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Retina

Characterization of the Disorganization of the Inner Retinal Layers in Diabetics Using Increased Axial Resolution Optical Coherence Tomography

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Purpose: To compare a novel high-resolution optical coherence tomography (OCT) with improved axial resolution (High-Res OCT) with conventional spectral-domain OCT (SD-OCT) with regard to their capacity to characterize the disorganization of the retinal inner layers (DRIL) in diabetic maculopathy.

Methods: Diabetic patients underwent multimodal retinal imaging (SD-OCT, High-Res OCT, and color fundus photography). Best-corrected visual acuity and diabetes characteristics were recorded. DR was graded using the international clinical diabetic retinopathy severity scale (DRSS). In each OCT B-scan, retinal layers were segmented and the loss of discernibility was annotated. DRIL areas were analyzed in en face projection using FIJI plugins. The Wilcoxon test and regression models were used for statistical analysis.

Results: In 93 eyes of 93 patients (mean age, 61.8 $\pm$ 12.9 years) DRIL was identified in 48 eyes. DRIL was most frequent in the central subfield (27%). In DRIL eyes, DRSS was significantly higher (4.43 $\pm$ 1.01 vs. 2.12 $\pm$ 1.66; $P < 0.001$), BCVA was significantly worse (0.34 $\pm$ 0.38 vs. 0.13 $\pm$ 0.22; $P < 0.001$), and the loss of discernibility of the individual inner retinal layers was significantly smaller in High-Res OCT compared with SD-OCT (0.21 $\pm$ 0.29 vs. 1.21 $\pm$ 1.21 mm^2; $P < 0.001$). The discernibility loss was greatest in the retinal nerve fiber layer and ganglion cell layer.

Conclusions: DRIL occurs in eyes with advanced diabetic retinopathy, with a characteristic spread: from the inner toward the outer retina. High-Res OCT shows significantly smaller DRIL areas compared with SD-OCT, because of a more precise delineation of the inner retinal layers.

Translational Relevance: Using OCT with increased axial resolution could enhance our understanding of DRIL development and progression, providing deeper insights into pathophysiological aspects, including malperfusion in the inner capillary plexus.

Introduction

Diabetic retinopathy (DR) is the leading cause of vision loss and avoidable blindness in adults aged 20 to 74 years, particularly in middle- and high-income countries.[1] Recent estimates indicate a global prevalence of 22.3% for DR among diabetic patients, with projections suggesting an increase to 160.5 million affected individuals worldwide by 2045.[2,3] Microvascular changes, neurodegeneration, and neuro-inflammatory responses play a crucial role in the pathogenesis.[4–6]

Spectral domain optical coherence tomography (SD-OCT) has become an important tool in retinal screening displaying cross-sectional images of the retina, facilitating precise diagnosis and management of retinal diseases.[7–9] The use of SD-OCT is the most common approach in clinical retinal imaging nowadays.

In several clinical studies, OCT biomarkers in DR[10,11] have been proven as predictors for functional

and anatomical outcomes in diabetic macular edema, such as macular central subfield thickness, intraretinal cyst size, presence of epiretinal membranes, subretinal fluid, the integrity of the outer retina, and the disorganization of the retinal inner layers (DRIL).[12–17]

The presence of DRIL is highly correlated with visual outcome and is considered a new surrogate biomarker.[18–20] DRIL is defined as the loss of the discernibility of the inner retinal layers, including the retinal nerve fiber layer (RNFL), the ganglion cell layer (GCL), the inner plexiform layer (IPL), and the inner nuclear layer (INL).[19,21] This functional impairment is probably caused by dysfunctional communication between photoreceptors and ganglion cells,[20] as well as a major dysfunction in Müller cells.[22] Previous studies have shown that DRIL correlates with intraretinal microvascular changes that present as an enlargement of the foveal avascular zone (FAZ)[23,24] in OCT angiography (OCTA), as well as altered outer retinal layers.[25] It remains unclear whether the enlargement of the FAZ in the OCTA preceded the development of DRIL or vice versa. Nevertheless, Moein et al. demonstrated that the coexistence of an enlarged FAZ and DRIL is associated with a reduction in visual acuity as compared with the presence of an enlarged FAZ alone.[43] Involvement of the outer retina in DRIL has also been shown to affect visual outcome.[26] In addition, functional testing including retinal microperimetry shows a reduction in retinal sensitivity in patients with DRIL especially in these cases when outer retina and photoreceptors are involved.[27]

The development of DRIL and its distribution across the retina are not yet fully understood. An investigational OCT device, high-resolution OCT (High-Res OCT), provides SD-OCT imaging with improved axial resolution (2.9 µm compared with 7.2 µm in the conventional OCT device) by using a shorter central wavelength (853 µm instead of the 880 nm). Additionally, an increased signal-to-noise ratio is obtained by increasing the power in the sampling arm to 2.2mW.[28–31]

Von der Emde et al.[32] demonstrated improved inter- and intra-reader agreement of High-Res OCT compared with conventional SD-OCT in segmentation retest reliability analysis,[28] as because High-Res OCT enabled a more detailed identification of retinal layers.

In the current study, we aimed to further characterize the loss of delineation of the individual inner retinal layers by using the investigational High-Res OCT device and compare DRIL areas in High-Res OCT with conventional SD-OCT. We hypothesize that High-Res OCT will provide a more detailed assessment of DRIL, which will further enhance its suitability as a biomarker for disease severity in DR.

Methods

Patient Selection and Image Acquisition

This prospective cross-sectional study was conducted at the University Eye Hospital Bonn, Germany, between May 2023 and February 2024. The study protocol was approved by the ethics committee of the University of Bonn (#305/21) and complied with the tenets of the Declaration of Helsinki. Written informed consent was obtained from every patient prior to study inclusion and after explaining the benefits and risks of this study.

Patients aged 18 years or older with type 1 or type 2 diabetes were enrolled, regardless of DR status. Exclusion criteria were the presence of any other retinal disease, including age-related macular degeneration, retinal dystrophy, macular or lamellar holes, retinal vein or artery occlusion, or poor image quality due to optic media opacities (e.g., severe cataracts, vitreous floaters) and refraction errors (>5 diopters [D] spherical, >2 D cylindrical). If both eyes met the inclusion criteria, the eye with the better image quality was selected by using an ordinal qualitative grading scale (from 1 [low quality] to 10 [high quality]).[28]

The medical history including type of diabetes, time since first diagnosis of diabetes, hemoglobin A1c (HbA1c), current diabetes therapy, and cardiovascular risk factors were recorded using patient self-report. DR was graded using the international clinical DR severity scale (DRSS) in clinical assessment.[33] All participants underwent best-corrected visual acuity (BCVA) testing, biomicroscopy of the anterior segment, a Goldmann applanatory measurement of the intraocular pressure, and indirect funduscopy (after pupil dilation with 1.0% tropicamide and 2.5% phenylephrine).

The retinal imaging protocol included conventional SD-OCT (30° × 25°, ART 25, 241 B-scans, Spectralis HRA-OCT 2; Heidelberg Engineering, Heidelberg, Germany), High-Res OCT (30° × 25°, ART 25, 241 B-scans; axial resolution: 2.9 µm, wavelength 853 μm, power 2.2 mW, Heidelberg Engineering) as well as color fundus photography (131° Clarus, Carl Zeiss Meditec AG, Jena, Germany). The investigational High-Res OCT is based on the Spectralis technology and achieves improved optical axial resolution by leveraging an expanded spectral bandwidth (137 nm vs. 50 nm) facilitated by a super luminescent diode-based light source. Furthermore, it exhibits increased OCT power at the pupil and a central wavelength shift. Beyond the advancement in axial resolution, the augmented OCT power holds promise for enhancing the signal-to-noise ratio.[28]

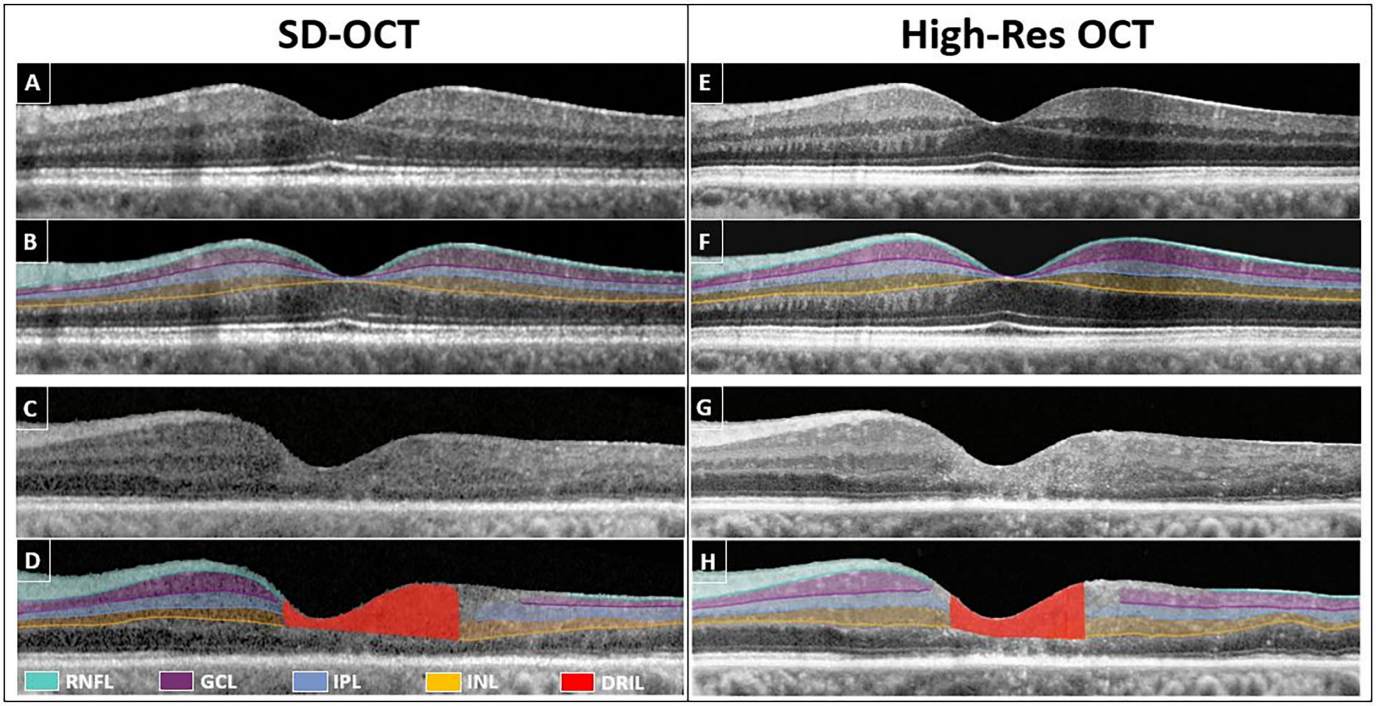

Figure 1. OCT layer annotation of the retinal inner layers. Inner retinal layers (RNFL, GCL, IPL, and INL) of a 54-year-old-female participant without DRIL in SD-OCT (**A**, **B**) and High-Res OCT (**E**, **F**) annotated and color-coded on the central B-scan. A 52-year-old-female participant with central DRIL in SD-OCT (**C**, **D**) and High-Res OCT (**G**, **H**). DRIL areas are marked in red in SD-OCT (**D**) and High-Res OCT (**H**).

Image Analysis

Volumetric SD-OCT and High-Res OCT imaging data were segmented using the device's internal software (Spectralis Viewer Module 6.3.2.0; Heidelberg Engineering Eye Explorer) and automatic retinal layer segmentation was reviewed in each of the 241 B-scans and manually corrected. Based on the anatomical landmarks as proposed in Staurenghi et al.,[34] the inner retinal layers were defined as: RNFL, between the internal limiting membrane and the posterior bounds of the following hyperreflective layer (layer no. 3, as in Staurenghi et al.[34]); GCL, hyporeflective layer posterior from RNFL (layer no. 4); IPL, hyperreflective layer posterior from GCL (layer no. 5); INL, hyporeflective layer posterior from IPL (layer no. 6); and outer plexiform layer, hyperreflective layer posterior from INL (layer no. 7). The loss of the discernibility of the inner retinal layers was graded by two trained readers (KW and LPA, who were not masked for the devices) (Fig. 1). Although not explicitly mentioned in the Sun et al. classification, we also included the RNFL–GCL complex because it is part of the retinal inner layers and could provide additional information on DRIL pathogenesis. Each retinal layer in each cross-section OCT scan was assessed for its visibility and ability to be separated from the neighboring layer. In our study, DRIL was defined as the loss of all retinal inner layers. DRIL dimensions from the cross-section OCT scans were then projected onto an en face image and further processed in FiJi (https://imagej.net/software/fiji/).[35] The en face areas were binarized, converted to square millimeters and an Early Treatment Diabetic Retinopathy Study (ETDRS) grid was projected, centered at the fovea. The pixels of all DRIL areas were counted and analyzed in relation to the position in the ETDRS grid. At every DRIL location, OCT scans were also graded for the presence of a macular edema (yes/no), as defined by Wilkinson et al.[33]

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics Version 27 (IBM, Armonk, NY). Wilcoxon tests for dependent samples were performed for the comparison of the discernibility loss areas in High-Res OCT and SD-OCT. We used Spearman's rank correlation to evaluate the relationship between DRIL size and its distribution in the EDTRS grid. Logistic regression analysis was used for the comparison of DRSS and DRSS-Edema Score[33] to the presence of DRIL, was well as for HbA1c, body mass index, arterial hypertension, and years since first diagnosis to DRIL, corrected for sex and age. Mean 95% confidence

intervals were calculated and significance level was set to a P value of 0.05. If needed, Bonferroni corrections for multiple testing were applied. The inter-reader reliability of the DRIL area measurements was tested by intra-class correlation coefficients.

Results

A total of 93 eyes of 93 subjects (mean age, 61.8 ± 12.9 years; 34 female [36.6%]) were enrolled in the study. Mean time since first diagnosis of diabetes was 16.7 ± 12.6 years, mean HbA_{1c} at baseline was 7.4 ± 1.2%; 18 patients suffered from type I diabetes (19.4%) and 75 (80.6%) had type II diabetes. The main cohort characteristics are summarized in Table 1.

Diabetes was controlled by oral medication in 33 patients (35.5%), by subcutaneous insulin in 30 patients (32.26%), or by a combination of insulin and oral medication in 26 patients (28%); in 3 participants, diabetes was controlled by diet alone (3.2%). Eighty-five patients (91.4%) had one or more cardiovascular risk factors, including arterial hypertension, hypercholesterinemia, previous cardiovascular event (e.g., myocardial infarction or stroke), smoking, and/or obesity according to the definition of the World Health Organization definition.[36]

Table 1. Characteristics of the Study Population

Participants, *n*	93
Eyes, *n*	93
Age, years, mean ± SD	61.8 ± 12.9
Sex	
Male, *n* (%)	59 (63.4)
Female, *n* (%)	34 (36.6)
Type of diabetes	
Type 1, *n* (%)	18 (19.4)
Type 2, *n* (%)	75 (80.6)
Duration of diabetes, years, mean ± SD	16.7 ± 12.6
HbA1c (%), mean ± SD	7.4 ± 1.2
Diabetes therapy	
Diet, *n* (%)	3 (3.2)
Oral medication, *n* (%)	33 (35.5)
Insulin, *n* (%)	30 (32.3)
Insulin + oral medication, *n* (%)	26 (27)
Cardiovascular risk factors	
Arterial hypertension, *n* (%)	57 (61.3)
Blood pressure systolic, mm Hg ± SD	135.8 ± 12.9
Blood pressure diastolic, mm Hg ± SD	83.7 ± 7.7
Hypercholesterolemia, *n* (%)	21 (22.6)
Cardiovascular events, n (%)	22 (23.9)
At least one cardiovascular risk factor (%)	85 (91.4)
Smoking, *n* (%)	31 (33.3)
Pack-years, mean ± SD	21.2 ± 14.6
Body mass index, kg/m^2, mean ± SD	28.8 ± 5.3

SD, standard deviation.

Table 2. Ocular Characteristics of the Study Participants (n = 93)

BCVA (logMAR), mean ± SD	0.3 ± 0.4
Intraocular pressure, mm Hg	16.1 ± 4
Eye	
Right, *n* (%)	42 (45.2)
Left, *n* (%)	51 (54.8)
Treatment in the study eye	
Current anti-VEGF, *n* (%)	38 (40.9)
Previous panretinal photocoagulation, *n* (%)	56 (60.2)
Previous vitrectomy, *n* (%)	3 (3.2)
Diabetic Retinopathy Disease Severity Scale	
No DR (1), *n* (%)	33 (35.5)
Mild NRDR (2), *n* (%)	5 (5.4)
Moderate nonproliferative DR (3), *n* (%)	7 (7.5)
Severe nonproliferative DR (4), *n* (%)	3 (3.2)
Proliferative DR (5), *n* (%)	45 (48.9)
Diabetic Macular Edema Disease Severity Scale	
Diabetic macular edema absent (1), *n* (%)	42 (45.2)
Mild diabetic macular edema (2), *n* (%)	8 (8.6)
Moderate diabetic macular edema (3), *n* (%)	10 (10.8)
Severe diabetic macular edema (4), *n* (%)	33 (35.5)

LogMAR, logarithm of the minimum angle of resolution; SD, standard deviation.

In 45 eyes (48.9%), proliferative DR was identified, 3 patients had severe nonproliferative DR (3.2%), 7 moderate nonproliferative DR (7.5%), 5 mild nonproliferative DR (5.4%), and in 33 eyes no DR changes were present (35.5%). Fifty-one eyes had a macular edema (54.8%), of which 33 eyes had severe (35.5%), 10 eyes moderate (10.8%), and 8 eyes mild macular edema (8.6%). In 42 eyes, no macular edema was present at time of examination (45.2%) (Table 2).

In 48 eyes of 48 patients (51.6% of all subjects), DRIL was detectable in SD-OCT and High-Res OCT,

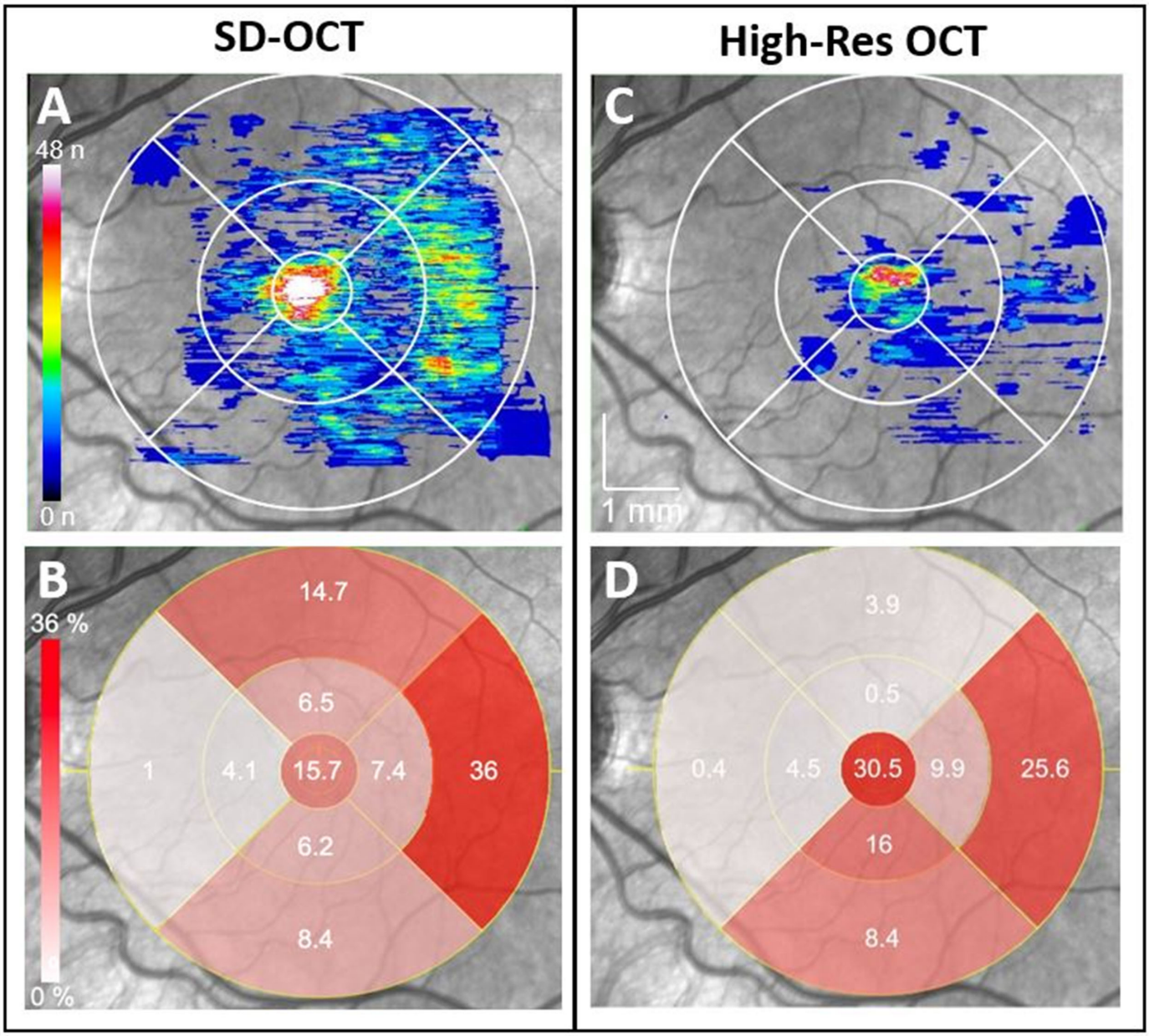

Figure 2. DRIL areas and distribution at the posterior pole for both SD-OCT and High-Res OCT. Color-coded projection of DRIL areas from all 48 patients in SD-OCT (**A**) and High-Res OCT (**C**) showing the DRIL size and their abundance (%) in relation to the ETDRS subfields (**B**, **D**). Because the DRIL area did not always respect the boundaries, the pixels of the color-coded DRIL projection were counted for each individual ETDRS subfield.

with no case where DRIL was detected in High-Res OCT only. The intraclass correlation coefficient for the DRIL area between the two graders was 0.88 for High-Res OCT and 0.76 for SD-OCT. Of those patients with DRIL, 14 (30.4%) had type I diabetes and 32 patients (69.6%) type II diabetes. In contrast, in the non-DRIL eyes, only 4 patients had type I diabetes (8.51%) and 43 patients had type II diabetes (91.5%) ($P < 0.001$). The time since initial diagnosis was significantly longer in the DRIL group (23.7 ± 16.3 years) compared with the non-DRIL group (13.2 ± 8.8 years; $P = 0.002$). In addition, the BCVA logarithm of the minimum angle of resolution (logMAR) was significantly worse in DRIL eyes (0.34 ± 0.38 logMAR vs. 0.13 ± 0.22 logMAR; $P < 0.001$) and DRSS significantly higher (4.43 ± 1.01 vs. 2.12 ± 1.66; $P < 0.001$) compared with no-DRIL eyes.

The distribution and size of the DRIL areas differed markedly between the SD-OCT and High-Res OCT.

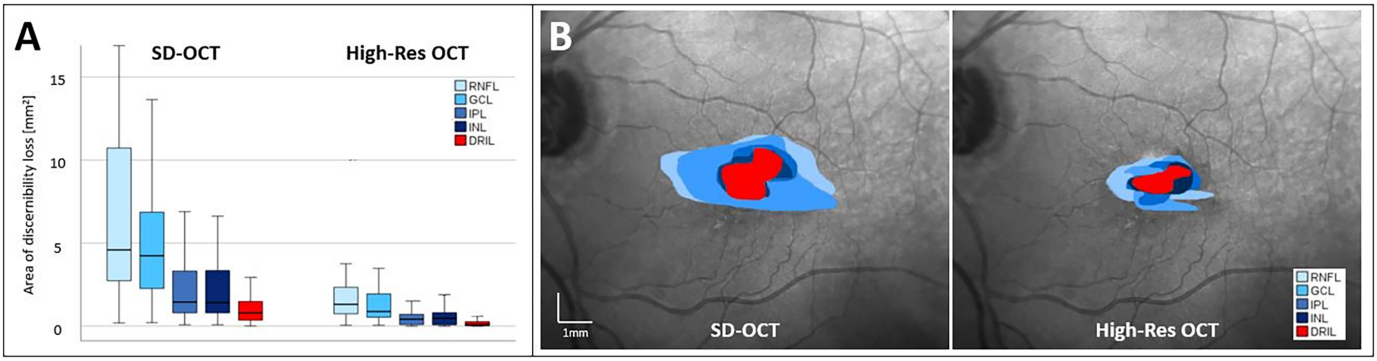

Figure 3. Discernibility loss of different retinal inner layers using both SD-OCT and High-Res OCT. (**A**) Mean size of inner retinal layer loss ($mm^2 \pm SD$) in 48 subjects with DRIL**.** Boxplots of the areas of the discernibility loss of individual retinal layers as revealed in SD-OCT (*left*) and High-Res OCT (*right*). The pattern reveals a loss from the inner to the outer retinal layers. Additionally, there is a notable difference in the dimensions of the RNFL and GCL ($P < 0.001$), whereas the IPL and INL exhibit comparable areas ($P = 0.996$) in SD-OCT. In High-Res OCT, DRIL areas were significantly smaller as compared with SD-OCT ($P < 0.001$). **(B)** An example of a 69-year-old man (diabetes type II, HbA1c 8,1%, duration of diabetes: 15 years). Discernibility loss of inner retinal layers in OCT scans of both modalities are projected onto the near-infrared reflectivity image. The discernibility of the RNFL, GCL, IPL, and INL are color coded. DRIL areas (loss of the ability to distinguish between all inner retinal layers) are marked in *red*. Data from High-Res OCT scans reveals smaller areas for affected retinal layers and subsequently DRIL areas.

Table 3. Comparison of the Study Populations' Characteristics in the DRIL vs. No-DRIL Groups

	DRIL	No-DRIL	*P* Value
Eyes, *n* (%)	48 (51.6)	45 (48.4)	
Age, years, mean ± SD	58.4 ± 12.6	65.09 ± 12.73	**0.048**
BCVA, logMAR, mean ± SD	0.34 ± 0.38	0.13 ± 0.22	**<0.001**
DRSS, mean ± SD	4.43 ± 1.01	2.12 ± 1.66	**<0.001**
DRSS: Edema, mean ± SD	3.38 ± 0.98	1.4 ± 0.86	**<0.001**
Type of diabetes, *n* (%)			
Diabetes type 1	14 (30.44)	4 (8.51)	**<0.001**
Diabetes type 2	32 (69.56)	43 (91.49)	**<0.001**
Duration of diabetes, years, mean ± SD	23.75 ± 16.33	13.17 ± 8.76	**0.002**
HbA1c (%), mean ± SD	7.70 ± 1.61	7.02 ± 0.87	**0.003**
Body mass index kg/m^2, mean ± SD	29.47 ± 5.64	28.27 ± 5.07	0.16

LogMAR, logarithm of the minimum angle of resolution; SD, standard deviation.
Boldface entries indicate statistical significance.

In SD-OCT, 120 areas could be identified, while only 68 were detectable in High-Res OCT scans. Additionally, DRIL areas in High-Res OCT were significantly smaller (0.21 ± 0.29 mm^2) than in SD-OCT (1.22 ± 1.20 mm^2; $P < 0.001$), which corresponds with only 17.2% of the area.

Regarding DRIL localization, in SD-OCT, DRIL areas were mainly localized in the temporal outer ETDRS subfield (36%), followed by the central subfield (15.7%) and the superior outer subfield (14.7%), (see Fig. 2). The nasal inner and outer subfields were least affected (4.1% and 1%, respectively). In High-Res OCT, the ETDRS central subfield was mostly affected (30.5%), followed by the temporal outer (25.6%) and the inner inferior (16%) subfields.

The analysis of the loss of the discernibility between the retinal inner layers revealed a specific pattern from the inner to the outer-inner retinal layers. In both SD-OCT and High-Res OCT mode, the loss of RNFL (7.01 ± 5.64 mm^2 vs. 2.59 ± 3.63 mm^2) was most pronounced, followed by GCL (5.63 ± 4.49 mm^2 vs. 1.42 ± 1.83 mm^2), IPL (2.17 ± 1.77 mm^2 and 0.55 ± 0.56 mm^2), and INL (2.19 ± 1.77 mm^2 and 0.61 ± 0.70 mm^2). The discernibility loss was greatest in the RNFL and GCL ($P < 0.001$). Figure 3 provides a detailed

comparison of these measurements and shows a clinical example.

The logistic multinomial regression analysis showed a correlation between the presence of DRIL and HbA1c ($P = 0.019$), arterial hypertension ($P = 0.013$), and the time since initial diagnosis ($P = 0.024$). There was also a significant correlation between the presence of DRIL and the DRSS ($P = 0.007$) and Edema Score ($P < 0.001$) (Table 3). There was no significant correlation between DRIL size, measured in SD-OCT, and DRSS ($P = 0.66$) or DRIL location (ETDRS central subfield vs. ETDRS inner and outer ring) and DRSS ($P = 0.28$). Furthermore, no correlation was identified between DRSS, location, and DRIL size on High-Res OCT ($P = 0.36$ and $P = 0.84$).

Discussion

This study demonstrates a significant difference in the en face DRIL area between High-Res OCT and SD-OCT in patients with diabetic maculopathy. First, across all eyes, we show that, on High-Res OCT, DRIL areas were only 17.2% of the size of the DRIL areas as measured on SD-OCT. DRIL was mainly located in the central and outer temporal subfields of the ETDRS grid. Second, DRIL is present in eyes with more advanced DR stages with a hypothesized lesion spread from the inner to the outer retina. Third, the appearance of DRIL is associated with worse visual acuity in our study cohort.

Impact of High-Res OCT on Retinal Layer Segmentation

High-Res OCT technology might enable a more precise delineation of the inner retinal layers by improved axial resolution and signal-to-noise-ratio. Also, a previous study showed that the inter- and intrareader reliability of retinal layer annotation is improved in High-Res OCT imaging.[28] Enhanced inter- and intrareader reliability is crucial for the objective and consistent characterization of retinal pathologies but has not led to any changes in clinical routine diagnosis yet because OCTs with improved resolution are still in an experimental stage and not available globally.

Topographically, the loss of discernibility of all retinal inner layers is smaller on High-Res OCT compared with conventional SD-OCT in our study cohort. This finding may indicate that the individual layers, that is, differences in reflectivity between individual retinal layers, are better distinguishable using the improved technical settings. Furthermore, other retinal features, such as hyperreflective foci and cystic spaces, could have a less significant impact on the delineation of the individual layers.[37]

A more precise discernibility of DRIL-related retinal layers could lead to a better understanding of DRIL pathogenesis and development. It is hypothesized that the discernibility loss represents a structural interruption in the visual transmission pathway with a subsequent loss of communication between the axons of the neurosensory retina and the ganglion cells.[20,38–40] Bipolar, amacrine, horizontal, and Müller cells may undergo reorganization with functional impairment.[21,25] This altered cell communication can be caused by impaired capillary perfusion, inflammatory events, chronic ischemia, and/or vascular leakage,[41] finally leading to a disruption of the regular structure of the retina.

Our study reveals a characteristic pattern of DRIL development suggesting a progress from the inner to the outer retina. This pattern might correlate with a different spread in lack of perfusion in the capillary plexus, from the inner to the outer plexus. Previous OCTA studies reported different drop-out patterns in the different capillary plexus, which could be the causative factors for the structural changes observed in our study.

Onishi et al.[42] reported that most of DRIL lesions in their study were correlated with nonperfusion in the superficial capillary plexus and/or middle capillary plexus and no flow in the deep capillary plexus. Several other studies confirmed these findings, showing an impaired blood flow in the superficial, middle, and deep capillary plexus.[43,44] Nicholson et al.[45] could also show that the sensitivity and specificity of DRIL in detecting capillary nonperfusion in OCTA was 84.4% and 100%, respectively. These OCTA findings support our hypothesis that the distribution pattern of DRIL is significantly impacted by retinal perfusion.

DRIL Topography

Several studies reported a negative impact of on visual acuity if DRIL is present. The abundance of DRIL in the central subfield impairs vision and is consistent with the current literature showing that an enlargement of the FAZ is associated with DRIL and an impairment of visual acuity.[43,46,47] Tsai et al.[46] specifically pointed out that the odds of coexisting DRIL increased by 42% with every 0.1 mm^2 increase of the FAZ area. In addition, a positive correlation between DRIL diameter and the size of the FAZ has already been demonstrated.[48] It is, however, essential to consider the foveal area and the absence of the retinal inner layers at the fovea while evaluating DRIL. In

2014, Sun et al.[20] defined foveal DRIL as "the inability to distinguish boundaries between any two of the inner retinal layers in greater than 50% of the foveal 1-mm zone." It was also considered that the normal macular contour does not constitute DRIL by itself. The precise horizontal width of the normal foveal contour, however, has not been specified.[20] Also, the variability in foveal shape which can also be observed in healthy people,[49] was not taken into account. Based on Poljak´s cellular neuroscience descriptions and recent review by Curcio and colleagues, the foveola is defined within a diameter of 350 µm, because this area contains only cones and a layer of angled Henle fibers instead of the retinal inner layers.[50] These considerations should be taken into account in future studies that define DRIL.

Impact of DRIL on Function

Our data show a negative correlation between the presence of DRIL and BCVA. This finding is consistent with several studies, which all showed that DRIL is associated with BCVA decrease and retinal sensitivity loss.[20,51–55] It was demonstrated that over an 8-month period an increasing horizontal DRIL spread was associated with a deterioration in BCVA,[20,52,56,57] especially in the 1-mm foveal zone where the effect seems to be independent of retinal thickness, as reported previously.[55,58] We further found that DRIL occurs more in eyes with severe DR and more in type I diabetics. Vujosevic et al.[27] have recently reported a correlation between the DR status and the severity of inner and outer retinal impairment. The retinal sensitivity and BCVA showed a greater impairment when the outer nuclear layer, external limiting membrane, and ellipsoid zone were involved, in addition to the presence of DRIL.[27]

Impact of Improved Axial Resolution OCT in Other Retinal Diseases

The enhanced axial resolution of the High-Res OCT indicates a more precise visualization of the individual retinal layers in our study, confirming similar findings in normal ageing and age-related macular degeneration.[28,29,59,60] This could also lead to advantages in imaging other retinal diseases, because DRIL is also associated with retinal vein occlusion.[56,57] In a recent study, Mahmoudi et al.[61] demonstrated that the identification of incomplete retinal pigment epithelium and outer retinal atrophy in age-related macular degeneration lesions can be facilitated using High-Res OCT compared with the conventional SD-OCT. Frank et al.[29] also showed that photoreceptor integrity loss was significantly higher in standard OCT compared with High-Res OCT. Also, a qualitative assessment of retinal features and quantitative measurements demonstrated higher inter-reader agreement with High-Res OCT than with standard SD-OCT.[61] Interestingly, the more precise delineation of retinal entities using High-Res OCT revealed significantly smaller DRIL lesions, a phenomenon that should continue to be observed in the future. One question that arises from this, and that cannot be answered satisfactorily at this time, is how the DRIL areas may become smaller as the resolution of the recording devices continues to improve. It has, however, to be mentioned that all DRIL in our study could be detected in both devices, and not in High-Res OCT alone. Also, obvious structural normality does not mean normal function. The structural changes that can be observed today can be examined very specifically for their functionality, especially in the areas that appear to regular in High-Res OCT but abnormal in conventional OCT.

Limitations and Strengths

We also acknowledge several limitations. Our study showed a higher prevalence of DRIL (51.7%) compared with other studies with a prevalence of 41.%,[27] 22.9%,[62] or 16%,[63] which might be due to a selection bias because the majority of patients in our clinic present with severe and advanced disease stages. Further studies will require longitudinal data to investigate the pattern of DRIL development and to analyze the natural history of diabetic macular ischemia in more detail. Also, in addition to visual acuity testing, functional tests like microperimetry might help to further improve our understanding of the functional impact of these OCT reflectivity alterations.

However, the strengths of this study are the use of a High-Res OCT device with improved axial resolution, which enabled us to show significant differences in the area size and frequency of DRIL detection in a large prospective study cohort. The very dense OCT imaging scanning protocol (242 B-scans) made it possible to detect changes in the inner retinal layers and, subsequently, the en face DRIL area very precisely.

Conclusions

We detected a significant difference in DRIL area in High-Res OCT compared with SD-OCT. These results highlight the potential of enhanced imaging

techniques, which could facilitate a deeper understanding of DR and DRIL underlying pathologies. OCTs with improved resolution are still at experimental stages in most cases, and thus currently prevent a universally valid implementation of a new classification system. Future research requires longitudinal datasets linked to retinal function to establish robust structure–function correlation and to further characterize DRIL as a biomarker for disease severity in DR.

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