabetes, and HbA1c showed no significant relationship. Of further clinical interest is the potential relation of the area of cysts to the retinopathy grading, but no significant correlation was found (Spearman rank correlation; \( P = 0.83 \)). The area of cyst in relation to the type of diabetes (insulin dependent and noninsulin dependent diabetes mellitus) revealed similar distributions (Kolmogorov–Smirnov; \( P = 0.78 \)) in both groups.

**DISCUSSION**

Fluorescein angiography in the diagnosis and classification of diabetic changes is well established.19 Previous angiographic studies in patients with CME have focused on the detection of the cystoid pattern in various diseases, e.g., identification of the appearance without quantitative evaluation.20–22 A recent case report showed stabilization of visual acuity after treatment and no significant correlation of capillary blood velocities and visual acuity over time.13 The present technique, which used a scanning laser ophthalmoscope and digital image analysis, made possible the detection of various features of lower contrast in the foveal microvasculature. In this study using fluorescein angiograms, it was possible to quantify the cystoid formation in the foveal and parafoveal area. Because both macular morphology and microcirculation contribute to the understanding of cystoid formation and provide quantitative measures, the introduced morphologic measurements then seem important.

The area of interest for studying macular microvasculature included 2.5° of the posterior pole. The on-line visualization of the images allowed recordings even in patients with severe visual impairment. We measured single cyst size, the number of cysts, the area of the cystoid formation in a 2.5° measurement field, and the FAZ in patients with diabetes. To the best of our knowledge, no quantitative histologic study is available to compare the size of single cysts (range, 0.05 to 0.45 mm²) found in this study. The area of cysts and the number of cysts showed a significant correlation to visual acuity. However, statistical analysis revealed an even higher correlation of the area of cysts to visual acuity than the number of cysts.

Previously, Smith et al.23 showed that the grading of the degree of retinal thickening in the central 5° of the macula in patients with diabetes with diffuse macular edema revealed no relationship to visual acuity. Nussenblatt et al.,23 however, found a significant relationship between retinal thickening and visual acuity in patients with uveitis with CME. Thus, the present work introduces a quantitative measurement of the severity of the cystoid component in patients with diabetes with CME.

Comparing the FAZ data of subjects with diabetes in this study with previously published data of healthy subjects,17 data of the subjects with diabetes were enlarged by 26%. Moreover, FAZ was not significantly related to count of cysts, area of cysts, or visual acuity. Interestingly, Smith et al.23 found that in patients with diabetes with diffuse macular edema, the size of FAZ remained independent of retinal thickening and correlated with visual acuity. Thus, FAZ appeared not to predict visual acuity in patients with diabetes with diffuse macular edema and cystoid changes.

In patients with diabetes with macular cysts, there was no significant relationship of the severity of retinopathy to visual acuity or to the area of cystoid changes. Furthermore, no obvious relation of type of diabetes mellitus and extension of cysts was found. For comparison to other clinical aspects of visual acuity (the ability to read normal rates, if 20/50 is the minimum acuity needed), an area of cyst severity of more than approximately 0.35 mm² and an average number of more than three cysts seem to be critical (Fig. 5). Focusing on the morphology and distribution of the cysts in the fovea as well as on the proximity of the cysts to the center might add further information in the interpretation of the cystoid changes.

In summary, the study introduced parameters to assess the extent of the cystoid formations in patients with diabetes and demonstrated a good relationship to visual acuity. The assessment of the severity of the cystoid component in diabetic maculopathy will eventually lead to a better understanding of the pathophysiology of diabetes and introduces a method to quantify the benefits of currently used therapy regimens.

**Key Words**

diabetes, cystoid macular edema, fluorescein angiography, diabetic retinopathy

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