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RETINAL DISORDERS

Morphology and fluorescein leakage in diabetic retinal microaneurysms: a study using multiple en face OCT angiography image averaging

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Abstract

Purpose To investigate the relevance of microaneurysm morphology in optical coherence tomography angiography (OCTA) image averaging and fluorescein leakage in diabetic retinopathy (DR).

Methods In 38 consecutive patients with DR, ten consecutive 3- × 3-mm fovea-centered OCTA (HS100, Canon Inc., Tokyo, Japan) and fluorescein angiography (FA) were performed, and averaged OCTA images were created based on the 10 images. After detecting all microaneurysms in FA images, the morphology was classified into four types (focal bulge, saccular/pedunculated, fusiform, and mixed) using averaged OCTA images. The correlation between microaneurysm leakage in FA, retinopathy stage, and microaneurysm morphology was estimated.

Results Thirty-eight eyes (50.0%) of the 33 patients were available for analysis, and 370 (63.5%) of the 583 FA-detected microaneurysms were morphologically classifiable (focal bulge, 46; saccular/pedunculated, 143; fusiform, 29; and mixed, 152) in OCTA. There was a significant correlation between stage and percentage of microaneurysm morphology and between morphology and the presence of leakage ($P < 0.0001$ and $P < 0.01$, respectively). The proportion of focal bulges decreased with stage progression, while the other three types increased with stage progression. The percentage of FA leakage for focal bulge, saccular/pedunculated, fusiform, and mixed was 41.3%, 66.4%, 82.8%, and 66.4%, respectively, and the fusiform type showed significant FA leakage.

Conclusion Microaneurysm morphology is correlated with the DR stage and FA leakage. Microaneurysm morphology recognition using OCTA image averaging may be useful for the clinical evaluation of DR.

Key messages

- Microaneurysms are not only an important finding in the diagnosis of diabetic retinopathy (DR), but their number is also a predictive marker of progression. However, the clinical significance of microaneurysm morphology remains unknown.
- It is reported that the morphological appearance of microaneurysms on optical coherence tomography angiography (OCTA) correlates with FA leakage. However, we must be aware that OCTA depicts the microaneurysms differently for each acquisition
- The current study using multiple en face OCTA image averaging showed the proportion of focal bulges of microaneurysms decreased with stage progression, while the other three types increased with stage progression of DR.
- The fusiform type of microaneurysms showed significant FA leakage in diabetic DR.

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Keywords Diabetic macular edema · Angiography · Imaging

Introduction

Microaneurysms are not the only important finding in the diagnosis of diabetic retinopathy (DR) [1], but their number is a predictive marker of progression [2]. Furthermore, vascular leakage from microaneurysms can cause exudative changes in diabetic macular edema (DME) [3, 4]. Therefore, the detection and evaluation of microaneurysm are clinically important in the clinical practice of DR. Previous pathological studies have proposed that there is a stage of microaneurysm formation with morphological changes [5, 6]. Recent high-resolution imaging using adaptive optics has revealed that the microaneurysm morphology is consistent with the pathological image and can be classified [7]. Furthermore, the number of microaneurysms has been shown to increase with the progression of disease [8]. However, the relationship between the retinopathy stage and its morphology remains unclear.

Fluorescein angiography (FA) has been the gold standard for microaneurysm detection for many years, but it is associated with a long examination time and possible allergy to contrast fluorescein dye [9]. Optical coherence tomography angiography (OCTA) is noninvasive and can be performed in a shorter time. It is also useful for microaneurysm detection, although its detection rate is inferior to FA [10–13]. Uji et al. introduced the utility of image averaging for OCTA image quality due to lower background noise and greater continuity of retinal microvasculature compared with a single unaveraged image [14]. Recently, we reported that image averaging of OCTA images could improve the detection rate of microaneurysms and recognize their morphology [15]. Schreur et al. reported that the morphological appearance in OCTA is correlated with FA leakage and retinal thickness [16]. However, the microaneurysm detection rate was 58% because a single OCTA image was used for evaluation. Spaide et al. [17] previously reported that repeated OCTA scans show different images of microaneurysms in eyes with DR. Furthermore, as we have also shown that the focal bulge type is difficult to detect with a single OCTA imaging [15], certain morphological types of microaneurysms tend to be undetectable, and the possibility of bias in the evaluated microaneurysm forms cannot be denied. In this study, we reevaluated the association of microaneurysm morphology with FA leakage and the distribution of morphology by DR stage using OCTA image averaging.

Materials and methods

This study was approved by the Institutional Ethics Committee of Kyushu University Hospital (Protocol No. 28473, UMIN000028656) and was performed following the tenets of the Declaration of Helsinki. Written informed consent was obtained from all patients after providing a detailed explanation of the study.

Patient population

This retrospective study included 76 eyes from 38 consecutive patients with DR who visited Kyushu University Hospital between April 2018 and December 2019. We excluded eyes with any other ocular disease that could cause microvascular disturbances in the retina or choroid (e.g., retinal vascular occlusion, age-related macular degeneration, and glaucoma).

Ophthalmic examination

All patients underwent FA using Spectralis HRA-OCT (Heidelberg Engineering, Heidelberg, Germany) with simultaneous injection of these contrast agent dyes. The FA images for this study were selected from the early phase (within 2 min of dye injection) and late phase (> 7 min after dye injection). We defined microaneurysms as hyperfluorescent dots in the early-phase FA imaging.

OCTA

In this study, OCTA imaging was performed on all patients using a commercial device (OCT-HS100; Canon Inc., Tokyo, Japan). The scanning area was a 3- × 3-mm fovea-centered region. We obtained en face OCTA images of the superficial capillary plexus (SCP) and deep capillary plexus (DCP) from each device, and low-quality images with signal strength less than 5 or images with artifacts were excluded from the study. The OCT-HS100 device had an A-scan rate of 70,000 scans/s and a wavelength of 855 nm. The vertical and axial resolutions were 20 and 3 mm, respectively. The segmentation line for the OCT-HS100 device was defined as follows: For SCP, the inner and outer boundaries were set at the inner limiting membrane and 50 mm below the inner plexiform layer (IPL), respectively. For the DCP, the inner and outer boundaries were set 50 mm below the IPL and at the outer plexiform layer, respectively. OCTA imaging with the OCT-HS100 device was performed over 10 consecutive times for each

eye, and we obtained 10 high-quality single images that satisfied the aforementioned acceptance criteria (signal strength ≥ 5). Furthermore, a multiple en face image averaging process was performed on these high-quality single OCTA images using image averaging software installed on the OCT HS-100 device.

Image evaluation and analysis

First, all microaneurysms were detected using FA images of the early phase, and then, microaneurysm-like points in the same location were detected using OCTA in the same patient. We classified microaneurysm-like points into four types (focal bulge, saccular/pedunculated, fusiform, or mixed type) in the averaged two OCTA images (SCP and DCP) based on the report by Dubow et al. [7] (Fig. 1). The morphology of the microaneurysms in OCTA and the leakage of each microaneurysm in the late-phase FA imaging were assessed by two independent retina specialists (YF and SS) using the averaged OCTA images and early phase FA images, respectively. Microaneurysm leakage was defined as the presence of one or more microaneurysms within a surrounding area of leakage, with the fluorescein signal intensity decreasing with increasing distance from the microaneurysm based on a previous report [18]. Leakage from dilated capillaries, veins, and arteries was distinguished from leakage from microaneurysms because it is typically more diffuse than that from microaneurysms and attenuates gradually with increasing distance from the source [18]. When the evaluations of the two observers differed, a third observer (YK) evaluated the morphology of OCTA and leakage in the FA. The *k* coefficient was 0.89 (95% confidence interval [CI], 0.85 – 0.93; $P < 0.0001$) and 0.93 (95% CI, 0.89 – 0.97; $P < 0.0001$) for the evaluation of the morphology in OCTA and the leakage in FA, respectively.

Statistical analysis

All statistical analyses were performed using a commercial software package (JMP Pro software version 12.0; SAS, Inc., Cary, NC, USA). Descriptive statistics, including mean, standard deviation, median, range, and percentages, were used where appropriate. The correlations between any two of the following variables were analyzed using Fisher's exact test. All associations were considered statistically significant at $P < 0.05$.

Results

Patients

Of the 76 eyes with DR in this study, 38 (50.0%) were excluded due to low image quality due to cataracts, vitreous hemorrhage, poor fixation, or image artifacts. A total of 38 eyes (50.0%) from 33 patients could be analyzed (mean age, 60.9 ± 12.2 years; 25 males and eight females; two eyes with mild nonproliferative DR (NPDR), 16 eyes with moderate NPDR, nine eyes with severe NPDR, 11 eyes with proliferative DR, 13 eyes with DME). Seventeen eyes (44.7%) from 15 patients had a history of anti-VEGF therapy.

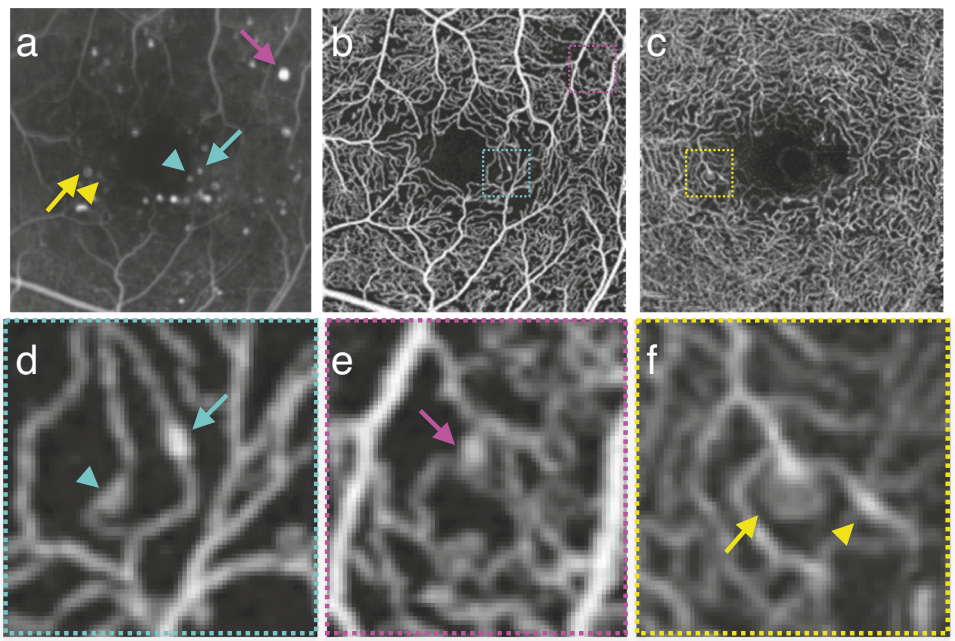

Fig. 1 Morphological classification of microaneurysms in representative optical coherence tomography angiography (OCTA) images (65-year-old male with moderate nonproliferative diabetic retinopathy in the left eye). Fluorescein angiography (FA) (**a**), superficial capillary plexus (**b**), and deep capillary plexus of OCTA (**c**) showing multiple microaneurysms in the macula (3 × 3 mm area). **d**–**f** Higher magnification of the OCTA images in **b** and **c**. Blue and yellow arrowheads indicate focal bulge-type microaneurysms. Blue, pink, and yellow arrows indicate fusiform-, mixed-, and saccular/pedunculated-type microaneurysms, respectively

Microaneurysms

Of the 583 FA-detected microaneurysms, 370 (63.5%) were morphologically classifiable (focal bulge, 46 (12.4%); saccular/pedunculated, 143 (38.6%); fusiform, 29 (7.8%); and mixed, 152 (41.1%)). There was a significant relationship between stage and percentage of microaneurysm morphology and between morphology and presence of fluorescein leakage ($P < 0.0001$, $P < 0.01$, respectively; Fig. 2; Tables 1 and 2). The proportion of focal bulges decreased significantly with stage progression, while the other three types increased with stage progression (Table 1). The percentages of FA leakage for focal bulge, saccular/pedunculated, fusiform, and mixed was 41.3%, 66.4%, 82.8%, and

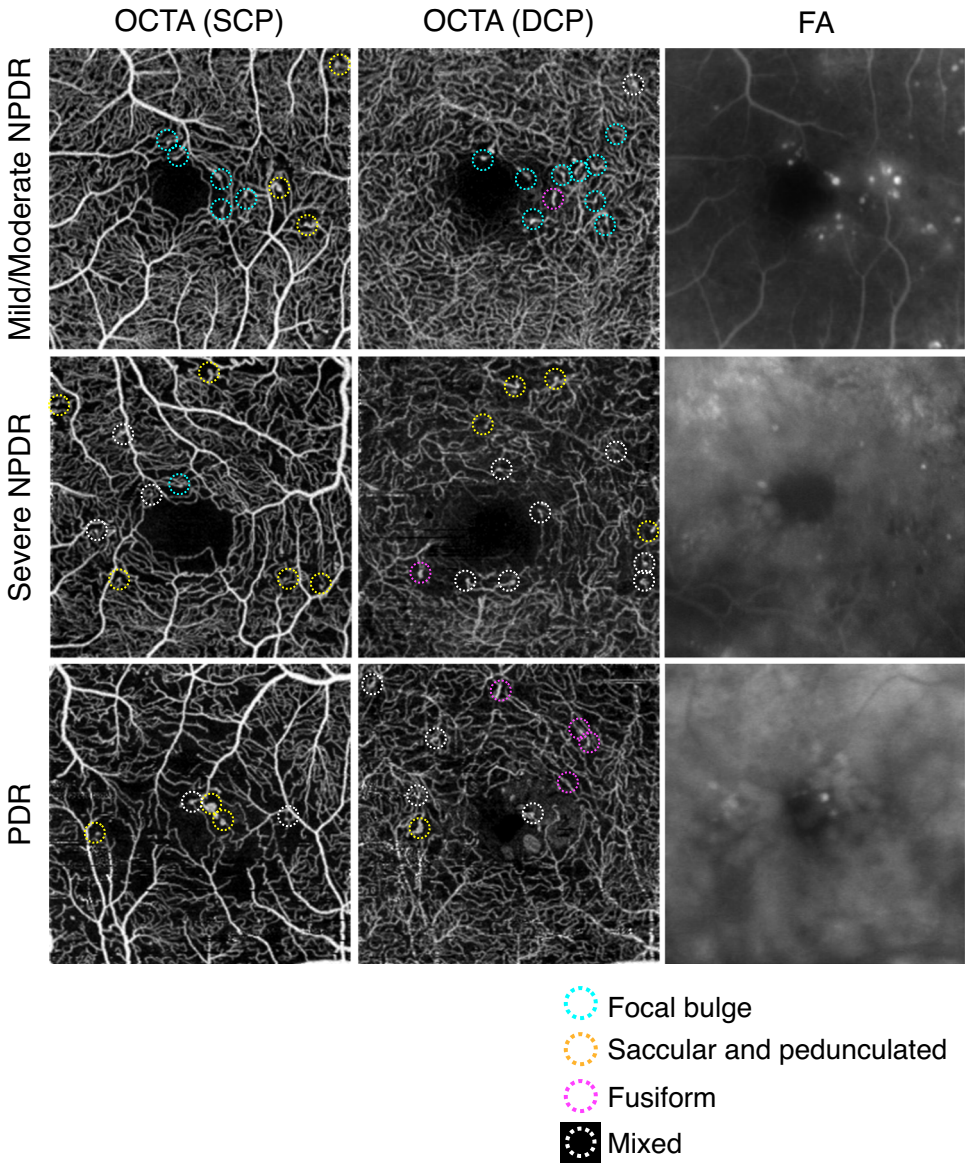

Fig. 2 Representative images of optical coherence tomography angiography (OCTA) and fluorescein angiography (FA) images in stages of diabetic retinopathy. Upper: 54-year-old male with mild nonproliferative diabetic retinopathy (NPDR) in the left eye. Middle: 69-year-old male with severe NPDR in the left eye. Lower: 40-year-old male with proliferative diabetic retinopathy (PDR) in the right eye. Blue, yellow, pink, and white dot circles indicate focal bulge type, saccular/pedunculated, fusiform, and mixed types of microaneurysms in OCTA images, respectively. FA images show the late stages. SCP superficial capillary plexus, DCP deep capillary plexus

Table 1 The proportion of microaneurysm morphology types in stages of diabetic retinopathy

	Focal bulge	Saccular and pedunculated	Fusiform	Mixed
Mild and moderate NPDR	41 (22.2%)	71 (38.4%)	5 (2.7%)	68 (36.8%)
Severe NPDR	5 (6.0%)	32 (38.1%)	10 (11.9%)	37 (44.0%)
PDR	0 (0%)	40 (39.6%)	14 (13.9%)	48 (46.5%)

NPDR nonproliferative diabetic retinopathy, *PDR* proliferative diabetic retinopathy

Table 2 The proportion of microaneurysms with and without fluorescence leakage in the morphology types

	Focal bulge	Saccular and pedunculated	Fusiform	Mixed
Leakage (+)	19 (41.3%)	95 (66.4%)	24 (82.8%)	101 (66.4%)
Leakage (−)	27 (58.7%)	48 (33.6%)	5 (17.2%)	51 (33.6%)

66.4%, respectively, and the fusiform type showed significant FA leakage (Table 2; $P < 0.001$).

Discussion

Schreur et al. [16] reported that the morphological appearance of microaneurysms on OCTA is correlated with FA leakage. However, we must be aware that OCTA depicts microaneurysms differently for each acquisition, as observed by Spaide et al. [17]. These facts motivated us to conduct this study using multiple OCTA image averaging. In this study, we reevaluated the microaneurysm morphology in DR stage and the correlation between FA leakage and morphology using 10×OCTA image averaging. In the early stages of DR, the focal bulge type was observed more frequently, and in the advanced stages, the other forms were observed more frequently. FA leakage tended to be less in the focal bulge type but more in other forms, especially the fusiform type. These results confirmed that focusing on the MA morphology of OCTA images without FA may be useful in understanding the activity of DR vascular lesions, consistent with a previous report by Schreur et al. [16].

Microaneurysms have been used as biomarkers in DR. The presence of microaneurysms has been widely accepted as the most useful finding in the diagnosis of DR on international disease severity scales [18]. This number has also been reported to be useful in predicting the progression of DR [2, 8]. However, the clinical significance of the morphology has not been elucidated because it has been difficult to accurately recognize the morphology due to fluorescein leakage in FA. Our results, along with the results of a previous study by Schreur et al. [16], have shown that the discrimination of morphology has clinical significance in the practice of DR.

In the present study, 63.5% of microaneurysms were recognizable by average OCTA, while 58% of microaneurysms detected by FA were recognizable by OCTA, as also reported by Schreur et al. [16]. Although the focal bulge type may be undetectable on a single OCTA image [15], both studies showed that the percentage of focal bulge type with leakage was low. In contrast, Schreur et al. reported that the irregular type had significantly more leakage, and our results showed that the fusiform type had more leakage [16]. This difference may be due to the presence or absence of an image averaging process.

In this study, we examined the percentage of microaneurysm morphology at each stage of DR. Interestingly, the focal bulge type was frequently observed in the early stages of DR and was not observed in PDR cases. Although Cogan et al. [6] considered the focal bulge type to be a preliminary microvascular change of microaneurysms based on histological observations, recent adaptive optics imaging revealed that the focal bulge type is one of the types recognized as microaneurysms in FA [7]. However, as Cogan et al. [6] predicted in autopsy eyes, the focal bulge may be an early form of microaneurysm that changes to other forms. Future longitudinal studies are required to verify this hypothesis. From a biological perspective, these differences in the morphology might be related to the stability of the vascular wall. It is known that VEGF and angiopoietin 2 increase with the progression of diabetic retinopathy [19]. These may act on pericytes and vascular endothelial cells to cause loss of pericytes and instability of the vessel wall, which may contribute to the formation of capillary aneurysms [20, 21].

We previously reported that turbulence in microaneurysms is associated with OCTA imaging [22]. Our previous observations showed that the focal bulge type was difficult to recognize on a single OCTA scan [15]. These results suggest that other types of microaneurysms are more likely to cause turbulence than focal bulges. This study showed that other types showed more leakage than the focal bulge type. Since several in vitro studies have reported that shear stress is involved in the blood-retinal barrier [23, 24], intramicroaneurysmal hemodynamics may be involved in the impairment of the blood-retinal barrier in DR.

Leakage microaneurysms are an indication of focal photocoagulation; therefore, FA is necessary for their detection. From the results of this study, morphological recognition using multiple OCTA image averaging may be useful for focal photocoagulation, since types other than the focal bulge type, especially fusiform, have more leakage. Uji et al. reported that averaging multiple OCTA images reduces background noise, which may help MA recognition [14]. However, the imaging time is longer than usual and needs to be improved by future technologies.

This study had several limitations. First, the sample size is small. Second, the examined field of view was small in the fovea, although microaneurysms in the DR can be observed anywhere in the retina. Third, patients with previous treatment for DME (e.g., anti-vascular endothelial growth factor therapy despite no recent treatment) were included, although these therapies might affect the morphology [25].

Author contribution Conception and design of the study: YF and SN. Data analysis and interpretation: YF, SN, YK, MA, and SS. Writing

of the article: YF and SN. Critical revision of the article: YK, MA, SS, IW, MY, and SK-H. Final approval of the article: YF, SN, YK, MA, SS, IW, MY, and SK-H. Data collection: YF, SN, YK, MA, SS, IW, and MY. Overall responsibility: SN.

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Data availability Yosuke Fukuda, Shintaro Nakao, and Yoshihiro Kaizu had full access to all study data and took responsibility for the integrity of the data and the accuracy of the data analysis.

Declarations

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the (place name of institution and/or national research committee) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Patient consent Written informed consent was obtained from all patients after a detailed explanation of the study.

Conflict of interest Shintaro Nakao has received consulting fee from Kowa and travel reimbursements and speaker fees from Novartis, Bayer Pharma, Canon Inc., Santen Pharmaceutical, Kowa, Senju Pharmaceutical, Ono Pharmaceutical, and MSD in the subject matter or materials discussed in this manuscript. The other authors have no financial disclosures: Yosuke Fukuda, Yoshihiro Kaizu, Mitsuru Arima, Sakurako Shimokawa, Iori Wada, Muneo Yamaguchi, and Atsunobu Takeda. All authors attest that they met the current ICMJE criteria for authorship.

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