Graefe's Archive for Clinical and Experimental Ophthalmology
https://doi.org/10.1007/s00417-026-07415-w

RESEARCH

Clinical and optical coherence tomography angiography-based risk factors for reduced retinal sensitivity in diabetic macular edema

Lucy J. Kessler[1,2,4] · Simon Kreutzenberger[3] · Werner Nahm[2,3] · Gerd U. Auffarth[1] · Martin Dugas[4] · Mai-Nhi Pham[1] · Yeryeong Eo[1] · Ramin Khoramnia[1,2,5]

Received: 24 October 2025 / Revised: 1 July 2026 / Accepted: 20 July 2026

Abstract

Purpose To compare microperimetric retinal sensitivity (RS) and Optical Coherence tomography angiography (OCTA)-derived perfusion metrics between eyes with diabetic macular edema (DME) and healthy controls, and to explore clinical and imaging parameters associated with lower RS within the diabetic cohort.

Methods Prospective cross-sectional study of 38 diabetic eyes from 31 patients and 25 control eyes. All participants underwent microperimetry and OCTA on the same day. RS and OCTA-derived vessel metrics were assessed using a standard/general microperimetry pattern and clinician-defined customized subgrids targeting areas of suspected reduced perfusion in the deep vascular complex. Between-group differences were analyzed using linear mixed-effects models with patient identity as a random intercept to account for inter-eye correlation. Within the diabetic cohort, generalized linear mixed-effects models were used to explore parameters associated with RS, including Best-corrected visual acuity (BCVA), anti-vascular endothelial growth factor (VEGF) treatment intensity, persistent intraretinal fluid, previous panretinal photocoagulation, cardial and cerebral comorbidity, Optical Coherence Tomography (OCT)-derived neuroretinal metrics, and OCTA-derived vessel metrics.

Results Compared with healthy controls, diabetic eyes showed significantly lower general macular RS and altered OCTA-derived perfusion metrics, particularly in the deep vascular complex. General macular RS was reduced by −3.99 dB in diabetic eyes compared with controls (95% CI: −5.51 to −2.48, $p<0.001$). OCTA-derived vessel metrics showed moderate correlations with general RS. Localized OCTA-guided subgrids did not provide additional functional information beyond the standard/general microperimetry pattern. Within the diabetic cohort, worse BCVA, previous panretinal photocoagulation, and persistent intraretinal fluid were associated with lower RS in exploratory mixed-effects models. Cardio- and cerebrovascular comorbidity showed a non-significant tendency toward lower RS.

Conclusion Eyes with DME showed reduced retinal sensitivity and altered OCTA perfusion compared with healthy controls. Focal OCTA-guided subgrids did not improve functional assessment beyond the standard/general microperimetry pattern. Reduced general RS in treated DME appears to reflect multifactorial mechanisms, including visual function, residual exudative activity, prior retinal treatment.

Key messages

What is known

- OCTA-derived vessel metrics are moderately associated with retinal sensitivity in diabetic retinal disease, but visual function in DME is likely influenced by multiple structural, vascular, and clinical factors.

What is new

- In anti-VEGF-treated DME, OCTA-derived vessel metrics showed moderate correlations with retinal sensitivity but did not provide a complete explanation for functional impairment. Exploratory mixed-effects models suggested associations of reduced retinal sensitivity with lower BCVA, previous PRP, and persistent IRF; cardiovascular and cerebrovascular comorbidity showed a non-significant trend and should be interpreted cautiously.
- OCTA-guided customized subgrids targeting DVC hypoperfusion did not show added functional benefit over the standard/general microperimetry pattern, suggesting that focal perfusion deficits alone may not capture the dominant determinants of retinal sensitivity loss in treated DME.

Extended author information available on the last page of the article

Published online: 28 July 2026

Keywords Diabetic macular edema · Microperimetry · Microvasculature · OCT biomarkers · OCTA biomarkers · Retinal sensitivity · Vessel area density · Ovessel diameter

Introduction

Diabetic macular edema (DME) remains a leading cause of visual dysfunction in diabetic retinopathy [1]. Although anti-vascular endothelial growth factor (VEGF) therapy has substantially improved anatomical and visual outcomes, visual impairment frequently persists despite apparent fluid control. This incomplete relationship between retinal morphology and visual function suggests that functional loss in DME is not explained by best-corrected visual acuity (BCVA) or retinal thickening alone but may reflect a combination of photoreceptor and neuroretinal dysfunction, microvascular compromise, and systemic vascular disease as proposed by several authors. In line with this, Mokrane et al. and Montesano et al. showed that retinal sensitivity (RS) is spatially associated with Optical coherence tomography angiography (OCTA)-derived superficial vessel density and OCT-derived inner retinal layer thickness, supporting the use of combined vascular and neuroretinal parameters when evaluating functional impairment in diabetic retinal disease. Bhaskaran et al. demonstrated that retinal nerve fiber layer (RNFL) was reduced in diabetic retinopathy patients compared to age-matched controls. Consistent with this concept, OCT studies have documented alterations of inner retinal layers in diabetes, supporting the inclusion of neurodegeneration-related markers, such as RNFL and ganglion cell layer thickness, when interpreting functional outcomes in DME [2–5].

Microperimetry provides spatially resolved measurements of RS at multiple macular loci. OCTA similarly generates spatially resolved maps of macular microvascular integrity, including vessel area density, vessel length density, branch point number, and vessel diameter index. Because both modalities assess overlapping macular regions, microperimetry and OCTA can be colocalized to investigate whether local perfusion deficits correspond to local functional loss and elucidate the structure-function-relationship in the macula [6].

Previous studies have demonstrated correlations between OCTA-derived vessel metrics and RS in microperimetry in diabetic retinal disease, with reported correlation coefficients for vessel area density in the superficial or deep vascular plexus ranging approximately from 0.33 to 0.55 [7–9]. These findings support a relevant structure–function relationship between macular perfusion and retinal sensitivity. However, they also indicate that OCTA-derived perfusion metrics explain only part of the variability in RS. Therefore, reduced retinal sensitivity in DME may depend not only on macular perfusion, but also on additional clinical, systemic, treatment-related, and neuroretinal factors [9–14].

Accordingly, one aim of this study was to determine whether clinical characteristics, systemic comorbidities, anti-VEGF treatment-related parameters, and OCT-derived neuroretinal metrics such as retinal nerve fiber layer integrity provide additional explanatory value for RS in microperimetry beyond established OCTA-derived perfusion metrics such as vessel area density.

As a secondary topographic analysis, we assessed whether customized microperimetry subgrids targeting OCTA-defined hypoperfused regions provide additional structure–function information compared with general macular RS and global OCTA metrics. This analysis was based on the premise that global OCTA metrics, derived from the entire OCTA image, may average areas of normal and reduced perfusion and could therefore dilute focal structure–function relationships. By colocalizing customized microperimetry subgrids with OCTA-defined regions of reduced perfusion, we tested whether locally hypoperfused areas show lower RS than the general macular pattern and whether local OCTA metrics correspond more closely to local RS than global measurements. If localized metrics showed stronger correspondence with RS than global metrics, this would support their inclusion in subsequent explanatory models; however, in the absence of added local structure–function information, general macular RS and global OCTA metrics would suffice for the primary multivariable analysis.

Thus, this cross-sectional study addressed two complementary objectives: the primary objective was to identify clinical, systemic, OCT-derived, and OCTA-derived parameters associated with general macular RS, while the secondary objective was to determine whether OCTA-defined hypoperfused regions correspond to localized reductions in RS.

Methods

Description of the diabetic retinopathy cohort and control subjects

Diabetic retinopathy (DR) patients and healthy controls were recruited between June and December 2023. DR inclusion criteria were: age ≥ 18 years; type 1 or type 2 diabetes mellitus with a documented duration > 5 years; a prior diagnosis of DME with ongoing anti-VEGF therapy; best-corrected visual acuity (BCVA) better than 1.3 logMAR; and stable fixation, defined on Macular Integrity Assessement

(MAIA) microperimetry by fixation stability indices with P1 > 85% (percentage of fixation points within 1°). Patients were examined at a visit when DME was considered most reduced/stable under ongoing anti-VEGF treatment (i.e., least intraretinal fluid across available recent visits), allowing residual but non–center-involved DME in accordance with International Council of Ophthalmology (ICO) definitions. For full stability criteria, see 'Definition of stable disease, central subfield thickness and residual macular edema' below.

Exclusion criteria were: history of retinal detachment, retinal disease such as macular degeneration, epiretinal membrane, arterial or venous occlusions, serous central retinopathy, inherited retinal diseases, corneal disease or other media opacities precluding high-quality imaging, refractive error < −6.0 diopter or > +3.0 diopter, prior macular laser treatment, ellipsoid zone disruption involving the analyzed macular region. Uncontrolled glaucoma was defined as prior glaucoma surgery and/or persistently elevated intraocular pressure with evidence of progressive glaucomatous damage and thus was excluded. Eyes with glaucomatous visual field loss affecting the central 10° (corresponding to the microperimetry test region) or more than 3 decibles of mean deviation were excluded. Eyes with controlled glaucoma were eligible only if intraocular pressure was within the normal range under topical medication alone, with no prior surgery and no central 10° visual field involvement. Patients with normal tension glaucoma were excluded.

Control subjects were recruited from the outpatient clinic. Inclusion and exclusion criteria matched those for patients, except for diabetes and DME history. Controls underwent OCT, OCTA, and fundoscopy to exclude macular or retinal abnormalities.

DR staging was determined by fundoscopy, with patients may having past panretinal photocoagulation (PRP; >2 years) and no active proliferative signs graded as moderate or mild. Data were recorded in a study-specific electronic system [15]. PDR was defined by clinical evidence of neovascularization and/or preretinal/vitreous hemorrhage at the study visit.

Clinical examination, OCT, OCTA and microperimetry were done at the same day. Subgrids for microperimetry assessement derived from the OCTA of the same day.

Definition of stable disease and central subfield thickness

Stable disease was defined as no treatment escalation during the three visits preceding the study examination, including no shortening of the anti-VEGF injection interval and no re-initiation of anti-VEGF therapy after a treatment pause. Additionally, absence of a worsening in best-corrected visual acuity of ≥ 0.2 logMAR compared to any BCVA value of the last three visits was required. No prespecified CST cutoff was applied. Instead, CST was used descriptively to confirm that the cohort did not show marked center-involving edema at the study visit. The median CST was 296 µm (IQR: 273–335 µm), consistent with an anti-VEGF-treated cohort with minimal residual thickening. Normative CST values for non-edematous eyes on Spectralis OCT System ((Heidelberg Engineering, Heidelberg, Germany) are typically ~ 265–315 µm [16]. In our cohort, the median CST was 296 µm (25%-Interquartile Range (IQR): 273 µm, 75%-IQR: 335 µm), reflecting an anti-VEGF–treated population with minimal residual thickening.

General and customized local pattern in microperimetry

Macular Integrity Assessment (MAIA, Software version v2.6) (Centervue Inc., San Jose, USA) was used for microperimetry (MP). Participants were dilated and dark adapted in a dimmed room for 10 min before testing under mesopic conditions. For study eyes, one was randomly selected for testing. The general pattern used a 10° circular design with 37 stimuli.

To enable spatially resolved structure–function analysis, the standard pattern was complemented by customized rectangular subgrids targeting regions of suspected hypoperfusion on DVC OCTA en face images. Because OCTA imaging and microperimetry were performed during the same study visit, objective post-processing of vessel density maps was not immediately available at the time of testing. Therefore, an experienced clinician identified suspected areas of perfusion compromise directly on the DVC OCTA image and used this assessment to position the customized subgrids.

Perfusion status within each customized region was graded as normal, capillary dropout approaching normal (CD to normal), capillary dropout (CD), or severe capillary dropout (CD severe). This grading was used only to guide subgrid placement and was subsequently validated quantitatively by measuring vessel area density within the exact same customized subgrid areas. Quantitative vessel density values for the global OCTA image and customized grids according to these grading categories are shown in Supplementary Fig. 1.

The customized protocol was designed to test whether denser probing of OCTA-defined hypoperfused regions provides additional functional information beyond general macular sampling. To keep testing conditions comparable, the total number of stimuli and test duration were kept similar between the general and customized protocols, with approximately 30–40 stimuli per examination distributed across three to four rectangular subgrids. Areas with

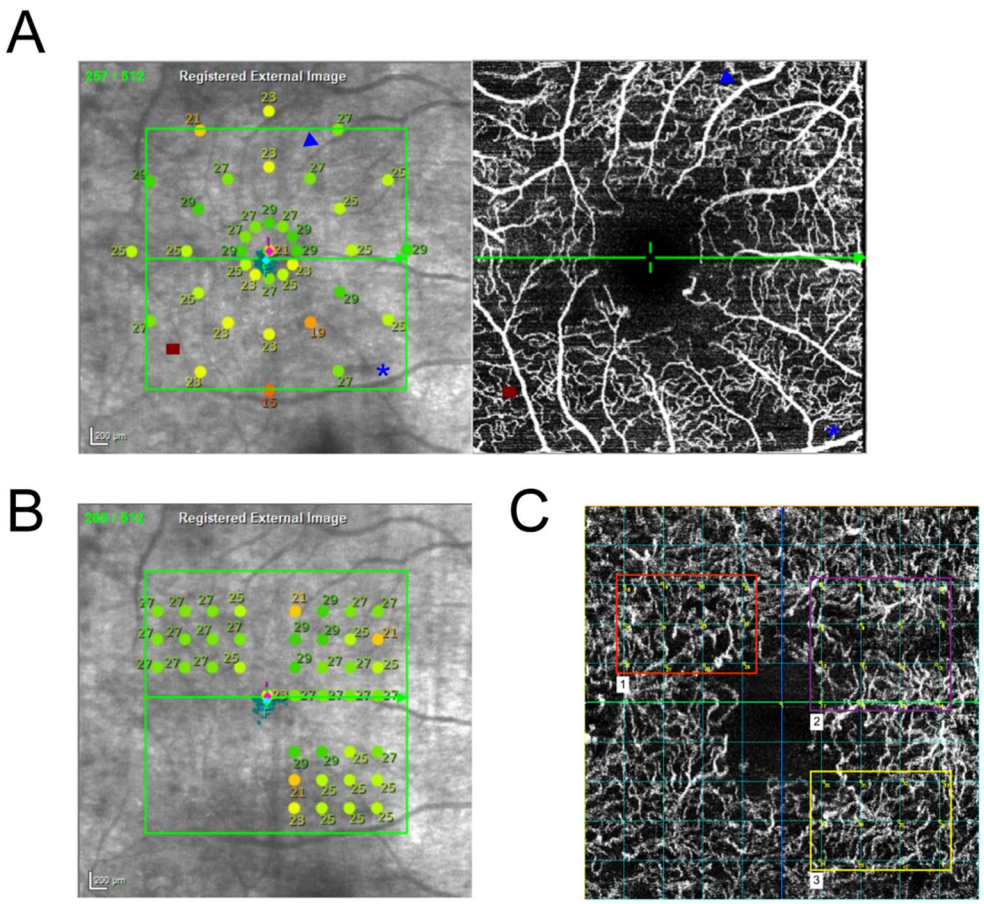

Fig. 1 **A** The vessels from the superficial vacular complex in the en face infrared images from the microperimtery device and OCT were used for registration by the research software SP-X1701. The OCTA corresponds to the area within the green rectangular frame in the infrared image on the left side. Notably, the general pattern of the microperimetry was superimposed on the en face image of the OCTA. The blue triangle, blue asterisks and the red rectangle represents vessels that were used for registration in this example. **B** For each diabetic patient, a customized microperimetry pattern with stimuli focused on areas in the OCTA with pronounced VAD loss or vessel abnormalities such as microaneurysms was created. **C** demonstrates the corresponding areas in the OCTA for the stimuli shown in B as colored boxes in red, purple and yellow

intraretinal fluid or ellipsoid zone disruption were excluded, and random subgrids were used when capillary dropout was minimal.

The customized protocol was designed to test whether denser probing of OCTA-defined hypoperfused regions provides additional functional information beyond general macular sampling. To keep testing conditions comparable, the total number of stimuli and test duration were kept similar between the general and customized protocols, with approximately 30–40 stimuli per examination. Customized stimuli were distributed across three to four rectangular subgrids. Areas with intraretinal fluid or ellipsoid zone disruption were excluded, and random subgrids were used when capillary dropout was minimal.

Figure 1 shows the general and customized pattern and the colocalization with OCTA. Colocalization between microperimetry results with OCTA was ensured using the research software SP-X1701 by Heidelberg Engineering (Spectralis Viewing Module ver. 6.9.5.703) [17, 18]. Both microperimetry and OCTA registration were device-integrated: the MAIA microperimetry system uses its own built-in scanning laser ophthalmoscope (SLO) for real-time fundus tracking and stimulus placement, while the Spectralis OCTA uses TruTrack active eye tracking with SLO-based fundus imaging as the spatial reference frame. Colocalization between the two modalities was achieved using the Heidelberg Engineering research software SP-X1701 (Spectralis Viewing Module ver. 6.9.5.703), which aligns both datasets to the same SLO fundus reference via vessel-based landmark registration.

A 4−2 projection strategy, Goldmann III stimulus size, 200 ms duration, and 36 dB luminance range were used, with eye-tracking and fixation quality metrics included.

OCT acquisition for macula volume scan and retinal nerve fiber layer (RNFL) scan, segmentation quality control

Spectral-domain OCT imaging was performed using the Spectralis OCT2 system (Heidelberg Engineering, Heidelberg, Germany), and export via HeyEx. Macular imaging followed a standardized protocol using Fast Volume mode (25-line macular line-scan (20° x 20°), Automatic Real-Time averaging with 25 frames, section spacing 240 µm). All examinations were obtained under pharmacologic pupil dilation. Automated retinal layer segmentation generated by the device software was manually reviewed in all cases and, when required, corrected by an experienced clinician

to ensure accurate delineation of retinal boundaries. The Spectralis OCT uses the same Q score (0 to 40) for both structural OCT and OCTA, with the manufacturer recommending more than 15 as the minimum threshold. We used images with Q score >/= 25.

Standard glaucoma preset was used for RNFL circle scan

Other OCT biomarkers — including disorganization of the inner retinal layers (DRIL), hyperreflective foci, and inner retinal layer thickness measurements — were not formally analyzed, as their systematic grading was beyond the prespecified scope of this study and would require dedicated grading protocols that were not established at the time of data collection.

Quantification of vessel metrics in the OCTA

Fovea-centered 15° × 15° OCTA volumes (default: five B-scan repeats) were acquired using a spectral-domain OCT system (Spectralis, Heidelberg Engineering). Superficial (SVC) and deep vascular plexus (DVC) slabs were generated using the device's automated layer segmentation and exported as en face TIFF images. Segmentations were manually verified by LJK and MNP. Projection artifacts were addressed using the proprietary Projection Artefact Removal algorithm (Spectralis OCTA module, Heidelberg Engineering), and all scans underwent a clinical image-quality review prior to inclusion. Given that the analysis was restricted to eyes with minimal or no DME (per CST-based criteria), projection artifacts were expected to be limited.

Images were processed in Matlab_R2024a with annotation lines adjusted to gray value 0 to avoid vasculature density interference [19]. Regions of interest were annotated and retained for further analysis. Image processing and quantification were applied similarly to en face images and customized microperimetry regions.

The authors followed the nomenclature and metric definitions by Sampson et al. [20]. Histogram-based binarization (Otsu's method) was performed using Matlab's 'imbinarize,' with stored thresholds. Vessel Area Density (VAD) was calculated as:

$$Vessel\ Area\ Density = {}^{Number\ of\ white\ pixels}\Big/_{Overall\ number\ of\ pixels}$$

Distance maps from binarized images were created using Matlab's 'bwdist,' and mean distances were calculated. Skeletonization applied the 'bwmorph' thinning method to calculate Vessel Length Density (VLD):

$$Vessel\ Length\ Density = {}^{Number\ of\ centerline\ pixels}\Big/_{Overall\ number\ of\ pixels}$$

The Vessel Diameter Index (VDI) was calculated by dividing Vessel Area Density by Vessel Length Density, indicating the mean diameter of vessels within the analyzed region:

$$Vessel\ Diameter\ Index = {}^{VAD}\Big/_{VLD} = {}^{Number\ of\ white\ pixels}\Big/_{Number\ of\ centerline\ pixels}$$

Branchpoints were extracted with the 'bwmorph' branchpoints function but were not normalized, as all images captured 10°x10° retinal eccentricity. Detailed protocols for VAD and VDI are available in a prior publication [21].

Axial length was not available for all participants and therefore no axial-length–based magnification correction was applied; to reduce magnification-related variability, we restricted inclusion to eyes with refractive error between −6.0 and +3.0 diopters and used a standardized OCTA acquisition protocol across all subjects.

Definition of dependent and independent variables and statistical analysis

The main dependent variable was retinal sensitivity (RS) measured by microperimetry and expressed in decibels. For group comparisons and primary multivariable analyses, general macular RS from the standard microperimetry pattern was used. For the localized structure–function analysis, local RS from customized subgrids was compared with OCTA-derived perfusion metrics measured within the corresponding regions of interest. Local RS was additionally analyzed as a secondary dependent variable.

Independent variables included clinical parameters, systemic comorbidities, structural OCT-derived parameters, and OCTA-derived vessel metrics. Clinical variables comprised BCVA in logMAR, anti-VEGF injections per year, persistent intraretinal fluid despite anti-VEGF therapy, and previous panretinal photocoagulation. Systemic variables included diabetes-related and cardiovascular/cerebrovascular comorbidities. In the multivariable mixed-effects models, cardio- and cerebrovascular disease was defined as a composite patient-level variable comprising coronary heart disease, myocardial infarction, or stroke. Arterial hypertension was not included in this variable because it was highly prevalent and was considered separately as a common cardiovascular risk factor rather than as manifest cardio- or cerebrovascular disease. OCT-derived variables included central retinal thickness and RNFL thickness. OCTA-derived variables included vessel area density, vessel length density, branch point number, vessel diameter index, and mean distance to the nearest vessel, assessed in the superficial and deep vascular complexes.

Because some participants contributed both eyes, mixed-effects models with patient identity as a random intercept were used for group comparisons of BCVA, OCTA metrics, fixation stability, and retinal sensitivity, as well as for multivariable analyses of RS. Age was compared between diabetic patients and healthy controls using Welch's t-test, as this test does not assume equal variances between groups and is appropriate for comparing continuous variables between two independent groups with unequal sample sizes.

Pearson correlation coefficients were calculated to assess univariable associations between OCTA-derived vessel metrics, clinical parameters, treatment-related variables, and RS. Candidate variables were considered for multivariable modeling if they showed a relevant univariable association with RS, defined as an absolute correlation coefficient > 0.3 and/or statistical significance, or if they were considered clinically relevant based on the study rationale.

Generalized linear mixed-effects models (GLMM) were used to evaluate parameters associated with RS. Because RS is a positive continuous variable, Gamma models with a log link were fitted. Subject-ID was included as a random intercept to account for inter-eye correlation. Candidate predictors were added in an exploratory stepwise approach, and model fit was compared using the Akaike Information Criterion (AIC), together with convergence behavior, biological plausibility, and statistical significance of included predictors.

All estimates are reported with 95% confidence intervals and p-values.

Statistical analysis and visualization were performed in RStudio/R version 4.3.1.

Results

This analysis included 25 eyes from 24 healthy controls and 38 eyes from 31 diabetic patients. Demographics and anti-VEGF treatment details are in Table 1. Age was not significantly different in both groups (95% CI: -4.3 to 9.3, $p > 0.05$). Diabetic patients had worse visual acuity than controls, with an adjusted mean difference of 0.217 logMAR (95% CI: 0.128 to 0.306, $p < 0.001$). Cardiovascular and cerebrovascular risk factors were similar (50% vs. 60%), with higher percentages in the diabetic group. Hypertension was most common (58% in controls, 74% in diabetics), followed by risk factors including previous stroke, myocardial infarction and coronary artery disease (8% in controls, 25% in diabetics). Half of diabetic patients received ongoing anti-VEGF therapy, averaging six injections annually. Most diabetics had proliferative or severe non-proliferative DR.

Table 1 Demographics and anti-VEGF characteristics of study patients and controls

Demographic characteristics	ControlsN=24	Diabetic patientsN=31
Number of study eyes	25	38
Age (years, mean ± SD)	57.80 ± 15.93	61.21 ± 10.93
Male (n; in %)	12 (50%)	23 (74%)
BCVA in logMAR	0.04 ± 0.07	0.25 ± 0.21
Type 2 Diabetes (n; in %)	N.A.	25 (80%)
Cardio- and cerebrovascular risk factors (i.e. hypertension, coronary artery disease, previous stroke or myocardial infarction)	15 (60%)	22 (70%)
HbA1c in %	N.A.	7.65
Pseudophakic Eyes (n; in %)	5 (20%)	20 (52%)
Presence of non-center involved DME (n; in %), otherwise dry macula	N.A.	25 (65%)
History of panretinal photocoagulation (PRP) sessions (n; in %)	N.A.	29 (76%)
Ongoing anti-VEGF therapy (n; in %)	N.A.	21 (55%)
Number of anti-VEGF injections for the past 12 months (n; in %)	N.A.	6.05 ± 2.73
Diabetic retinopathy stages (n; in %)	N.A.	
Mild NPDR		7 (18%)
Moderate NPDR		8 (21%)
Severe NPDR		12 (31%)
PDR		12 (31%)

SD standard deviation, *N.A.* not applicable, *BCVA* best corrected visual acuity, *HbA1c* glycated hemoglobin, *VEGF* vascular endothelial growth factor, *NPDR* non-proliferative diabetic retinopathy, *PDR* proliferative diabetic retinopathy

Diabetic patients showed reduced perfusion in OCTA and retinal sensitivity in microperimetry

OCTA and microperimetry metrics are presented in Table 2. Overall retinal sensitivity (RS) and OCTA parameters derived from the entire image, included vessel area density (VAD), vessel length density, branching point number, vessel diameter index, and mean distance to the nearest vessel were compared between healthy controls and diabetic patients. All DVC parameters were significantly altered in the diabetic group (all p-value < 0.05; see Table 2), while in SVC, only vessel diameter index and length density differed significantly from healthy controls. Diabetic patients had significantly lower retinal sensitivity than controls with an adjusted mean difference of -3.99 dB (95% CI: -5.51 to -2.48, $p < 0.001$).Fixation stability showed no significant differences between controls and diabetics for both patterns (95% CI: -2.23 to 1.97; $p > 0.05$).

Table 2 OCTA and microperimetry metrics of study patients and controls

OCTA metrics	Controls Mean ± SD	Diabetic patients Mean ± SD	Adjusted mean difference (DR – Control)	95% CI	mixed effects *p*-value
SVC					
vessel area density (VAD) (mean ± SD)	0.21 ± 0.05	0.19 ± 0.05	-0.0281	-0.060 to 0.004	$p > 0.05$
Branch point number (mean ± SD)	4656 ± 1462	4008 ± 1152	-825	-1603 to -47.76	$p > 0.05$
Mean distance to nearest vessel (mean ± SD)	7.66 ± 4.42	8.43 ± 2.66	0.258	-1.75 to 2.26	$p > 0.05$
Vessel diameter index (mean ± SD)	3.80 ± 0.20	3.98 ± 0.34	0.178	0.02 to 0.33	0.024
Vessel length density (mean ± SD)	0.056 ± 0.015	0.048 ± 0.011	-0.01	-0.02 to -0.002	0.020
DVC					
vessel area density (mean ± SD)	0.26 ± 0.05	0.20 ± 0.04	-0.065	-0.097 to -0.033	$1.28 * 10^{-4}$
Branch point number (mean ± SD)	8830 ± 2014	6333 ± 1596	-2714	-3822 to -1606	$8.60 * 10^{-6}$
Mean distance to nearest vessel (mean ± SD)	3.98 ± 1.65	5.89 ± 1.8	1.52	0.41 to 2.62	0.008
Vessel diameter index (mean ± SD)	3.04 ± 0.16	3.22 ± 0.20	0.18	0.08 to 0.28	$4.82 * 10^{-4}$
Vessel length density (mean ± SD)	0.08 ± 0.01	0.06 ± 0.01	-0.02	-0.03 to -0.02	$2.81 * 10^{-6}$
Microperimetry metrics					
Retinal sensitivity in dB, general pattern (mean ± SD)	27.03 ± 1.23	22.96 ± 3.48	-3.99	-2.48–5.51	$2.04 * 10^{-6}$
Retinal sensitivity in dB, customized local pattern (mean ± SD)	n.a.	22.80 ± 3.64	n.a.	n.a.	n.a.
Fixation stability in %, general pattern (mean ± SD)	97.72 ± 4.08	97.12 ± 4.04	-0.128	-2.23–1.97	n.s.
Fixation stability in %, customized pattern ((mean ± SD)	n.a.	96.97 ± 5.08	n.a.	n.a.	n.a.

SVC superficial vascular complex, *DVC* deep vascular complex, *dB* decibel, *n.s.* non-significant defined as p-value > 0.05. *n.a.* not applicable

*compared to retinal sensitivity general pattern in diabetic group

OCTA parameter and retinal sensitivity correlation assessment

DVC metrics mean vessel distance ($r = -0.55$, $p < 0.05$) and vessel length density ($r = -0.59$, $p < 0.05$) showed the strongest correlations with RS, while other parameters ranged from $r = -0.39$ to 0.59 ($p < 0.05$). In SVC, correlations were lower ($r = -0.23$ to 0.36, $p < 0.05$), except for mean vessel distance, which was not significant (Fig. 2).

In stepwise linear analysis, Vessel Length Density was found to be a significant predictor for retinal sensitivity in the diabetic group, but not in healthy Controls.

Subgrid OCTA parameters from DVC showed lower correlations with focal RS than OCTA parameters from the entire image and RS from the general pattern in microperimetry, with coefficients R^2 ranging from 0.20 to 0.26 ($p < 0.05$). Vessel diameter index and all OCTA parameters from SVC were not significantly correlated with local RS.

Impact of clinical parameters on vessel area density and retinal sensitivity

Clinical parameters that might influence the vessel area density in DVC or RS in microperimetry were analyzed. Correlation coefficient greater than 0.3 was found for RS in general and local pattern ($r = 0.80$, $p < 0.05$), RS in general pattern with BCVA ($r = -0.42$, $p < 0.05$) and global RNFL ($r = 0.41$, $p < 0.05$), VAD in local pattern and RS in general pattern ($r = 0.49$, $p < 0.05$). Age, HbA1c, and the number of anti-VEGF injections per year showed no correlation with the VAD or RS (Table 3).

Risk factors for reduced retinal sensitivity

In the general retinal sensitivity pattern, worse BCVA and previous PRP were significant predictors of lower retinal sensitivity. A 0.1-unit increase in logMAR BCVA was associated with a 2.77% reduction in retinal sensitivity (95% CI: -3.29% to -2.25%, $p < 0.01$). Absence of PRP was associated

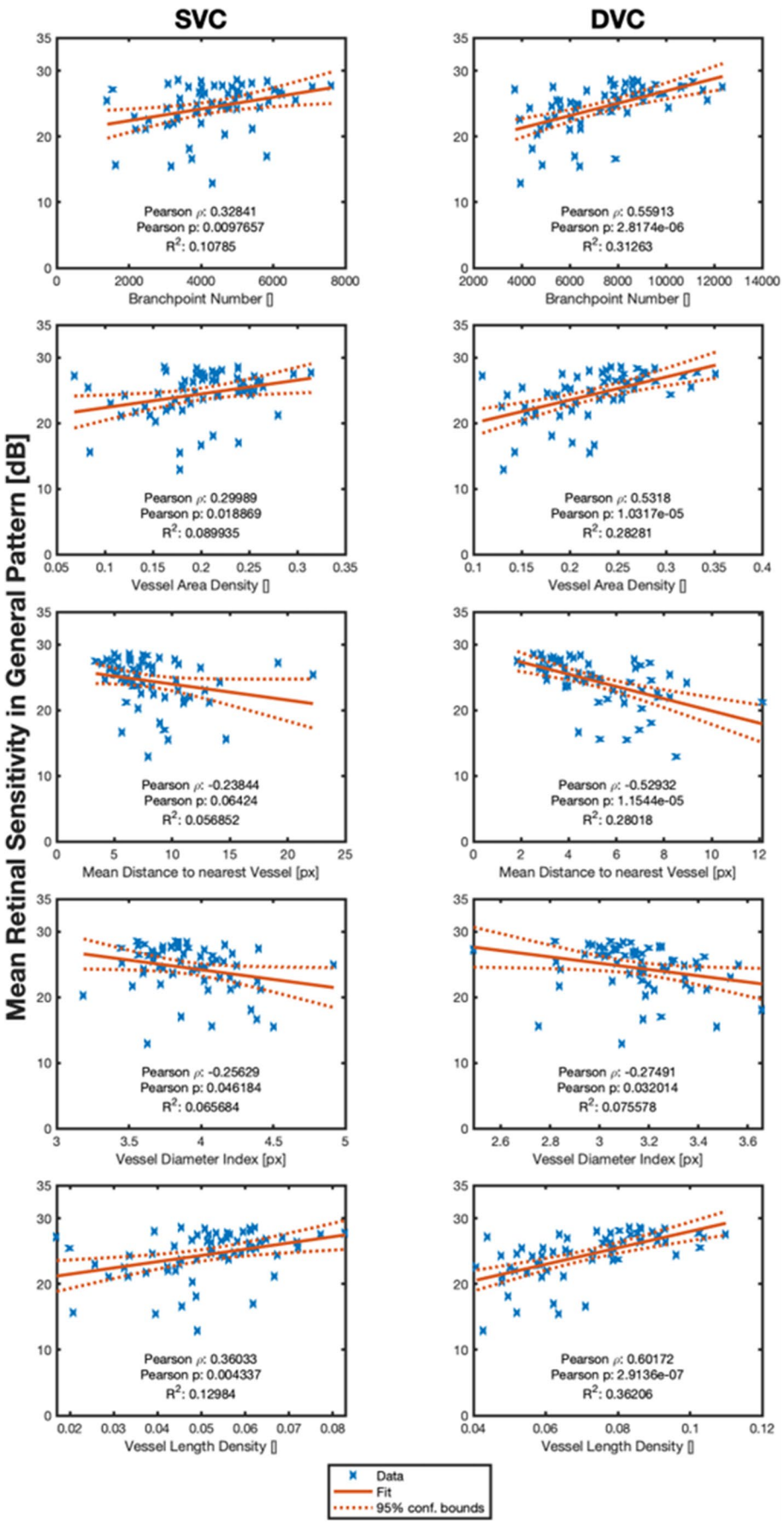

Fig. 2 Pearson's correlation between mean retinal sensitivity and OCTA parameters in superficial vascular complex (SVC) and deep vascular complex (DVC). Branchpoint numbers are counted as total numbers, vessel area density and vessel length density are expressed as ratio

Table 3 Correlation between clinical DR and anti-VEGF parameters and visual function

Variable	Age	BCVA (logMAR)	HbA1c	Mean VAD in local pattern	Retinal sensitivity in general pattern	Retinal sensitivity in local pattern	Anti-VEGF injections per year
Age							
BCVA (logMAR)	0.11						
	[-0.26, 0.46]						
HbA1c	0.13	0.05					
	[-0.25, 0.46]	[-0.31, 0.41]					
Mean VAD in local pattern	−0.04	−0.21	−0.21				
	[-0.39, 0.33]	[-0.53, 0.16]	[-0.53, 0.16]				
Retinal sensitivity in general pattern	−0.04	−0.42*	−0.10	0.49**			
	[-0.39, 0.33]	[-0.68, −0.07]	[-0.45, 0.27]	[0.15, 0.72]			
Retinal sensitivity in local pattern	0.01	−0.19	−0.12	0.35	0.80**		
	[-0.35, 0.37]	[-0.52, 0.18]	[-0.46, 0.25]	[-0.01, 0.63]	[0.62, 0.90]		
Anti-VEG injections per year	0.10	−0.13	−0.17	0.07	−0.09	−0.20	
	[-0.27, 0.45]	[-0.47, 0.24]	[-0.50, 0.21]	[-0.29, 0.42]	[-0.43, 0.28]	[-0.52, 0.17]	
RNFL global	0.07	0.03	−0.30	0.21	0.41*	0.27	−0.24
	[-0.29, 0.4]	[-0.33, 0.39]	[-0.60, 0.06]	[-0.17, 0.53]	[0.06, 0.67]	[-0.10, 0.58]	[-0.55, 0.14]

Numbers in square brackets indicate the 95% confidence interval for each correlation. * indicates $p < 0.05$. ** indicates $p < 0.01$

with 26.61% higher retinal sensitivity (95% CI: 20.54% to 32.98%, $p<0.01$), indicating lower retinal sensitivity in eyes with previous PRP.

Absence of cardio and- cerebrovascular risk factors showed a tendency toward higher retinal sensitivity, but this association did not reach statistical significance (+21.23%, 95% CI: -3.13% to 51.72%, $p=0.093$). Absence of persistent IRF was associated with higher retinal sensitivity (+6.62%, 95% CI: 3.03% to 10.34%, $p<0.01$). The final model including BCVA, cardio- and cerebrovascular risk factors, persistent IRF, and previous PRP showed lower AIC than the comparator model including BCVA and previous PRP (AIC 114.1 vs. 141.9).

RS from local pattern was tested as dependent variable as well. BCVA and previous PRP remained significant predictors. A 0.1-unit increase in logMAR BCVA was associated with a 0.60% reduction in local retinal sensitivity (95% CI: -0.81% to -0.39%, $p<0.01$), and absence of previous PRP was associated with 87.45% higher local retinal sensitivity (95% CI: 83.84% to 91.13%, $p<0.01$). Cardio- and cerebrovascular risk factors again showed a non-significant tendency (+30.84%, 95% CI: -3.26% to 76.97%, $p=0.081$) (Fig. 3).

Black dots represent individual eyes. White dots represent model-adjusted predicted retinal sensitivity averaged over the observed covariate distribution. Error bars indicate 95% confidence intervals of the predictions.

Discussion

This cross-sectional study evaluated retinal sensitivity in eyes with DME using both standard/general microperimetry and OCTA-guided customized local subgrids. The study was designed to address two related questions: first, whether clinical, systemic, anti-VEGF treatment-related, OCT-derived, and OCTA-derived parameters are associated with general macular retinal sensitivity; and second, whether localized OCTA-defined hypoperfused regions provide additional structure–function information beyond global OCTA metrics and the standard microperimetry pattern. Overall, diabetic eyes showed reduced retinal sensitivity and altered OCTA perfusion metrics compared with healthy controls. However, the explanatory analyses did not identify a strong set of clinically actionable predictors for reduced retinal sensitivity. Moreover, customized local subgrids did not provide additional functional information beyond the general macular pattern. These findings suggest that retinal sensitivity loss in treated DME is likely multifactorial and is not sufficiently explained by focal OCTA perfusion deficits alone.

Our study aligns with prior research demonstrating correlations between VAD in the superficial or deep vascular plexus and RS in microperimetry, reported as 0.33 to 0.55, similar to our findings (0.35 to 0.49) [9, 22, 23].

Prior OCTA work suggests that deep-layer perfusion metrics (DVC) are often more sensitive to DR severity than

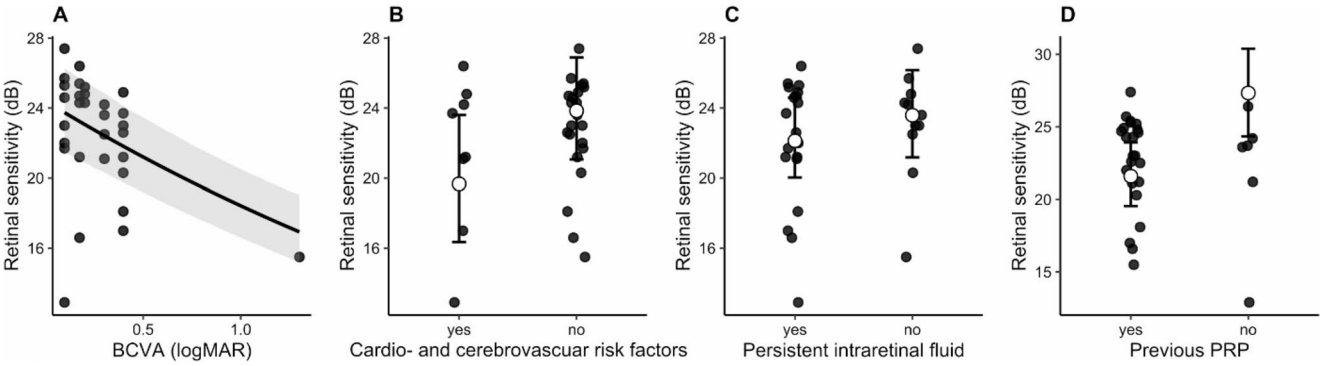

Fig. 3 Predictors of general retinal sensitivity in the inter-eye GLMM analysis

superficial metrics, particularly in earlier stages: Ashraf et al. reported that DVC vessel density/length density were already reduced in mild NPDR compared with no DR, whereas SVC metrics were not, indicating that early microvascular loss may be more apparent in deeper plexuses [24]. Consistent with this depth-specific vulnerability, deep capillary nonperfusion metrics have also been shown to predict clinically significant DR outcomes even after adjusting for baseline DR severity and BCVA." [25]. Functionally, Scarinci et al. demonstrated a spatial colocalization of DVC capillary nonperfusion with reduced microperimetric sensitivity in diabetic macular ischemia, providing a mechanistic rationale to focus on DVC when mapping perfusion to retinal sensitivity [12]. Against this background, we prioritized DVC-based perfusion measures rather than SVC for our primary correlation analyses and for guiding the subgrids concept.

The absence of a measurable advantage of OCTA-guided customized grids is an important methodological finding. Although the customized subgrids were placed over regions with objectively lower vessel area density, local retinal sensitivity within these regions was not lower than the general macular retinal sensitivity of the same eye. Thus, the expected focal structure–function relationship between localized DVC hypoperfusion and localized RS loss was not observed in this cohort. This suggests that focal OCTA-defined hypoperfusion alone may not be sufficient to explain the spatial distribution of retinal sensitivity loss in anti-VEGF-treated DME.

Several factors may have contributed to this finding. The standard and customized protocols were designed with similar stimulus counts and test duration, which may have limited differences in sampling density. In addition, functional impairment in treated DME may be spatially diffuse or influenced by prior edema, neuroretinal damage, treatment history, or systemic vascular disease rather than by current focal perfusion deficits alone. Finally, mean RS values may dilute subtle pointwise differences, and residual registration error between OCTA and microperimetry cannot be fully excluded.

Datlinger et al. found RS can remain unaffected despite smaller non-perfused areas in the DVC, suggesting compensatory mechanisms or photoreceptor tolerance to ischemia [26]. This highlights the need to explore the spatiotemporal relationship between structural abnormalities and retinal dysfunction.

As expected, and reported from previous studies, BCVA was significantly associated with retinal sensitivity, reflecting the well-established overlap between central visual acuity and macular function [10, 27, 28]. We therefore do not present the BCVA–RS relationship as a novel finding. Rather, BCVA was included as a clinically relevant covariate to contextualize microperimetry outcomes and to adjust for overall visual function. Previous PRP and persistent IRF were also associated with lower retinal sensitivity in the mixed-effects models. These findings are biologically plausible, as previous PRP may reflect more advanced ischemic diabetic retinopathy, while persistent IRF may indicate ongoing or recurrent exudative activity. However, these associations should not be interpreted as causal effects, because the cross-sectional design cannot distinguish whether these variables directly contribute to reduced RS or act as markers of more advanced or longer-standing disease.

Cardio- and cerebrovascular comorbidity showed a tendency toward lower retinal sensitivity, but the association was not statistically robust in the final analysis and should be interpreted with particular caution. The variable represented a composite history of coronary artery disease, myocardial infarction, or stroke, and the subgroup size was limited overall. Therefore, this finding may reflect a broader systemic vascular disease burden rather than an independent determinant of retinal sensitivity. Larger cohorts with more detailed systemic vascular phenotyping are needed to clarify whether cardio- and cerebrovascular comorbidity contributes independently to functional impairment in DME.

Interestingly, OCTA metrics were not among the significant predictors for RS, even though VAD from local pattern strongly correlated with the general RS in linear regression and stepwise linear model identified vessel length density as significant predictors for retinal sensitivity [29]. Possible explanations include significant individual variability in vessel impairment [30], which complicates

objective quantification of its effects. From the technical aspect, potential influencing factors include the size of the region of interest that was chosen for automated quantification, amount of image averaging and other preset parameters during the image acquisition as well as algorithms applied in the image processing. Kawai et al. presented a study that confirms that scan sizes affects the quantification of vessel metrics such as vessel density and vessel length density [31]. Since we applied the same quantification algorithms to assess vessel metrics of the corresponding OCTA in both the customized subgrid and the general MP pattern, differences in the ratio, composition, and characteristics of small and large vessels may arise in the smaller subgrids. We therefore speculate that these differences could affect the quantification results, thus leading to weaker correlation coefficients for the correlation between RS and OCTA metrics that derived from the customized subgrids.

Our study has several limitations that need to be addressed. Although we attempted to exclude the effects of macular edema by recruiting only patients without center-involving macular edema or ellipsoid zone abnormalities, we cannot rule out the impact of prior damage from DME or prolonged functional improvement following the resolution of IRF. However, comparable fixation stability between DR and control persons is suggestive for comparable foveal fixation ability. Residual registration error inherent to any device-based alignment represents another limitation. The OCT acquisition protocol generated data beyond what was formally analyzed in this study. Biomarkers such as DRIL, hyperreflective foci, and granular inner retinal layer thickness measurements were not included in the predictive models. These parameters have been associated with functional impairment in DME and may carry additional explanatory value for retinal sensitivity beyond the variables examined here. The macular OCT protocol used in this study — a 25-line fast volume scan over a 20°×20° field with a section spacing of 240 µm — provides sufficient coverage for central subfield thickness measurement and detection of intraretinal fluid but represents relatively sparse spatial sampling. This limitation is inherent to the tradeoff between field coverage and spatial resolution under a standardized, clinically feasible acquisition protocol, and may have resulted in underdetection of OCT biomarkers that could independently contribute to the observed variation in retinal sensitivity.

Because most associations were modest and the cohort size was limited, the explanatory models should be regarded as exploratory and hypothesis-generating rather than as a basis for clinical prediction.

In summary, this study confirms that eyes with DME show reduced retinal sensitivity and altered OCTA perfusion metrics compared with healthy controls, and that OCTA-derived vessel metrics show moderate associations with RS. However, neither localized OCTA-guided subgrids nor the evaluated clinical, systemic, treatment-related, OCT-derived, and OCTA-derived parameters provided a strong or clinically definitive explanation for reduced retinal sensitivity. These findings support the concept that functional impairment in treated DME is multifactorial and cannot be inferred reliably from focal OCTA perfusion deficits or single imaging biomarkers alone. Future studies with larger cohorts, longitudinal follow-up, pointwise OCT/OCTA–microperimetry registration, and more detailed OCT biomarker grading are needed to clarify the relative contributions of vascular, neuroretinal, and treatment-related factors to retinal sensitivity loss.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00417-026-07415-w.

Acknowledgements We thank Dr. Michel Teussink (Heidelberg Engineering GmbH) for his support and for providing the research software.

Author contributions Conceptualization: Kessler, LJ; Kreutzenberger, S.Data curation: Pham, MN; Eo, Y; Kessler, LJFormal analysis: Kreutzenberger, S., Kessler, LJResources: Khoramnia, R., Nahm, W., G. U. Auffarth, Dugas, M.Writing – original draft: Kessler, LJ, Kreutzenberger, S.Writing – review and editing: all authors.

Funding None.

Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Bioethics Committee of University of Heidelberg (No.S-156/2023). Written informed consent was obtained from all participants. This study is registered in the German Clinical Trials Register. The clinical trial registration number is: DRKS00024399.

References

1. Zhang J et al (2022) Diabetic macular edema: current understanding, molecular mechanisms and therapeutic implications. Cells 11(21):3362. https://doi.org/10.3390/cells11213362
2. Cheung CMG et al (2021) Looking Ahead: Visual and Anatomical Endpoints in Future Trials of Diabetic Macular Ischemia. Ophthalmologica 244(5):451–464
3. Mokrane A et al (2021) Retinal Sensitivity Correlates With the Superficial Vessel Density and Inner Layer Thickness in Diabetic Retinopathy. Invest Ophthalmol Vis Sci 62(14):28
4. Montesano G et al (2017) Structure–function relationship in early diabetic retinopathy: a spatial correlation analysis with OCT and microperimetry. Eye 31(6):931–939
5. Bhaskaran A et al (2023) Study of retinal nerve fiber layer thickness in diabetic patients using optical coherence tomography. Indian J Ophthalmol 71(3):920–926

6. Markan A et al (2020) Novel imaging biomarkers in diabetic retinopathy and diabetic macular edema. Ther Adv Ophthalmol 12:2515841420950513
7. Yang D et al (2023) Assessment of Parafoveal Diabetic Macular Ischemia on Optical Coherence Tomography Angiography Images to Predict Diabetic Retinal Disease Progression and Visual Acuity Deterioration. JAMA Ophthalmol 141(7):641–649
8. Sun JK et al (2014) Disorganization of the Retinal Inner Layers as a Predictor of Visual Acuity in Eyes With Center-Involved Diabetic Macular Edema. JAMA Ophthalmol 132(11):1309–1316
9. Levine ES et al (2022) Multiscale Correlation of Microvascular Changes on Optical Coherence Tomography Angiography with Retinal Sensitivity in Diabetic Retinopathy. Retina 42(2):357–368
10. Vujosevic S et al (2006) Diabetic macular edema: correlation between microperimetry and optical coherence tomography findings. Invest Ophthalmol Vis Sci 47(7):3044–3051
11. Parravano M et al (2022) Impact of Intravitreal Anti-VEGF Therapy on Microperimetry of the Retinal Nonperfusion Areas of Patients with Proliferative Diabetic Retinopathy. Ophthalmol Therapy 11(6):2117–2128
12. Scarinci F, Varano M, Parravano M (2019) Retinal Sensitivity Loss Correlates with Deep Capillary Plexus Impairment in Diabetic Macular Ischemia. J Ophthalmol 2019:p7589841
13. Biffi E et al (2022) Retinal biomarkers of Cerebral Small Vessel Disease: A systematic review. PLoS ONE 17(4):e0266974
14. Sinclair SH et al (2022) Diabetes mellitus associated neurovascular lesions in the retina and brain: A review. Front Ophthalmol (Lausanne) 2:1012804
15. Dugas M et al (2024) Next-generation study databases require FAIR, EHR-integrated, and scalable Electronic Data Capture for medical documentation and decision support. npj Digit Med 7(1):10
16. Grover S et al (2009) Normative Data for Macular Thickness by High-Definition Spectral-Domain Optical Coherence Tomography (Spectralis). Am J Ophthalmol 148(2):266–271
17. Montesano G et al (2018) Improving Visual Field Examination of the Macula Using Structural Information, vol 7. Translational Vision Science & Technology, pp 36–36. 6
18. Giammaria S et al (2022) Elucidating macular structure–function correlations in glaucoma. Sci Rep 12(1):10621
19. The MathWorks I (2026) *MATLAB*. The MathWorks, Inc.: Natick, MA
20. Sampson DM et al (2022) Towards standardizing retinal optical coherence tomography angiography: a review. Light: Sci Appl 11(1):63
21. Kessler LJ et al (2023) Impact of Lens Opacity on Optical Coherence Tomography Angiography Metrics. Curr Eye Res 48(10):965–972
22. Pereira F et al (2019) Microperimetry and OCT angiography evaluation of patients with ischemic diabetic macular edema treated with monthly intravitreal bevacizumab: a pilot study. Int J Retina Vitreous 5:24
23. Tsai WS et al (2024) Topographic Correlation of Microperimetry With Structural Characteristics in Diabetic Macular Ischemia. Am J Ophthalmol 257:25–33
24. Ashraf M et al (2020) Vascular Density of Deep, Intermediate and Superficial Vascular Plexuses Are Differentially Affected by Diabetic Retinopathy Severity. Invest Ophthalmol Vis Sci 61(10):53
25. Ong JX et al (2023) Deep Capillary Nonperfusion on OCT Angiography Predicts Complications in Eyes with Referable Nonproliferative Diabetic Retinopathy. Ophthalmol Retina 7(1):14–23
26. Datlinger F et al (2021) Assessment of Detailed Photoreceptor Structure and Retinal Sensitivity in Diabetic Macular Ischemia Using Adaptive Optics-OCT and Microperimetry. Invest Ophthalmol Vis Sci 62(13):1
27. Okada K et al (2006) Correlation of retinal sensitivity measured with fundus-related microperimetry to visual acuity and retinal thickness in eyes with diabetic macular edema. Eye (Lond) 20(7):805–809
28. Okada K et al (2006) Correlation of retinal sensitivity measured with fundus-related microperimetry to visual acuity and retinal thickness in eyes with diabetic macular edema. Eye 20(7):805–809
29. Hoffmann S et al (2025) OCT Angiography Deep Vascular Complex Quantification Correlation to Microperimetry Sensitivity in Diabetic Retinopathy and Healthy Controls. Investig Ophthalmol Vis Sci 66(8):77–77
30. Linderman R et al (2017) Assessing the Accuracy of Foveal Avascular Zone Measurements Using Optical Coherence Tomography Angiography: Segmentation and Scaling. Transl Vis Sci Technol 6(3):16
31. Kawai K et al (2021) Prevention of Image Quality Degradation in Wider Field Optical Coherence Tomography Angiography Images Via Image Averaging. Transl Vis Sci Technol 10(13):16

Authors and Affiliations

Lucy J. Kessler[1,2,4] · Simon Kreutzenberger[3] · Werner Nahm[2,3] · Gerd U. Auffarth[1] · Martin Dugas[4] · Mai-Nhi Pham[1] · Yeryeong Eo[1] · Ramin Khoramnia[1,2,5]

✉ Lucy J. Kessler
lucyjoanne.kessler@med.uni-heidelberg.de

[1] University Eye Hospital, Heidelberg University, Im Neuenheimer Feld 400, 69120 Heidelberg, Germany

[2] HEIKA – Heidelberg Karlsruhe Strategic Partnership, Heidelberg University, Karlsruhe Institute of Technology (KIT), Karlsruhe, Germany

[3] Institute of Biomedical Engineering, Karlsruhe Institute of Technology, Fritz-Haber-Weg 1, Karlsruhe, Germany

[4] Institute of Medical Informatics, Heidelberg University, Im Neuenheimer Feld 130.3, 69120 Heidelberg, Germany

[5] Department of Ophthalmology, University Hospital Carl Gustav Carus, TU Dresden, Fetscherstraße 74, 01307 Dresden, Germany