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Atrophy of the central neuroretina in patients treated for diabetic macular edema

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ABSTRACT.

Purpose: **To examine the prevalence of central retinal atrophy in patients treated for diabetic macular edema (DME) in a clinical setting.**

Methods: **Retrospective data analysis of patients with DME, focusing on those who developed central retinal thinning after DME treatment at the Department of Ophthalmology, Medical University Vienna. Patient characteristics and clinical data including best-corrected visual acuity (BCVA), spectral domain optical coherence tomography and fluorescence angiography images were reviewed and DME treatment strategies analysed using descriptive statistics. The correlation between visual acuity and ocular, systemic or DME treatment factors was calculated using linear regression models and ANCOVAS.**

Results: **A total of 6684 outpatient visits by 1437 patients with diabetes were analysed. Out of 149 patients, who had had a central subfield thickness (CST) below 200 μm, 32 (36 eyes) had previously been diagnosed with a centre involving DME with an average CST of 473 $\pm$ 103 μm and average visual acuity of 0.62 $\pm$ 0.44 logMAR at first presentation. At the time of central atrophy, 29 (81%) out of 36 eyes had a history of laser treatment, 11 (31%) a vitrectomy, 32 (88%) repeated intravitreal injections of anti-vascular endothelial growth factor (VEGF; mean 5.3 $\pm$ 3.8) and 22 (61%) intravitreal corticosteroid injections (mean 2.5 $\pm$ 2.7). Visual function (0.67 $\pm$ 0.43 logMAR) at the time of atrophy was not significantly correlated to central retinal thickness (191 $\pm$ 7 μm) or any other ocular, systemic or treatment factors.**

Conclusions: **Only 4% of patients treated for DME developed central retinal thinning in our observation period. On average, our atrophy patients had higher CST and lower BCVA when they first presented with DME compared to the overall DME cohort, and they received a combination of intravitreal injections and laser for DME treatment. Central retinal atrophy might not be attributed to excessive use of intravitreally applied anti-VEGF or any other DME therapy alone.**

Key words: anti-VEGF – intravitreal injection – diabetic macular edema – optical coherence tomography – retinal atrophy

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Introduction

Repeated intravitreal injections of vascular endothelial growth factor (VEGF) inhibitors are currently the first line therapy in the treatment of diabetic macular edema (DME) and other exudative macular diseases such as neovascular age-related macular degeneration (AMD) or retinal vein occlusion (Grunwald et al. 2014; Schmidt-Erfurth et al. 2014; Stuart et al. 2015; The Diabetic Retinopathy Clinical Research Network 2015; Yeh et al. 2015, Bressler et al. 2016). The number of indications for intravitreal anti-VEGF treatment has increased due to the favourable treatment response regarding edema resolution, regression of neovascularization and reduction in overall diabetic retinopathy (DR) severity, and retreatment criteria have also been loosened. However, along with the beneficial effects of edema resolution and visual acuity gain, retinal pigment epithelium (RPE) atrophy as well as changes in retinal nerve fibre and the ganglion cell layer, have been described after repeated anti-VEGF treatment (Grunwald et al. 2014; Beck et al. 2016). Previous reports have shown that depressed VEGF-A levels could also reduce the innate neuroprotective capabilities that directly impact neural cell survival (Nishijima et al. 2007). Therefore, concerns are being raised that sustained anti-VEGF suppression could lead to retinal damage, especially in patients with diabetes as neurosensory degeneration and

microvascular malperfusion are hallmarks of diabetic disease (Kern & Barber 2008).

Before the introduction of anti-VEGF therapy, focal/grid laser treatment has been standard of care for DME and is still recommended in some cases (ICO Guidelines for Diabetic Eye Care 2017, Schmidt-Erfurth et al. 2017). Conventional laser photocoagulation involves targeted damage of retinal tissue to produce a therapeutic benefit. Complications like enlargement of laser scars or subretinal fibrosis are quite frequent and responsible for poor visual outcome if present close to the fovea (Lovestam-Adrian & Agardh 2000).

The aim of our study was to investigate the number of patients with DME affected by central retinal atrophy in a clinical setting and identify predictive factors for the emergence of retinal atrophy.

Materials and Methods

Analysis of the registry database of patients with DR treated at the Department of Ophthalmology and Optometry, Medical University, Vienna between February 2012 and July 2016. The registry was established at the outpatient clinic of diabetic eye complications, a tertiary referral centre. Treatment was decided at the discretion of the retinal specialists. The study protocol was approved by the Institutional Review Board of the Medical University, Vienna and adhered to the tenets of the Declaration of Helsinki.

Study population

Eyes with central retinal atrophy defined by a central subfield thickness (CST) value $\leq$200 μm measured in macular cube scans (512 $\times$ 128 or 200 $\times$ 200) with spectral domain optical coherence tomography (SDOCT; Cirrus, Zeiss Meditec, Jena, Germany) were chosen for further analyses. Thereof only those who had previously presented with a centre involving DME (CST $\geq$305 μm in a Cirrus SDOCT macular cube scan 512 $\times$ 128 or 200 $\times$ 200) were included. If the first presentation with DME was before the implementation of the registry database (before 02/2012), patient's medical records and images were retrieved from the archive. Spectral domain optical coherence tomography (SDOCT) scan segmentation of the retinal boundaries was corrected manually in the case of segmentation errors or decentred macula scans. Exclusion criteria covered retinal vein occlusion, AMD and any maculopathy other than DR, spherical equivalent greater than $\pm$3 dpt and poor SDOCT image quality defined as an inability to reliably delineate the internal limiting membrane (ILM) and RPE. Spectral domain optical coherence tomography (SDOCT) stacks of all patients meeting the inclusion criteria were reviewed thoroughly by a retina specialist for concomitant diseases such as vitreomacular traction syndrome, macular hole or signs of AMD including drusen, choroidal neovascularization or pigment epithelial detachment. Patients with epiretinal membrane (ERM) were excluded when the membrane showed any impact on the retina like traction or retinal folds.

Data collection

Medical history including the type and onset of diabetes mellitus (DM) and ocular history were recorded in the registry and the paper-based medical records before the implementation of the registry, respectively. Best-corrected visual acuity (BCVA, 10 m Snellen), intraocular pressure, CST and clinical findings on slit lamp examination as well as dilated fundus biomicroscopy were systematically collected in the registry. The Snellen equivalent was converted to logMAR for statistical analysis.

All SDOCT scans of patients included in our analysis were systematically reviewed by a retinal specialist for morphological changes as follows: the central scans of SDOCT images acquired at the first diagnosis of the centre involving macula edema as well as at the first occurrence of CST thinning were evaluated for cystoid changes, subretinal fluid (SRF), continuity of photoreceptors and signs of RPE atrophy. Retinal pigment epithelium (RPE) atrophy was defined as RPE thinning with an enhanced underlying choroidal SDOCT signal. Quantitative SDOCT measures included CST and ganglion cell-inner plexiform layer (GCIPL) thickness as calculated by an automated algorithm provided by the CIRRUS SDOCT software (version 7.0.1.290, Carl Zeiss Meditec, Jena, Germany). Segmentation errors of the ILM and RPE within the central mm were corrected manually if necessary to generate a valid CST value. Patients whose image quality was insufficient to delineate the ILM and RPE were excluded from the analysis. The ganglion cell analysis algorithm of the CIRRUS SDOCT software calculates the mean GCIPL thickness within an elliptical annulus centred on the fovea with vertical inner and outer radius measures of 0.5 and 2.0 mm, respectively, whereas the horizontal inner and outer radius of the ellipsis measures are 0.6 and 2.4 mm. Segmentation errors could not be corrected for the automated GCIPL analyses due to software limitations.

The first fluorescence angiography (FA) image taken after the appearance of CST thinning in SDOCT was graded for any signs of capillary dropout within the macula and beyond the arcades. The area of the foveal avascular zone (FAZ) was measured by outlining the innermost capillaries manually in early phase FA images (<2 min).

Statistics

Descriptive statistics (means, standard deviations, absolute and relative frequencies) are presented for the whole set of cases with atrophy.

A linear regression model was fitted for age, sex, diabetes type, diabetes duration prior to treatment and morphological baseline characteristics such as the presence of SRF, hard exudates (HE) and photoreceptors irregularity to explain the difference in BCVA at the time of DME and central retinal atrophy. Additionally, we investigated whether the morphological variables graded in SDOCT and FA images (CST, photoreceptors, RPE atrophy, GCIPL thickness, FAZ size, signs of ischaemia) at the time of central atrophy or time leading up to the atrophy had a statistically significant effect on the BCVA after treatment. ANCOVA models were fitted to explain the BCVA after treatment by every one of the above-mentioned variables and the BCVA prior to treatment. These analyses were conducted for 31 patients with atrophy.

The whole dataset of patients with DME (n = 554) diagnosed between Feb 2012 and July 2016, among them

n = 20 cases with atrophy, was used to analyse factors affecting time to atrophy occurrence by Cox regression corrected for age, gender and year of diagnosis.

Risk to develop atrophy was analysed by conditional logistic regression in a nested case-control study. The 20 atrophy cases were matched to 40 controls by age (5-year-age group), sex and date of diagnosis (±3 months).

All analyses were performed using R 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 6684 outpatient visits by 1437 patients with diabetes were reviewed. One hundred eighty-four eyes of 149 patients had a CST ≤200 μm at least once at their outpatient visits. Among these 36 eyes of 31 patients (12 female) have previously been diagnosed with a centre involving DME without any concomitant macular disease and were therefore eligible for study inclusion. The 147 eyes with CST ≤200 μm which were excluded from further analysis either had signs of AMD (drusen or pigment epithelium detachment) or presented with vitreomacular traction or macular hole. One eye was excluded from further analyses as its medical record was incomplete. The mean CST of the remaining 36 eyes was 473 ± 103 μm at the time of DME and 191 ± 7 μm at the time of central thinning. The characteristics of patients with DME who developed CST thinning are shown in Table 1, and two examples are displayed in Fig. 1. The mean time to develop CST thinning below 200 μm after initial diagnose of DME was 40 ± 24 months.

Best-corrected visual acuity

The mean BCVA was 0.62 ± 0.44 logMAR and 0.67 ± 0.43 logMAR at the time the centre showed DME and atrophy, respectively. The mean change in BCVA was 0.05 logMAR (p = 0.44), although individual changes were quite diverse: after edema shedding to CST <200 μm BCVA improved in 10 eyes and deteriorated in 12 eyes (Fig. 2). Best-corrected visual acuity (BCVA) prior to treatment was the only variable with a statistically significant effect on the BCVA change and BCVA after treatment. Patients who on average had a better BCVA (i.e. a lower logMAR) before treatment had on average a higher increase in logMAR (i.e. a greater worsening of BCVA) than those who had a worse BCVA before treatment.

No baseline characteristic (age, sex, diabetes type and diabetes duration prior to treatment) or morphological criterion evaluated at baseline (SRF, HE and external limiting membrane integrity) was found to have a statistically significant effect on the change in BCVA or the final BCVA. At the time of central retinal thinning, there was no statistically significant correlation between morphologic characteristics (CST, photoreceptor integrity, RPE atrophy, GCIPL thickness, FAZ size and signs of ischaemia) and BCVA.

Table 1. Characteristics of patients and eyes at two time points: when diabetic macula edema (DME) was present (first column) and when central retinal thinning below 200 μm occurred after treatment of the centre involving DME (second column).

n = 32; 36 eyes	DME >305 μm	CST <200 μm
Age (years) ±SD	59.5 ± 9	63 ± 9
Sex	17 male, 15 female	17 male, 15 female
Eye	20 od, 16 os	20 od, 16 os
Diabetes type 2	27	27
Insulin treatment	23	23
DM duration (years) ±SD	17.4 ± 10.1	21.1 ± 10.4
DR severity		
Mild, n (%)	2 (6)	1 (3)
Moderate, n (%)	3 (8)	5 (14)
Severe, n (%)	15 (42)	5 (14)
Proliferative, n (%)	16 (44)	25 (69)

Age and diabetes mellitus (DM) duration differ significantly between both time points (p < 0.001). CST = central subfield thickness, DR = diabetic retinopathy, SD = standard deviation.

DME treatment

The different treatment modalities of DME applied in these patients are summarized in Table 2. All patients were injected with either anti-VEGF or corticosteroids and 80% additionally had a history of macular laser treatment. About one half of the eyes (48%) received trimodal DME treatment with anti-VEGF, corticosteroids and macular laser.

Morphologic details

Morphologic characteristics graded in SDOCT at baseline and at the time of retinal thinning are summarized in Table 3, and two examples are displayed in Fig. 1. Out of the 36 eyes with central retinal thinning after DME resolution, 8 (22%) showed a window defect of the RPE in the central SDOCT scan which had not been present at the time of the edema (Fig. 1). Analyses of FA images taken after central retinal thinning had occurred and revealed a mean FAZ area of 0.827 (±0.83) mm^2. Thirty-one (86%) eyes had signs of nonperfusion beyond the arcades, of these 30 (83%) also had capillary dropout within the macula area. Three examples of FA images with the corresponding SDOCT scan are displayed in Fig. 3.

Epiretinal membrane (ERM) was detected on SDOCT scans in 12 (33%) patients with edema; however, the membrane did not reveal any impact on the retinal architecture like signs of traction or retinal folds. Photoreceptors appeared irregular in most of the patients (n = 30, 83%) presenting with a centre involving edema. After edema resolution, photoreceptors appeared normal in seven patients (19%) and were irregular (n = 14, 38%) or missing (n = 15, 42%) in the rest of eyes. In the case of RPE atrophy, all eyes (n = 8, 22%) displayed irregular or missing photoreceptors at the atrophic area (Fig. 3E). In nine eyes (25%), the RPE appeared normal while the photoreceptors were missing (Fig. 3C). Central retinal thinning alone did not always imply a loss of photoreceptors (Fig. 3A).

Comparison to edema collective

Baseline characteristics of all 554 patients with DME who were registered between Feb 2012 and July 2016

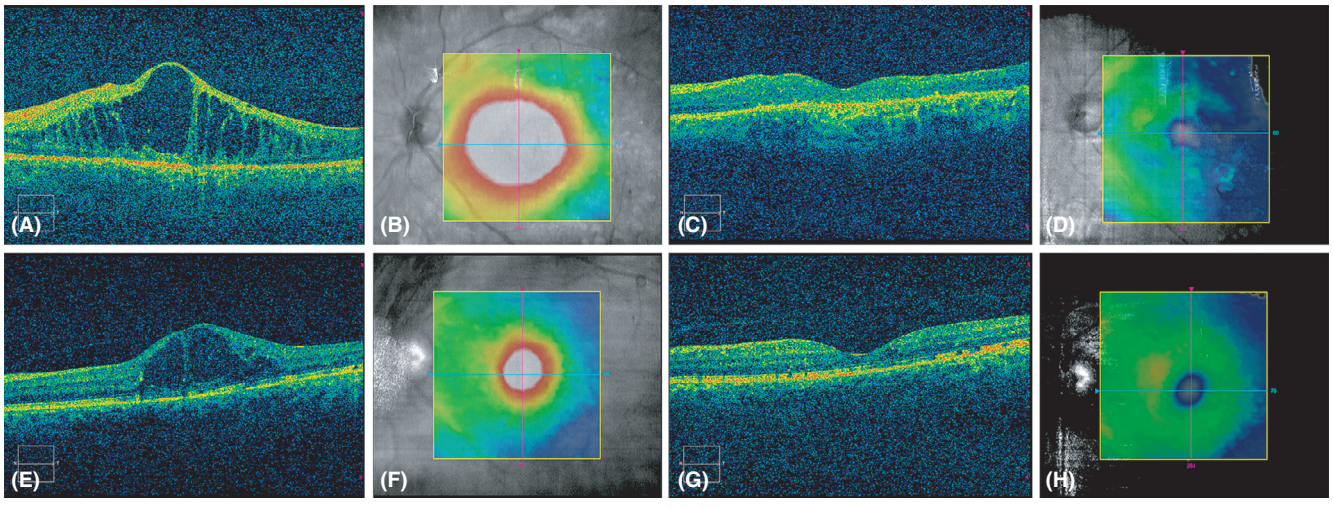

Fig. 1. Central spectral domain optical coherence tomography (SDOCT) scans of two cases of diabetic macular edema that converted to central retinal thinning after treatment. Next to the cross-section SDOCT scan the corresponding infrared image with a colour-coded retinal thickness overlay is displayed (B, D, F, H). The upper line shows a loss of photoreceptors in both SDOCT scans (A, C) with an enhanced signal transduction to the choroid. Spectral domain optical coherence tomography (SDOCT) scans of the lower line (E, G) display irregular photoreceptors at the fovea that seem to be more pronounced at the time of edema (E). The SDOCT signal is mostly absorbed by the retinal pigment epithelium, which appears to be normal.

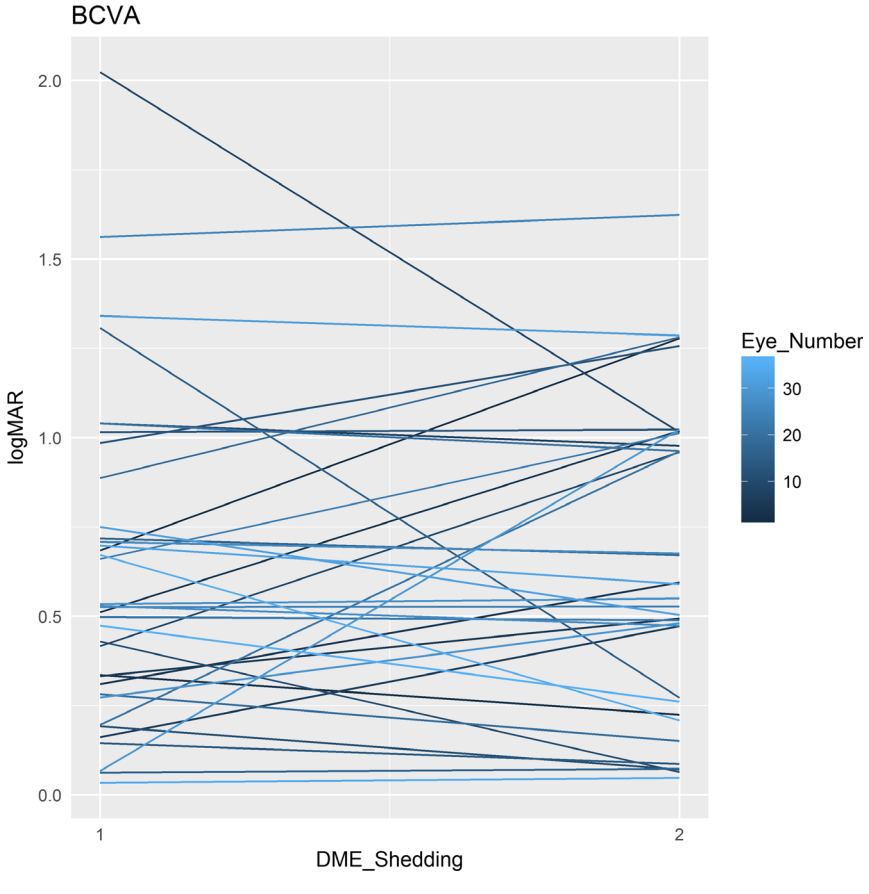

Fig. 2. Best-corrected visual acuity at the time of diabetic macular edema (1) and at the time of atrophy (2) for each patient. Edema shedding seemed to have a diverse effect on retinal function: 10/36 eyes improved while 12/36 eyes deteriorated.

and did (n = 20) or did not (n = 534) develop retinal atrophy after DME treatment were analysed with respect to factors affecting the time to atrophy by Cox regression. No DME treatment was significantly associated with duration until atrophy development (Table 4). However, patients with good visual acuity at time of edema had a lower hazard to develop retinal atrophy after edema treatment (p = 0.001). Since the chance to observe a certain set of therapies may depend on duration of follow-up, the risk to develop atrophy was determined by conditional logistic regression in a set of atrophy cases matched to control patients by age, sex and date of onset of DME therapy. Patients developing atrophy had a significantly higher CST (p < 0.001), and lower BCVA (p = 0.001) at time of therapy onset and had a history of macular laser treatment (p = 0.022; Fig. 4).

Discussion

Repeated intravitreal injections have been shown to be safe and effective in the treatment of exudative macular disease for most patients, but some do not benefit. In comparison with pro re nata (PRN) treatment, monthly anti-VEGF application has been associated with a higher incidence of macular atrophy in patients with AMD (Grunwald et al. 2014). Although macular atrophy, defined as a demarked area of absent RPE, is usually not prevalent in the course of DR, an atrophy of the neurosensitive retina reflected as a reduced retinal thickness has been described (Sikorski et al. 2013; Channa et al. 2014). In rodents, blocking all VEGF isoforms showed a dose-dependent decrease in ganglion cells

Table 2. Treatment modalities applied in 36 eyes of 32 patients before central retinal thinning occurred.

Treatment modality	Eyes *n* (%)	Median *n* of treatments (range)
Anti-VEGF	32 (88)	4 (1–15)
Corticosteroids	22 (61)	1 (1–11)
Focal laser/grid	29 (81)	
Combination of macular laser + corticosteroids + anti-VEGF	16 (44)	
Panretinal laser	30 (83)	
Vitrectomy	11 (31)	
Vitrectomy and silicon oil filling	3 (8)	

VEGF = vascular endothelial growth factor.

Table 3. Morphological characteristics evaluated in spectral domain optical coherence tomography (SDOCT) images at the time the centre-showed diabetic macular edema (DME) and at the time of central retinal thinning (atrophy) in 36 eyes of 32 patients.

SDOCT	DME	Atrophy
CST (μm), mean ± SD	473 ± 102	191 ± 7
GCIPL thickness (μm), mean ± SD	59 ± 26	71 ± 25
Cystoid changes, *n* (%)	34 (94)	5 (18)
ERM, *n* (%)	12 (32)	12 (32)
Subretinal fluid, *n* (%)	12 (33)	0
Hard exudates, *n* (%)	7 (19)	3 (12)
RPE atrophy, *n* (%)	0	23 (64)
Photoreceptors		
Normal, *n* (%)	5 (14)	7 (19)
Irregular, *n* (%)	30 (81)	14 (38)
Missing, *n* (%)	1 (3)	15 (42)

While the central subfield thickness (CST) changed significantly ($p < 0.001$) the GCIPL thickness did not ($p = 0.161$).
ERM = epiretinal membrane, GCIPL = ganglion cell-inner plexiform layer, RPE = retinal pigment epithelium, SD = standard deviation.

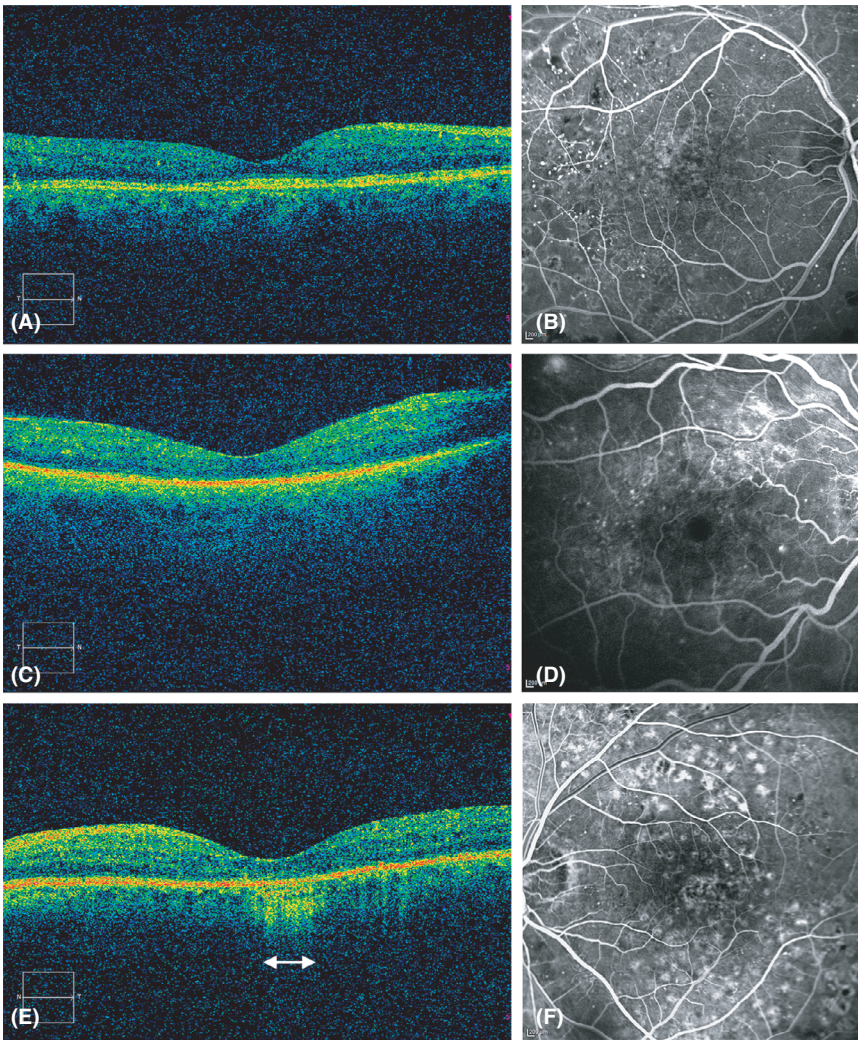

Fig. 3. Spectral domain optical coherence tomography (SDOCT) scans (left column) and corresponding early phase fluorescence angiography (FA) images (right column) of patients with a centre involving retinal atrophy. The photoreceptors of the first patient appear normal (A) but the FA image (B) shows scattered fluorescence from the grid laser. In the SDOCT scan of the second patient (C), the retinal pigment epithelium (RPE) gives a strong signal reflection but photoreceptors are not visible. The FA image (D) shows a regularly shaped foveal avascular zone without central transillumination. The third patient displays a distinct area of RPE atrophy with a window defect (E, left right arrow) at the centre. A transillumination defect is seen in the corresponding early phase FA image (F), most likely resulting from extensive application of macular laser.

(Nishijima et al. 2007). Ganglion cell layer/inner plexiform layer thickness loss has been previously described after DME treatment (Bonnin et al. 2015; Prager et al. 2018). In our study cohort, 80% of patients had a history of intravitreal injections as well as macular laser. Only two eyes (6%) developed central retinal thinning below 200 μm after anti-VEGF therapy alone. The number of anti-VEGF injections applied in these two eyes was so small (3 and 4 injections, respectively) that retinal thinning cannot be solely attributed to anti-VEGF therapy. In the RIDE/RISE trial, approximately 75% of patients who received monthly anti-VEGF injections for 36 months needed further *pro re nata* treatment and no harmful effects on retinal integrity were reported. (Boyer et al. 2015) However, patients in our study cohort had on average worse BCVA and higher CST than age/sex-matched DME patients from our registry and mostly received multiple treatment modalities, which suggests the presence of recalcitrant edema. Also the presence of capillary dropout, that was present in more than 80% of atrophy patients as well as the high prevalence of proliferative diabetic retinopathy (PDR) indicate overall advanced disease. Early treatment of DME before the vision deteriorates might be essential for good visual function after edema resolution. (Boyer et al. 2015).

In our retrospective analysis, we reviewed the medical records of 1437 patients with diabetes and could identify only 36 eyes of 32 patients that developed atrophy of the neuroretina below 200 μm after treatment of the centre involving DME. Over an observation period of 4 years, the incidence

Table 4. Risk evaluation to develop retinal atrophy after treatment for diabetic macular edema (DME).

Predictor	Parameter	Hazard ratio	95% confidence interval		p-value
Grid/focal laser	0.51	1.67	0.56	5.02	0.360
PRP	1.21	3.35	0.42	26.53	0.252
VE	−1.02	0.36	0.09	1.45	0.150
Anti-VEGF	0.62	1.86	0.21	16.41	0.577
Triam/Ozurdex	0.54	1.72	0.59	5.02	0.319
BCVA	−4.60	0.01	0.00	0.15	**0.001**
CST	0.00	1.00	0.99	1.00	0.323

Patients with lower best-corrected visual acuity (BCVA) at the time of edema had a significantly greater risk (highlighted in bold print) to develop retinal atrophy after DME treatment.
CST = central subfield thickness, PRP = panretinal photocoagulation, VE = vitrectomy, VEGF = vascular endothelial growth factor.

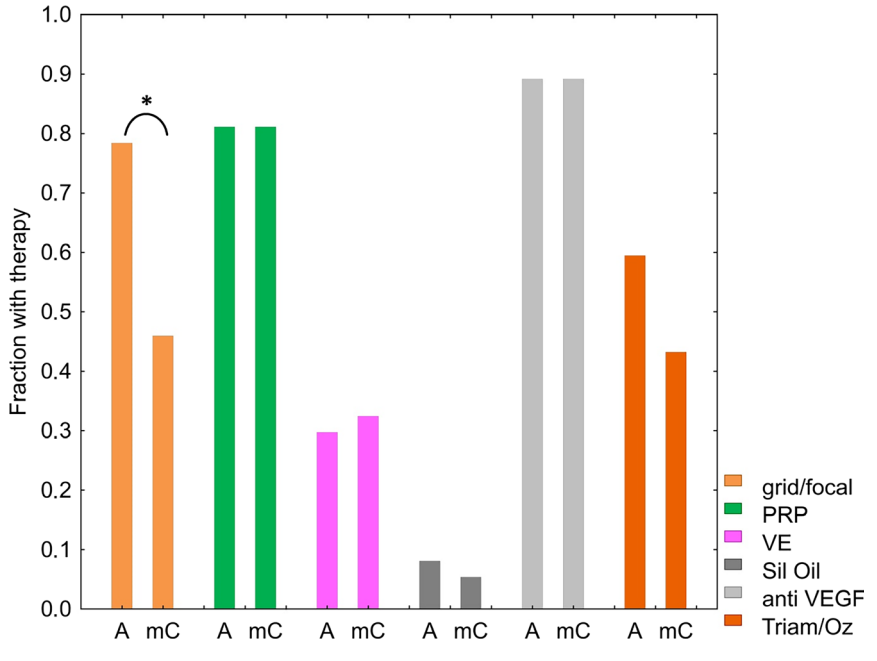

Fig. 4. In order to compare treatment strategies between patients, who developed retinal thinning (A) and the overall cohort with diabetic macular edema, a sex- and age-matched control (mC) was randomly assigned to each atrophy patient. Macular laser photocoagulation (grid/focal) was the only treatment that was preferably applied in patients with diabetic macular edema, who later developed atrophy.

of central retinal thinning was only 4%. Similarly to patients with edema, who showed an only modest correlation between CST and BCVA, our patient cohort with central retinal atrophy revealed a wide range of BCVA from 20/20 to 20/400. (The Diabetic Retinopathy Clinical Research Network 2007; Bressler et al. 2018) However, only seven eyes (19%) had a BCVA of 20/40 or better. Patients with a worse visual acuity at the time of edema on average lost less vision after developing retinal atrophy, which can be attributed to a ceiling effect. In parallel, patients with worse visual acuity at baseline turned out to have a statistically significant lower BCVA at the time of central retinal thinning. This accords with previously published data (Sophie et al. 2015; Wells et al. 2016).

Morphologic baseline characteristics at the time the centre involving DME were similar to larger study cohorts (Domalpally et al. 2015; Gerendas et al. 2017). The mean CST was 473 ± 102 μm, almost all patients displayed intraretinal cystoid changes, one-third showed SRF and 19% showed HE. We could not identify any characteristics that correlated to a change in BCVA following DME resolution. Surprisingly, morphologic factors graded in SDOCT and FA after edema resolution also did not correlate with visual acuity, although FAZ size and photoreceptor integrity have been suggested to impact visual function. (Maheshwary et al. 2010; Samara et al. 2017).

Aetiology and morphometry of central retinal thinning in our study patients differ substantially from geographic atrophy secondary to AMD. Geographic atrophy is defined as progressive degeneration of photoreceptors, pigment epithelium and choriocapillaris in late-stage AMD. Retinal atrophy in our study is solely defined by the retinal thinning of the central mm below 200 μm, which did not necessarily affect the photoreceptors or the RPE. However, foveal RPE atrophy defined as a window defect in SDOCT was present in eight eyes (22%) in the central SDOCT scan. In six eyes of these the atrophic areas were secondary to macular laser scars, only two eyes developed RPE atrophy without any prior macular laser treatment. Channa et al. (2014) described a correlation of foveal atrophy defined as retinal thinning accompanied by a window defect in FA and poor visual outcome in patients treated for DME. In our study cohort, signs of RPE atrophy were independent of visual acuity at the time of retinal atrophy. Though RPE atrophy was present, it did not always involve the entire foveal area so residual cells might preserve visual function. Also photoreceptor integrity graded in SDOCT did neither correlate to visual function. Photoreceptor integrity alone might not warrant good visual function as the visual signal needs further processing and transmission. Loss of bipolar cells or ganglion cells is attributed to low visual function. In our patients, GCIPL thickness was lower at the time of edema than after edema resolution. This could be explained by intraretinal fluid accumulation in neighbouring layers that compresses surrounding structures or by segmentation errors, which occur frequently in DME. Mean GCIPL thickness in our patients after edema resolution was lower than described in patients with diabetes without edema (Bonnin et al. 2015).

Reduced GCIPL thickness might be a sign of impaired ganglion cell integrity and loss of synapses, which attributes to visual impairment. Likewise, the disorganization of retinal inner layers has an impact on visual function, independent from the integrity of photoreceptors or RPE. (Sun et al. 2015) Diabetes harms the retina in several ways through microvascular and neuronal damage, so multiple variables are needed to characterize the overall disease. Though SDOCT gives us valuable insight into retinal morphology, none of the factors evaluated in this study correlated solely to visual acuity.

A few limitations of this study need to be acknowledged. Firstly, it is a retrospective analysis which is limited by the images and data available. We did not have OCT angiography images or any information about the choroid, so we cannot discuss the impact of diabetic choroidopathy (Wang et al. 2017). Secondly, detailed morphological grading was only performed for eyes that developed central retinal thinning after edema resolution, which turned out to be a rather small number. However, atrophy might also be prevalent when the retina is still swollen, but patients with atrophic edema were not included in our analyses. (Bolz et al. 2014) A subgroup analysis was done for a fairly small number of 20 eyes since central retinal atrophy after DME treatment is rare. The remaining 16 eyes first presented with DME before the introduction of the electronic registry, hence the information was collected from paper-based medical records which impede a comparison with the entire DME cohort at this time. A third of patients showed an ERM in the OCT images at the time of edema. Epiretinal membrane (ERM) is quite prevalent in patients with diabetes, especially after panretinal photocoagulation. Although we have excluded patients with retinal folds or vitreoretinal traction syndrome, we cannot exclude a possible impact of ERM on central retinal thinning. Progression of DR severity as well as metabolic factors secondary to DM was not included as covariates in our analysis. Considering the small number of patients, we primarily focused on morphologic characteristics in OCT and FA. However, we acknowledge that DR is a complication of a systemic disease, with multiple factors possibly contributing to our outcomes. Lastly, although the photoreceptor damage and RPE loss were graded, the extent of foveal involvement was not quantified.

To conclude, central retinal atrophy is fairly rare in patients treated for DME and based on our data might not be attributed to excessive use of intravitreally applied anti-VEGF or any other DME therapy alone. Higher CST and lower BCVA than our overall DME cohort at baseline could be identified as risk factors for central retinal atrophy and poor visual outcome. Most patients, who developed retinal atrophy received multiple treatments for DME including anti-VEGF, intravitreal corticosteroids and macular laser suggesting they had recalcitrant edema in advanced disease. Visual function might prevail in thin retinas as long as the key retinal cells are alive and interconnected, which could not be reflected by the morphology variables visible in SDOCT or FA.

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