Clinical Research

Aqueous angiopoietin-like levels correlate with optical coherence tomography angiography metrics in diabetic macular edema

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Abstract

• AIM: To quantitatively detect aqueous levels of angiopoietin-like (ANGPTL)3, ANGPTL4, and ANGPTL6 and investigate their correlation with optical coherence tomography angiography (OCTA) findings in patients with diabetic macular edema (DME).

• METHODS: This cross-sectional study included 23 patients (27 eyes) with type 2 diabetes and 16 control subjects (20 eyes). All patients underwent OCTA imaging and ultra-wide field fundus photography. Diabetic patients were categorized into two groups according to the presence or absence of diabetic retinopathy (DME group, 14 patients, 16 eyes); and non-diabetic retinopathy (NDR) group, 9 patients, 11 eyes, respectively. Aqueous levels of ANGPTL3, ANGPTL4, and ANGPTL6 were assessed using suspension array technology, and foveal-centered 3×3 mm² OCTA scans were automatically graded to determine the central, inner, and full vessel density (CVD, IVD, FVD); central, inner, and full perfusion density (CPD, IPD, FPD), foveal avascular zone (FAZ) area, FAZ perimeter, and FAZ circularity index (FAZ-CI) on superficial capillary plexuses. Additionally, central subfield thickness (CST), cube volume (CV), and cube average thickness (CAT) were measured in a model of macular cube 512×128.

• RESULTS: Aqueous ANGPTL3 levels were not significantly different among the three groups (P>0.05). ANGPTL4 levels were significantly higher in the DME group than the control group (P<0.05). In the whole cohort, the aqueous ANGPTL3 levels correlated negatively with the IVD, FVD, IPD, and FPD, and positively with the CV and CAT. The aqueous ANGPTL4 levels correlated negatively with the CVD, IVD, FVD, CPD, IPD, and FPD, and positively with the FAZ perimeter, CST, CV, and CAT. The aqueous ANGPTL6 levels correlated negatively with the IVD, FVD, IPD, FPD, FAZ-CI and positively with CST, CV, CAT.

• CONCLUSION: ANGPTL4 and ANGPTL6 may be associated with vascular leakage in DME and may represent good targets for DME therapy. In addition, OCTA metrics may be useful for evaluating macular ischemia in DME.

• KEYWORDS: diabetic retinopathy; diabetic macular edema; optical coherence tomography angiography; angiopoietin-like; vascular leakage


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INTRODUCTION

The incidence of diabetic retinopathy (DR), an ocular microvascular complication of hyperglycemia, increases with the prevalence of diabetes[1-3]. Specifically, diabetic macular edema (DME) is the leading cause of vision loss in patients with diabetes and can occur at any DR stage[4]. It has been reported that 2 million people experience vision problems caused by DME worldwide[5]. The main pathophysiological event in DME is the disruption of the blood-retinal barrier, caused by vascular endothelial growth factor (VEGF) and other pro-inflammatory cytokines, which in turn leads to retinal blood vessel leakage[5]. Major therapeutic measures for DME involve the intravitreal injection of VEGF inhibitors and corticosteroids[6]. Given that corticosteroids are associated with ocular adverse effects such as cataracts and glaucoma, anti-VEGF therapy is generally regarded as the first-line option for patients with DME[6]. Although anti-VEGF drugs have been
efficacious in improving not only the prognosis, but also best
corrected visual acuity\textsuperscript{[7]}, some patients do not respond to this
therapy\textsuperscript{[8]}. Therefore, investigating the role of other cytokines
in the pathogenesis of DME is necessary.
Angiopoietin-like (ANGPTL) proteins are a class of secreted
glycoproteins with a structure similar to that of angiopoietin.
The eight members of this class are associated with
angiogenesis and vascular leakage\textsuperscript{[8-10]}. Of these, ANGPTL3
has been shown to induce corneal angiogenesis in rats\textsuperscript{[11]}
Additionally, patients with type-2 diabetes mellitus show
elevated serum ANGPTL3 levels, which correlate positively
with DR severity\textsuperscript{[12]}. ANGPTL4 has been a research hot spot
in recent years. Although the role of this protein in promoting
angiogenesis and increasing vascular permeability is still
debated\textsuperscript{[13]}, anti-ANGPTL4 therapy has shown positive effects
on ischemic retinopathy, including DR\textsuperscript{[14-16]}. A recent study
has demonstrated that targeted inhibition of ANGPTL4 can
decrease vascular permeability significantly in mice\textsuperscript{[10]}. Oike \textit{et al}\textsuperscript{[11]}
have found that ANGPTL6, another proangiogenic factor,
duces \textit{in vitro} and \textit{in vivo} skin and corneal angiogenesis and
promotes skin vascular leakage in mice. Despite these data,
the effects of ANGPTL3, 4, and 6 on DR have not been fully
determined yet.

Optical coherence tomography angiography (OCTA) is a non-
invasive fundus imaging technique that has attracted much
attention due to its potential to substitute fundus fluorescein
angiography (FFA) in the diagnosis of retinal vascular diseases.
OCTA obtains blood vessel images at different segmentation
slabs and quantitatively estimates the macular capillary
loss in patients with diabetes\textsuperscript{[18-20]}. Therefore, quantifying
microvascular changes using OCTA greatly contributes to the
screening, diagnosis, and disease surveillance of DR.
In this study, we aimed to measure aqueous ANGPTL3,
ANGPTL4, and ANGPTL6 levels in patients with DME and
assess their correlation with OCTA metrics.

**SUBJECTS AND METHODS**

**Ethical Approval** All subjects provided written informed
consent before specimens were collected. The study was
approved by the Institutional Ethical Review Board of the First
Affiliated Hospital of Xi’an Jiaotong University and abided by
the formulation of the Helsinki Declaration.

**Subjects** This cross-sectional study included 39 patients (47
eyes) who underwent cataract surgery or intravitreal injection
for DME in the Department of Ophthalmology of the First
Affiliated Hospital of Xi’an Jiaotong University, China. All
patients underwent OCTA imaging and ultra-wide field fundus
photography. According to Diabetic Retinopathy Disease
Severity Scale and center-involved DME (CI-DME) definition
by Diabetic Retinopathy Clinical Research Network (DRCR.
et), patients were categorized into one of the following
three groups: a control group, which included patients with
no diabetes; a non-diabetic retinopathy (NDR) group, which
included diabetic patients without apparent retinopathy; and
DME group, which included diabetic patients with CI-DME.
Patients with a history of intraocular surgery (including
intravitreal injection of anti-VEGF drugs), other oculopathies
(such as uveitis, retinitis pigmentosa, glaucoma, age-
related macular degeneration, and progressive hypertensive
retinopathy), or serious systemic conditions (including heart,
liver, kidney, and autoimmune diseases) were excluded from
the study.

**Aqueous Humor Collection, Preservation, and Assessment**
Before cataract surgery or intravitreal injection, an anterior
chamber puncture was performed through the cornea limbus
to obtain 0.05 mL of aqueous humor using a 1 mL insulin
disposable syringe. The samples were injected into a labeled
eppendorf tube, placed on ice, and transferred to a -80°C
tfreezer. The levels of ANGPTL3, ANGPTL4, and ANGPTL6
in the aqueous humor were detected using suspension array
technology (LXSAHM-13, R&D Systems, Minneapolis, MN,
USA).

**Image Acquisition Protocol** High-quality (signal strength ≥7)
OCTA images were obtained using a Zeiss Cirrus 5000 HD-
OCT Angioplex device (Carl Zeiss Meditec, Inc., Dublin, CA,
USA) at half an hour after mydriasis. Each eye was scanned
using a 3×3-mm\textsuperscript{2} protocol in the superficial capillary plexus
(inner limiting membrane to inner plexiform layer) and a
macular cube 512×128 protocol (inner limiting membrane to
retinal pigment epithelium) in the macular area. Retinal vessels
were automatically measured using the built-in software
(CIRRUS 11.0, Carl Zeiss Meditec). CIRRUS macular scan
regions were derived from the Early Treatment Diabetic	Retinopathy Study (ETDRS) grid. Therefore, OCTA metrics
consisted of central, inner, and full vessel density (CVD, IVD,
and FVD, respectively); central, inner, and full perfusion
density (CPD, IPD, and FPD, respectively); foveal avascular
zone (FAZ) area, FAZ perimeter, and FAZ circularity index
(FAZ-CI). Additionally, central subfield thickness (CST),
cube volume (CV), and cube average thickness (CAT) were
measured using a macular cube 512×128 protocol. Vessel
density (VD) was defined as the total length of perfused blood
evessels per unit area in the region of measurement, perfusion
density (PD) was defined as the total area of perfused blood
evessels per unit area in the region of measurement, and FAZ-
CI was defined as the ratio of the FAZ area to a perfect circle
that had the same perimeter as the FAZ.

**Statistical Analysis** All statistical analyses were performed
using GraphPad Prism 8.0.2 (GraphPad, San Diego, CA,
USA). Classified data were compared using the Chi-square
test. Continuous data are expressed as mean±standard
deviation (SD) and were evaluated with a one-way ANOVA test followed by Bonferroni post hoc tests. Multivariate or Kruskal-Wallis tests were conducted for normally and non-normally distributed variables, respectively. The Spearman’s test was used to perform correlation analysis. The test standard was α=0.05, and statistical significance was considered at P<0.05.

RESULTS

Demographic Features  The study included 16 non-diabetic patients (20 eyes, control group) and 23 diabetic patients (27 eyes). Of the latter, 9 (11 eyes) were categorized into the NDR group and 14 (16 eyes) into the DME group. Baseline characteristics did not significantly differ between groups (Table 1).

Aqueous ANGPTLs Levels  The control, NDR, and DME groups had comparable mean aqueous ANGPTL3 levels (675.8±78.93, 670.6±135.9, and 789.2±194.5 pg/mL, respectively; P>0.05 for all comparisons; Figure 1A). Mean aqueous ANGPTL4 levels were 3380±1373, 3717±1623, and 33744±26078 pg/mL in the control, NDR, and DME groups, respectively (Figure 1B). The DME group exhibited significantly higher ANGPTL4 levels than the control and NDR groups (P<0.0001 and P<0.001). The difference between the control and NDR groups in this regard was not statistically significant (P>0.05). Finally, the mean aqueous ANGPTL6 levels in the control, NDR, and DME groups were 23.93±25.09, 29.69±42.57, and 49.87±34.04 pg/mL, respectively (Figure 1C). The DME group had significantly higher ANGPTL6 levels than the control group (P<0.05). The other two comparisons were not statistically significant.

Changes in OCTA Metrics  The complete data on OCTA metrics are shown in Table 2. The CVD of the DME group was remarkably lower than that of the control group (P=0.002), and there was no significant difference among the other groups (both P>0.05). The IVD and FVD were significantly lower in the DME group than in the NDR and control groups. All PD metrics were significantly lower in the DME group compared to the control group, while being similar between the DME and NDR groups. The FAZ area of the DME group was significantly higher than that of the control group, but similar to that of the NDR group. The FAZ perimeter and CI of the DME group were significantly worse than those of the control and NDR groups.

Correlation between Aqueous ANGPTL3, ANGPTL4, and ANGPTL6 Levels and OCTA Metrics  Finally, we investigated the correlation between aqueous ANGPTL3, ANGPTL4, ANGPTL6 levels, and OCTA metrics (Table 3). Pearson’s correlation analysis showed that aqueous ANGPTL3 levels correlated negatively with IVD, FVD, IPD, and FPD, and positively with CV and CAT in all patients. In turn, aqueous ANGPTL4 levels correlated negatively with CVD, IVD, FVD, CPD, IPD, FPD, and positively with FAZ perimeter, CST, CV, and CAT in all patients. In turn, aqueous ANGPTL6 levels correlated negatively with CVD, IVD, FVD, CPD, IPD, FPD, and positively with FAZ-CI, and positively with CST, CV, and CAT.

DISCUSSION

This study showed that patients with DME presented higher aqueous ANGPTL4 and ANGPTL6 levels than control subjects. Regarding OCTA metrics, patients with DME showed a lower VD, PD, and FAZ-CI and a larger FAZ area
Table 2: Descriptive statistics for OCTA metrics in the control, NDR, and DME groups.

<table>
<thead>
<tr>
<th>Metrics</th>
<th>Control</th>
<th>NDR</th>
<th>DME</th>
<th>P1</th>
<th>P2</th>
<th>P3</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVD</td>
<td>10.16±2.70</td>
<td>7.25±3.34</td>
<td>6.72±2.73</td>
<td>0.069</td>
<td>&lt;0.0001*</td>
<td>0.964</td>
</tr>
<tr>
<td>IVD</td>
<td>21.21±1.36</td>
<td>20.01±2.16</td>
<td>17.16±2.73</td>
<td>0.313</td>
<td>&lt;0.0001*</td>
<td>0.018*</td>
</tr>
<tr>
<td>FVD</td>
<td>19.97±1.36</td>
<td>18.53±2.04</td>
<td>15.94±2.62</td>
<td>0.150</td>
<td>&lt;0.0001*</td>
<td>0.024*</td>
</tr>
<tr>
<td>CPD</td>
<td>0.20±0.10</td>
<td>0.12±0.06</td>
<td>0.13±0.05</td>
<td>0.046*</td>
<td>0.021*</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>IPD</td>
<td>0.38±0.02</td>
<td>0.37±0.03</td>
<td>0.34±0.05</td>
<td>0.544</td>
<td>0.004*</td>
<td>0.419</td>
</tr>
<tr>
<td>FPD</td>
<td>0.36±0.02</td>
<td>0.34±0.03</td>
<td>0.31±0.04</td>
<td>0.135</td>
<td>0.0012*</td>
<td>0.804</td>
</tr>
<tr>
<td>FAZ area</td>
<td>0.27±0.10</td>
<td>0.36±0.13</td>
<td>0.36±0.10</td>
<td>0.213</td>
<td>0.0274*</td>
<td>0.999</td>
</tr>
<tr>
<td>FAZ perimeter</td>
<td>2.28±0.48</td>
<td>2.05±1.04</td>
<td>2.91±0.51</td>
<td>&gt;0.999</td>
<td>0.002*</td>
<td>0.018*</td>
</tr>
<tr>
<td>FAZ-CI</td>
<td>0.63±0.07</td>
<td>0.69±0.14</td>
<td>0.55±0.11</td>
<td>0.528</td>
<td>0.047*</td>
<td>0.036*</td>
</tr>
</tbody>
</table>

P1: Control vs NDR, P2: Control vs DME, P3: NDR vs DME. *Statistically significant difference. NDR: Diabetic patients without retinopathy; DME: Diabetic patients with macular edema; VD: Vessel density; CVD: Central vessel density; IVD: Inner vessel density; FVD: Full vessel density; PD: Perfusion density; CPD: Central perfusion density; IPD: Inner perfusion density; FPD: Full perfusion density; FAZ: Foveal avascular zone; CI: Circularity index.

Table 3: Correlation coefficients between OCTA parameters and aqueous levels of ANGPTLs in the complete cohort (r (P))

<table>
<thead>
<tr>
<th>Parameters</th>
<th>ANGPTL3</th>
<th>ANGPTL4</th>
<th>ANGPTL6</th>
</tr>
</thead>
<tbody>
<tr>
<td>VD</td>
<td>-0.034 (0.822)</td>
<td>-0.362 (0.013)*</td>
<td>-0.271 (0.068)</td>
</tr>
<tr>
<td>IVD</td>
<td>-0.407 (0.005)*</td>
<td>-0.563 (&lt;0.0001)*</td>
<td>-0.479 (&lt;0.001)*</td>
</tr>
<tr>
<td>FVD</td>
<td>-0.377 (0.009)*</td>
<td>-0.582 (&lt;0.0001)*</td>
<td>-0.475 (&lt;0.001)*</td>
</tr>
<tr>
<td>PD</td>
<td>0.001 (0.995)</td>
<td>-0.297 (0.043)*</td>
<td>-0.215 (0.151)</td>
</tr>
<tr>
<td>IPD</td>
<td>-0.407 (0.005)*</td>
<td>-0.482 (0.001)*</td>
<td>-0.396 (0.007)*</td>
</tr>
<tr>
<td>FPD</td>
<td>-0.368 (0.011)*</td>
<td>-0.500 (&lt;0.001)*</td>
<td>-0.401 (0.006)*</td>
</tr>
<tr>
<td>FAZ area</td>
<td>-0.064 (0.672)</td>
<td>0.156 (0.296)</td>
<td>0.089 (0.555)</td>
</tr>
<tr>
<td>Perimeter</td>
<td>-0.009 (0.953)</td>
<td>0.334 (0.022)*</td>
<td>0.149 (0.323)</td>
</tr>
<tr>
<td>CI</td>
<td>-0.168 (0.258)</td>
<td>-0.231 (0.119)</td>
<td>-0.333 (0.024)*</td>
</tr>
<tr>
<td>CST</td>
<td>0.221 (0.136)</td>
<td>0.508 (&lt;0.001)*</td>
<td>0.312 (0.035)*</td>
</tr>
<tr>
<td>CV</td>
<td>0.311 (0.033)*</td>
<td>0.443 (0.002)*</td>
<td>0.332 (0.024)*</td>
</tr>
<tr>
<td>CAT</td>
<td>0.313 (0.032)*</td>
<td>0.430 (0.003)*</td>
<td>0.325 (0.028)*</td>
</tr>
</tbody>
</table>

*Statistically significant difference. VD: Vessel density; CVD: Central vessel density; IVD: Inner vessel density; FVD: Full vessel density; PD: Perfusion density; CPD: Central perfusion density; IPD: Inner perfusion density; FPD: Full perfusion density; FAZ: Foveal avascular zone; CI: Circularity index; CST: Central subfield thickness; CV: Cube volume; CAT: Cube average thickness.

Although not significantly different between groups, ANGPTL3 levels had a positive correlation with CV and CAT, and a negative correlation with inner and full vessel and perfusion densities. Notably, ANGPTL4 and ANGPTL6 levels exhibited a significant correlation with most alterations in OCTA metrics.

Although patients with DR were shown to have elevated serum ANGPTL3 levels in a previous study,[12] we could not demonstrate that aqueous ANGPTL3 levels were significantly higher in patients with DME than in the control group. This might have been due to the limited quantity of aqueous humor specimens and the insufficient expression of ANGPTL3 in the aqueous humor.

ANGPTL4 participates in many body processes including glycolipid metabolism,[21] energy homeostasis,[22] tumorigenesis,[23] angiogenesis, and increased vascular permeability.[24] A study found that ANGPTL4 caused endothelial cell junction breakage both in vitro and in the lungs, increased vascular permeability, and promoted lung metastasis of breast cancer cells.[25] Using gene expression analysis, Xin et al[10] determined that HIF-1α, which is a transcription factor involved in angiogenesis,[26] increases the expression of ANGPTL4 in hypoxic Müller cells and ischemic retinal tissues, and ANGPTL4 promotes vascular permeability, both in vivo and in vitro. Additionally, ANGPTL4 knock-out mice exhibit immature endothelial tight junctions in the retinal vascular plexus.[27] Furthermore, ANGPTL4...
results in activation of the Rho/ROCK signaling pathway, cell
connection disruption, and retinal vascular leakage in mice
by binding to neuropilins\cite{16}, while the inhibition of the HIF-1α/
ANGPTL4 signal transduction pathway reduces hypoxia-
induced cell permeability in ARPE-19 cells\cite{29}. Our results
showed that aqueous ANGPTL4 levels were significantly
higher in patients with DME than in healthy patients and
diabetic patients without DR. These findings are consistent
with those of a previous report by Kwon \textit{et al}\cite{29} that showed
that aqueous ANGPTL4 levels were significantly higher in
patients with DME (including those with proliferative and
non-proliferative DR) than in healthy controls. Other studies
analyzing patients with DR have revealed similar results\cite{36-37,39}.
Based on this evidence, we speculate that ANGPTL4 induces
retinal vascular permeability in DME patients.

In a previous study\cite{37}, ANGPTL6 promoted angiogenesis and
induced vascular leakage in mice. Researchers showed that
when ANGPTL6 was injected into the dermis, a large amount
of Evans blue dye leakage was found at the injection site.
To the best of our knowledge, this is the first study to assess
ANGPTL6 levels in the aqueous humor of diabetic patients.
Our results showed that these were significantly higher in
the DME group than in the control group. Considering the
previous evidence, we speculate that ANGPTL6 is associated
with retinal microvascular leakage in patients with DME.

Retinal ischemia and DME are the main features of DR. Before
the advent of OCTA, FFA was the main method for assessing
retinal ischemia, which was mainly diagnosed by the increment
of the FAZ area and loss of capillaries in the macular area\cite{32}.
Considering that FFA is invasive and time-consuming, and
can not recognize DME and distinguish retinal microvascular
changes, the emergence of OCTA represents a significant
advancement that compensates for these shortcomings. OCTA
can not only obtain images of retinal blood vessels quickly and
non-invasively, but can also distinguish DME from capillary
nonperfusion\cite{33}. Various OCTA metrics are currently used to
evaluate macular ischemia, including PD, FAZ area, FAZ
circumference, and FAZ-CI\cite{34}. The Zeiss OCTA 5000 offers
three scan sizes: 3×3, 6×6, and 8×8 mm². In this study, we
chose the 3×3-mm² scan based on a report\cite{35} that suggests that
this scan size may be the best predictive sensitivity for DR, just
like the finding in patients with DME.

Although the DME group showed a significantly lower
PD in the deep capillary plexuses compared with the non-
DME group, this metric was not significantly different in the
superficial capillary plexuses\cite{36}. In this study, vessel
and perfusion density metrics were considerably lower in
DME eyes than in control eyes. These findings are consistent
with those of several previous studies\cite{37-39}. Specifically, Ting
\textit{et al}\cite{38} showed that the PD was lower in DME patients than
in non-DME patients, regardless of whether the superficial
capillary plexuses or deep capillary plexuses were affected.
Additionally, Kim \textit{et al}\cite{39} found that among patients with
mild non-proliferative DR, patients with DME exhibited
significantly lower vessel and perfusion density than non-DME
patients. In accordance with our results, previous studies\cite{36-37,40}
found that the FAZ area was significantly higher in patients
with DME than in healthy subjects or diabetic patients without
DME. Additionally, this study showed that DME eyes had a
larger FAZ perimeter and lower FAZ-CI than control eyes.
These results suggest that OCTA metrics may be helpful for
evaluating macular ischemia. It is worth noting that, compared
with the NDR group, DME IVD, FVD, and FAZ-CI were
significantly lower and FAZ parameters were higher in the DM
subgroup, which may indicate that microvascular alterations
in the macula may constitute risk factors for DME. Our
research team will conduct a long-term follow-up to verify this
hypothesis.

Based on the observation that aqueous ANGPTL4 levels
 correlate positively with the capillary non-perfusion zone,
Kwon \textit{et al}\cite{29} suggested that expression of this protein is
induced by retinal ischemia. In our study, aqueous ANGPTL4
levels correlated negatively with vessel and perfusion densities
of all partitions, while ANGPTL3 and ANGPTL6 did so
with all vessel and perfusion metrics except CVD and CPD.
Given that, as previously mentioned, decreases in vessel
and perfusion densities are indicative of macular ischemia,
our results support the fact that ANGPTL3, ANGPTL4, and
ANGPTL6 are induced by retinal ischemia.

Studies have confirmed that ANGPTL3 promotes podocyte
permeability\cite{41}. In this study, aqueous levels of the three
ANGPTL proteins correlated positively with CV and CAT,
while ANGPTL4 and ANGPTL6 levels did so with CST as
well. It is widely known that CST, CV, and CAT are all closely
related to macular edema, which in turn can be caused by
vascular leakage. In previous studies, aqueous ANGPTL4
levels correlated positively with CV in DME patients\cite{29}
and with CST and CV in patients with macular edema caused by
retinal vein branch occlusion\cite{15}. These results further support
the hypothesis that ANGPTL3, ANGPTL4, and ANGPTL6
promote vascular permeability and induce DME.
This study had several limitations. First, because of the
small sample size, patients who had undergone panretinal
photocoagulation could not be excluded; this might have
affected the OCTA measurement results. Finally, whether
the various OCTA metrics are the most efficient indicators
for evaluating macular ischemia still needs to be confirmed
by large-scale studies. Additionally, the OCTA measurement
range was small, which made the application of ultra-wide-
field OCTA particularly important.
In conclusion, this study showed that compared with control subjects, patients with DME had higher aqueous ANGPTL4 and ANGPTL6 levels, a lower VD, PD, and FAZ-CI, and a larger FAZ area and FAZ perimeter. Most importantly, ANGPTL4 and ANGPTL6 levels showed a significant correlation with alterations in OCTA parameters (such as CST, CV, CAT, and vessel and perfusion densities) that are indicative of macular edema. These results strongly suggest that ANGPTL4 and ANGPTL6 are associated with vascular leakage in DME. We speculate that these proteins could be potential targets in DME therapy. In addition, OCTA metrics may help evaluate macular ischemia in DME.

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Aqueous ANGPTLs in DME


