Aqueous Level of ANGPTL4 Correlates with the OCTA Metrics of Diabetic Macular Edema in NPDR

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Purpose. To investigate the aqueous levels of angiogenic factors in nonproliferative diabetic retinopathy (NPDR) patients with diabetic macular edema (DME) and to ascertain their association with optical coherence tomography angiography (OCTA) metrics. Methods. This study enrolled 21 NPDR eyes with DME (NPDR/DME+), 17 NPDR eyes without DME (NPDR/DME-), and 16 diabetic eyes without retinopathy (DWR). Luminex bead-based multiplex array was used to measure the levels of 25 cytokines. OCTA system with a scan area of 3×3 mm was used to measure retinal thickness (RT), retinal volume (RV), superficial vessel density (SVD), deep vessel density (DVD), foveal avascular zone (FAZ) area, perimeter and acircularity index. Results. The levels of ANGPTL4 were significantly different among the three groups (P < 0.05), in which NPDR/DME+ group had the highest level and NPDR/DME- group had a higher level than the DWR group (all, P < 0.0167). OCTA examination showed that, compared with DWR and NPDR/DME- group, RT and RV increased and the whole/parafoveal DVD decreased in NPDR/DME+ group (all, P < 0.05). Meanwhile, NPDR/DME- group had lower parafoveal DVD than the DWR group (P < 0.05). Correlation analysis showed that the levels of ANGPTL4 were positively correlated with foveal and parafoveal RT and RV and negatively correlated with whole and parafoveal DVD in NPDR patients (all, P < 0.05). As the influencing factor of RT, RV, and DVD, every additional 10^3 pg/ml of ANGPTL4 was associated with an increase in foveal and parafoveal RT of 4.299 μm and 3.598 μm, respectively. Every additional 10^6 pg/ml of ANGPTL4 was associated with an increase in foveal and parafoveal RV of 3.371 mm³ and 17.705 mm³, respectively. Every additional 10^4 pg/ml of ANGPTL4 was associated with a decrease in whole and parafoveal DVD of 1.705% and 1.799%, respectively. Conclusions. The level of ANGPTL4 in aqueous humor of NPDR patients with DME was significantly increased and ANGPTL4 might predict RT, RV, and parafoveal DVD of DME in NPDR patients.

1. Introduction

Diabetic retinopathy (DR) is one of the most destructive microvascular complications of diabetes mellitus. Intraocular neovascularization and diabetic macular edema (DME) are two major clinicopathologic features during the development and progression of DR [1, 2]. The occurrence of neovascularization is closely related to the duration of diabetes mellitus. Patients with recently diagnosed diabetes mellitus have a lower risk of proliferative diabetic retinopathy (PDR) involving neovascularization than those with longer duration [3]. DME is a major cause of visual impairment in DR patients, which can occur at any stage of DR, even at early and mild nonproliferative diabetic retinopathy (NPDR) stage [4]. Therefore, the prevention and early diagnosis of DME in NPDR are extremely important.

The pathogenesis of DME is multifactorial and remains unknown. Recent studies suggest that DME occurrence is induced by the breakdown of the blood-retina barrier (BRB) and the consequent increases in vascular permeability, vascular leakage, and fluid accumulation within the macula, which causes retina thickening, macular dysfunction,
and visual impairment [5]. Angiogenesis and inflammation play a critical role in the pathogenesis of DME involving many exudative cytokines [6–9].

As a potent angiogenesis factor, vascular endothelial growth factor (VEGF) can increase vascular permeability in DME pathogenesis [10]. At present, anti-VEGF therapy is a first-line treatment for DME. Studies have shown that VEGF inhibition effectively improved visual acuity and reduced macular thickness [11]. Nevertheless, the responses to anti-VEGF therapy were distinct in different cases. Specifically, persistent DME did not improve even after several administrations of anti-VEGF drugs [4, 11]. The above findings reveal that other mechanisms, independent of VEGF, may also contribute to DME.

However, previous studies mainly focused on inflammatory factors in DME, but not angiogenic factors. Furthermore, the conclusions from these studies were only based on the comparison of cytokine levels between DME and nondiabetic control [7, 11, 12], which could not rule out the interference of diabetes and DR severities on cytokine level.

Here, we choose 25 angiogenic factors based on established and hypothesized angiogenesis pathway in DR and DME [13, 14], compared cytokines levels in the aqueous humor of NPDR patients with or without DME, and then investigated the effects of differentially expressed cytokines on optical coherence tomography angiography (OCTA) metrics to explore the potential molecular markers for DME in NPDR patients.

2. Methods

2.1. Study Subjects. This study included 21 eyes of 21 NPDR patients with DME (NPDR/DME+) who received intravitreal injection of anti-VEGF agents in the ophthalmology department of Xuzhou First People’s Hospital from July 2017 to December 2018. 33 eyes of 33 senile cataract patients with diabetes mellitus who underwent phacoemulsification at the same time were enrolled, in which 17 eyes of 17 NPDR patients without DME (NPDR/DME-) and 16 eyes of 16 diabetic patients without retinopathy (DWR) were identified by slit-lamp biomicroscopy, fundus photography, and OCTA three days after the operation. DWR group served as controls. The inclusion criteria were as follows: (1) NPDR patients with DME, DME was defined with one or more of the follows: retinal thickening at or within 500 μm of the macular center; hard exudates at or within 500 μm of the macular center, also associated with adjacent retinal thickening; one or more zones of retinal thickening with one optic disc size, at least part of which within the range of one optic disc diameter in the macular center [15]. The diagnosis and classification of NPDR were based on the standards published by the international ophthalmological association [16]. (2) Senile cataract patients with type 2 diabetes mellitus who received phacoemulsification were diagnosed as NPDR without DME or DWR. Exclusion criteria were as follows: (1) proliferative diabetic retinopathy; (2) a history of vitreous hemorrhage, retinal detachment, intraocular surgery (except cataract surgery) or ocular trauma; (3) anti-VEGF or laser therapy previously; (4) complication with uveitis, glaucoma, optic nerve disease, or other eye diseases; (5) low signal strength index (SSI < 50), blink artifacts or motion. This study followed the Declaration of Helsinki and was approved by the Ethics Committee of Xuzhou First People’s Hospital (approval number: xyyill [2017] 008). Informed consent was obtained from all patients.

2.2. Ophthalmic Examination. All patients underwent comprehensive ophthalmic examination, including visual acuity, intraocular pressure, slit-lamp biomicroscopy, fundus photography, and OCTA. The images were diagnosed by two independent doctors, and cases with a discrepancy were reviewed by the third doctor with a higher qualification. OCTA (Optovue, Inc., Fremont, CA, USA) was performed using the angio retina mode. For each eye, a 3 × 3 mm area centered on the fovea was scanned. Retinal thickness (RT) and retinal volume (RV) in the foveal and parafoveal area were automatically calculated by the built-in software from internal limiting membrane (ILM) to retinal pigment epithelium (RPE) layer. The fovea was defined as the circle area within the central 1 mm of the macula. Parafovea was defined as an area from the central 1 mm to the central 3 mm ring of the macular [17]. The OCTA images were automatically segmented to superficial capillary plexuses (SCP) and deep capillary plexuses (DCP) using the built-in software segmentation algorithm. The SCP was segmented with an inner boundary at 3 μm beneath the ILM and an outer boundary at 15 μm beneath the inner plexiform layer (IPL). The DCP was segmented with an inner boundary 15 μm beneath the IPL and an outer boundary at 70 μm beneath the IPL [18]. The vessel density values for the SCP and DCP in the whole, foveal, and parafoveal zones were calculated by the Angiovue Analytics built-in software. Vessel density was calculated as the percentage of pixels with flow signal above the preset decorrelation threshold in the defined region. FAZ area, perimeter, acircularity index, and FD-300 vessel density were automatically obtained via the FAZ assessment tool. FAZ surrounded by a continuous vascular closed ring was taken from ILM to outer plexiform layer (OPL). FD-300 was defined as a 300 μm ring around the FAZ [17].

2.3. Sample Collection. Aqueous humor was collected before cataract surgery or intravitreal injection of anti-VEGF agents. After topical anesthesia, 100 μL undiluted aqueous humor was withdrawn aseptically using an insulin syringe with a 30G needle at 1 mm inside the corneal limbus, which was placed in a 0.5 mL sterile Eppendorf tube and then stored at -80°C until measurement.

2.4. Measurement of Cytokines. Twenty-five cytokines, including epidermal growth factor (EGF), hepatocyte growth factor (HGF), heparin-binding EGF-like growth factor (HB-EGF), fibroblast growth factor 1 (FGF-1), FGF-2, FGF-19, FGF-21, FGF-23, granulocyte colony-stimulating factor (G-CSF), bone morphogenetic protein 9 (BMP-9), Endoglin, Endothelin-1, Leptin, Follistatin, α-Fetoprotein, FABP1, interleukin-8 (IL-8), Angiopoietin-2 (ANG-2), angiopoietin-like 3 (ANGPTL3), ANGPTL4, ANGPTL6, placental growth
incubate with agitation on a plate shaker overnight at 4°C.

Aqueous humor of the 3 groups were compared by Kruskal-Wallis test; one-to-one multiple comparisons were performed by Mann–Whitney U test, a:

Table 1: Demographic characteristics of the 3 groups.

| Characteristic          | DWR (N = 16) | NPDR/DME- (N = 17) | NPDR/DME+ (N = 21) | P value (among the 3 groups) |
|-------------------------|--------------|---------------------|---------------------|-----------------------------|
| Age (yrs)               | 67.94 ± 8.80 | 64.47 ± 7.19        | 64.76 ± 11.61       | 0.675                        |
| Male gender, no. (%)    | 5 (31.25%)   | 7 (41.18%)          | 14 (66.67%)         | 0.054                        |
| BMI                     | 24.80 ± 3.16 | 24.19 ± 1.88        | 25.97 ± 3.27        | 1.895                        |
| MAP                     | 100.33 ± 7.41| 105.02 ± 12.35      | 101.95 ± 11.07      | 0.844                        |
| Fasting plasma glucose (mmol/l) | 6.72 ± 1.43 | 7.42 ± 1.91        | 6.51 ± 1.32         | 1.667                        |
| HbA1c (%)               | 7.48 ± 1.25  | 7.97 ± 1.48         | 7.56 ± 0.98         | 0.789                        |
| Duration of diabetes (yrs) | 7.88 ± 5.94 | 11.88 ± 4.96       | 11.20 ± 9.21        | 1.485                        |

BMI: body mass index; MAP: mean arterial pressure; HbA1c: hemoglobin A1c; —: not analyzed. Values are mean ± standard deviation unless otherwise indicated. *One-way analysis of variance with post hoc least significant difference multiple comparison tests. aChi-square test.

Table 2: Comparison of the cytokine levels in the aqueous humor among the 3 groups [M(IQ1,Q3)].

| Aqueous cytokines | DWR (pg/ml) (N = 16) | NPDR/DME- (pg/ml) (N = 17) | NPDR/DME+ (pg/ml) (N = 21) | $\chi^2$ value | P value |
|-------------------|-----------------------|-----------------------------|-----------------------------|----------------|---------|
| HGF               | 445.64 (286.17, 583.95)| 400.13 (353.31, 688.43)    | 626.10 (528.81, 805.84)    | 9.596          | 0.008   |
| HB-EGF            | 1.18 (1.02, 1.62)      | 1.21 (0.87, 1.48)          | 1.06 (0.92, 1.27)         | 1.586          | 0.453   |
| FGF-2             | 13.19 (11.17, 18.16)   | 15.75 (11.66, 19.81)       | 13.19 (9.33, 15.75)       | 1.803          | 0.406   |
| FGF-19            | 50.29 (33.56, 66.44)   | 39.42 (32.11, 53.29)       | 234.78 (35.51, 335.39)    | 8.362          | 0.015   |
| Endothelin-1      | 8.15 (6.24, 13.59)     | 8.83 (5.97, 10.64)         | 8.22 (5.78, 10.23)        | 0.763          | 0.683   |
| Leptin            | 68.33 (61.73, 80.97)   | 64.84 (57.66, 79.31)       | 88.26 (68.33, 135.53)     | 5.895          | 0.032   |
| IL-8              | 4.64 (3.32, 7.42)      | 7.16 (3.67, 8.14)          | 9.97 (6.95, 17.18)        | 12.276         | 0.002   |
| ANG-2             | 32.28 (26.52, 44.62)   | 36.52 (25.42, 44.92)       | 34.58 (25.13, 44.17)      | 0.014          | 0.993   |
| ANGPTL4           | 1529.50 (1078.50, 4347.25) | 2726.00 (2025.00, 12519.50) | 23778.00 (14490.00, 26311.50) | 31.902 | <0.001 |
| PLGF               | 1.25 (1.02, 1.79)      | 1.23 (1.07, 3.54)         | 3.75 (2.74, 6.56)         | 0.631          | <0.001  |
| VEGF-A             | 179.14 (132.90, 220.41) | 276.25 (159.75, 345.77)   | 363.93 (242.95, 564.12)   | 20.004         | <0.001  |
| VEGF-C             | 38.52 (29.76, 77.98)   | 45.36 (33.79, 65.16)       | 47.24 (34.26, 56.01)      | 0.076          | 0.963   |

HGF: hepatocyte growth factor; HB-EGF: heparin-binding EGF-like growth factor; FGF-2: fibroblast growth factor 2; FGF-19: fibroblast growth factor 19; IL-8: interleukin 8; ANG-2: angiopoietin-2; ANGPTL4: angiopoietin-like 4; PLGF: placental growth factor; VEGF-A: vascular endothelial growth factor-A; VEGF-C: vascular endothelial growth factor-C. Cytokine levels (pg/mL) are presented as median with interquartile range. The levels of cytokines in the aqueous humor of the 3 groups were compared by Kruskal-Wallis H test; one-to-one multiple comparisons were performed by Mann–Whitney U test, a: compared with control, $^aP<0.0167$, b: compared with NPDR/DME- group, $^bP<0.0167$. 

2.5. Statistical Analyses. Statistical analysis was performed with SPSS 19.0. Shapiro-Wilk test was used to assess the normal distribution of data.
normality of measurement variables. Normally distributed variables were expressed as mean ± standard deviation, whereas skewed distributed variables were expressed as median (Q1, Q3). Categorical variables were summarized as counts and percentage. Comparisons of categorical variables were performed using chi-squared test. One-way analysis of variance with post hoc least significant difference (LSD) multiple comparison tests was performed for normally distributed variables among the three groups. Kruskal-Wallis H test was performed for skewed variables among the three groups. Mann–Whitney U test was performed for skewed variables between two groups, and a P < 0.0167 (0.05/3) was considered significant for multiple comparisons. Spearman’s rank correlation test was performed to assess the association between cytokine levels and the OCTA metrics. The correlation coefficient was tested by Student’s t test and the cytokines with P < 0.05 were included for single-factor linear regression analysis, and the cytokines with P < 0.05 in the single factor linear regression were further included in the multiple linear regression model. RT (foveal and parafoveal), RV (foveal and parafoveal), and DVD (whole and parafoveal) were used as dependent variables, respectively, ANGPTL4 and VEGF-A were used as independent variables, stepwise multiple linear regression was used to evaluate the cytokines that affect OCTA metrics, and P < 0.05 was considered statistically significant.

3. Results

3.1. Demographic Characteristics. There were no significant differences in age, gender composition, body mass index (BMI), mean arterial pressure (MAP), fasting plasma glucose, HbA1c, and the duration of diabetes among the three groups (all, P > 0.05). There were no significant differences in severity degree of NPDR between NPDR/DME+ and NPDR/DME- groups (P > 0.05) (Table 1).
3.2. Comparison of Cytokine Levels in Aqueous Humor. The levels of ANGPTL4 among the three groups were significantly different from each other (\(P < 0.05\)). NPDR/DME+ group had the highest level of ANGPTL4 in the three groups, and NPDR/DME- group had a higher ANGPTL4 level than the DWR group (all, \(P < 0.0167\)). For HGF, IL-8, PLGF, and VEGF-A, NPDR/DME+ group had the highest levels in the three groups (all, \(P < 0.0167\)), but no significant difference between NPDR/DME- and DWR group was found (all, \(P > 0.0167\)). In addition, NPDR/DME+ group had a higher level of FGF-19 than the NPDR/DME- group (\(P < 0.0167\), but no significant changes were detected in NPDR/DME+ and NPDR/DME- groups, compared with the DWR group (all, \(P > 0.0167\)). There were no significant differences of HB-EGF, FGF-2, Endothelin-1, Leptin, ANG-2, and VEGF-C among the three groups (all, \(P > 0.05\)), and the levels of EGF, FGF-1, FGF-21, FGF-23, G-CSF, BMP-9, Endoglin, Follistatin, AFP, FABP1, ANGPTL3, ANGPTL6, and VEGF-D were lower than the minimum detectable levels of the panel (Table 2).

3.3. Comparison of OCTA Metrics. Compared with DWR and NPDR/DME- group, RT and RV in NPDR/DME+ group were significantly increased, and the whole/parafoveal deep vessel densities (DVD) were reduced (Figure 1, Table 3). Besides, NPDR/DME- group had a lower parafoveal DVD than the DWR group (all, \(P < 0.05\)) (Table 3). There were no significant differences of superficial vessel

### Table 3: Comparison of the OCTA Metrics among the 3 groups (mean ± SD).

| OCTA metrics         | DWR (N = 16) | NPDR/DME- (N = 17) | NPDR/DME+ (N = 21) | F value | P value |
|----------------------|--------------|--------------------|--------------------|---------|---------|
| RT (μm)              |              |                    |                    |         |         |
| Fovea                | 240.90 ± 20.57 | 237.54 ± 22.77     | 331.76 ± 90.87ab   | 15.617  | <0.001  |
| Parafovea            | 308.59 ± 13.68 | 313.18 ± 20.56     | 379.25 ± 76.61ab   | 12.061  | <0.001  |
| RV (mm³)             |              |                    |                    |         |         |
| Fovea                | 0.19 ± 0.02  | 0.19 ± 0.02        | 0.26 ± 0.07ab      | 15.640  | <0.001  |
| Parafovea            | 1.90 ± 0.09  | 1.93 ± 0.14        | 2.26 ± 0.41ab      | 9.838   | <0.001  |
| SVD (%)              |              |                    |                    |         |         |
| Whole                | 39.37 ± 4.48 | 40.20 ± 3.63       | 39.31 ± 5.16       | 0.211   | 0.810   |
| Fovea                | 12.24 ± 5.28 | 14.25 ± 5.24       | 15.04 ± 7.04       | 1.011   | 0.371   |
| Parafovea            | 42.35 ± 4.86 | 42.56 ± 4.11       | 41.01 ± 5.80       | 0.535   | 0.589   |
| DVD (%)              |              |                    |                    |         |         |
| Whole                | 49.05 ± 3.38 | 45.96 ± 4.54       | 42.35 ± 5.66ab     | 9.260   | <0.001  |
| Fovea                | 27.90 ± 5.24 | 25.08 ± 6.20       | 24.79 ± 9.06       | 0.962   | 0.389   |
| Parafovea            | 52.25 ± 3.70 | 48.64 ± 5.19a      | 44.76 ± 5.94ab     | 9.752   | <0.001  |
| FD-300 vessel density (%) | 43.57 ± 5.00 | 44.40 ± 5.19     | 42.54 ± 5.91       | 0.561   | 0.574   |

### Table 4: Correlation between cytokine levels in aqueous humor and OCTA metrics in NPDR eyes (n = 38).

| Cytokine | Foveal RT | Foveal RV | Parafoveal RT | Parafoveal RV | Whole DVD | Parafoveal DVD |
|----------|-----------|-----------|---------------|---------------|-----------|----------------|
| HGF      | 0.250     | 0.130     | 0.211         | 0.203         | 0.249     | 0.132          |
|          | r_s       | P value   | r_s           | P value       | r_s       | P value        |
| FGF19    | 0.315     | 0.054     | 0.332         | 0.042         | 0.314     | 0.055          |
|          | r_s       | P value   | r_s           | P value       | r_s       | P value        |
| IL-8     | 0.175     | 0.293     | 0.158         | 0.345         | 0.172     | 0.302          |
|          | r_s       | P value   | r_s           | P value       | r_s       | P value        |
| ANGPTL4  | 0.569     | <0.001    | 0.555         | <0.001        | 0.566     | <0.001         |
|          | r_s       | P value   | r_s           | P value       | r_s       | P value        |
| PLGF     | 0.363     | 0.025     | 0.352         | 0.030         | 0.365     | 0.024          |
|          | r_s       | P value   | r_s           | P value       | r_s       | P value        |
| VEGF-A   | 0.528     | 0.001     | 0.437         | 0.006         | 0.530     | 0.001          |
|          | r_s       | P value   | r_s           | P value       | r_s       | P value        |

RT: retinal thickness; RV: retinal volume; DVD: deep vessel density. Spearman test, \(P < 0.05\) was deemed to be statistically significant.
3.5. The Effect of Cytokines on OCTA Metrics. VEGF-A and ANGPTL4 with \( P < 0.05 \) in the single factor linear regression were further included in the multiple linear regression model (Table S1). Multiple regression analysis showed that the level of ANGPTL4 was an influencing factor for RT, RV, and DVD. The regression equations were fitted as follows: foveal RT = 223.422 + 4.299 × 10^{-3} × ANGPTL4, parafoveal RT = 294.302 + 3.598 × 10^{-3} × ANGPTL4, foveal RV = 0.176 + 3.371 × 10^{-6} × ANGPTL4, parafoveal RV = 1.838 + 17.705 × 10^{-6} × ANGPTL4, whole DVD = 46.587 − 1.705 × 10^{-4} × ANGPTL4, and parafoveal DVD = 49.265 − 1.799 × 10^{-4} × ANGPTL4. Every additional 10^7 pg/ml of ANGPTL4 was associated with an increase in foveal and parafoveal RT of 4.299 μm and 3.598 μm, respectively. Every additional 10^6 pg/ml of ANGPTL4 was associated with an increase in foveal and parafoveal RV of 3.371 × 10^{-6} and 1.799 × 10^{-4}, respectively. Every additional 10^5 pg/ml of ANGPTL4 was associated with a decrease in whole and parafoveal DVD of 1.705% and 1.799%, respectively. The level of VEGF-A had no effect on RT, RV, and DVD (all, \( P ≥ 0.05 \)) (Table 5).

4. Discussion

Our study found that the levels of HGF, FGF-19, IL-8, ANGPTL4, PLGF, and VEGF-A increased in the aqueous humor of NPDR/DME+ patients, compared with NPDR/DME- and DWR patients. Notably, the levels of VEGF-A and ANGPTL4 were correlated with RT, RV, and DVD, in which single factor linear regression showed that both VEGF-A and ANGPTL4 were the influencing factors for RT, RV, and DVD. These findings supported the previous reports that VEGF-A contributed to the pathogenesis of DME [20, 21]. Cytokines with \( P < 0.05 \) in the single factor regression were further included in the multiple linear regression model. Although the \( P \) value for VEGF-A was 0.05, we still considered VEGF-A as an influencing factor for macular edema in NPDR patients. Moreover, in the models with multiple cytokines, VEGF-A had a greater impact on foveal RT and RV than other OCTA metrics.
Our study also found that the three groups were different from each other in the levels of ANGPTL4. Kwon et al. reported that both NPDR and PDR groups with similar severities of DME had higher levels of ANGPTL4 than the cataract controls, and the PDR group had a higher level than the NPDR group [22]. Here, we found that both DME+ and DME- groups with similar severities of NPDR had higher ANGPTL4 levels than the DWR group, and the DME+ group had a higher level than the DME- group. These results suggested that ANGPTL4 was also associated with DME. Multiple regression analysis revealed that the level of ANGPTL4 in aqueous humor was an influencing factor for RT, RV, and DVD. NPDR patients with high levels of ANGPTL4 in the aqueous humor had higher foveal/parafoveal RT and RV and lower whole/parafoveal DVD than the patients with low levels of ANGPTL4.

As an angiogenesis factor, ANGPTL4 promotes the pathological processes of diverse eye diseases by enhancing angiogenesis, vascular permeability, and inflammation [23, 24]. Aqueous ANGPTL4 was obviously increased in PDR, inducing retinal neovascularization [25, 26]. Lu et al. demonstrated that ANGPTL4 regulated diabetic retinopathy, Xin et al. provided the evidence that hypoxic oxygen-induced retinopathy mouse model for ischemic retinopathy, and Toto et al. investigated the changes of retinal vessels in DME compared with normal controls and found a decrease in foveal and parafoveal DVD, especially in parafoveal area [30]. Similarly, we observed an obvious change in OCTA images should be analyzed in the future.

In conclusion, our study showed that microvascular change of NPDR patients with DME initially occurs at DCP with decreased vascular density in parafoveal area. The level of ANGPTL4 in aqueous humor was significantly increased in NPDR patients with DME, and ANGPTL4 was an influencing factor for RT, RV, and DCP, suggesting that ANGPTL4 may predict the progression of DME in NPDR patients.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Supplementary Materials

Supplemental Table 1: single factor linear regression between cytokines and OCTA metrics. Single-factor linear regression showed that ANGPTL4 and VEGF-A were the influencing factors of RT, RV, and DVD (all, \(P < 0.05\)). (Supplementary Materials)

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