

REVIEW ARTICLE

Eur J Med Transl Biosci. 2026;1(1):82–90 · Open Access · CC BY 4.0 · Selected from ICMTB, peer reviewed by members of the editorial board

OCT ANGIOGRAPHY BIOMARKERS IN DIABETIC RETINOPATHY: CURRENT EVIDENCE AND FUTURE PERSPECTIVES FOR PERSONALIZED OPHTHALMOLOGY

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Abstract

Optical coherence tomography angiography (OCT-A) enables noninvasive, depth-resolved assessment of retinal microvasculature and can reveal quantitative abnormalities before diabetic retinopathy (DR) is clinically visible. This review aims to synthesize evidence on the foveal avascular zone (FAZ), vessel density (VD), perfusion density (PD), vessel length density (VLD), and fractal dimension (FD), and to assess their potential contribution to individualized DR evaluation. A narrative review of English-language human studies published from January 2021 through December 2025 was conducted using PubMed/MEDLINE and reference-list screening. Original studies, systematic reviews, and meta-analyses reporting quantitative OCT-A outcomes in diabetes or DR were considered. VD and PD are consistently reduced as DR severity increases and may be abnormal in diabetes without clinically visible retinopathy. FAZ enlargement is more consistent after retinopathy develops, whereas evidence in preclinical disease is heterogeneous. VLD and FD capture capillary rarefaction and vascular-network simplification, but their values depend on scan size, segmentation, device, and image-processing method. Meta-analytic evidence supports good diagnostic and staging performance, while longitudinal data indicate that the most informative metric may vary by DR severity and retinal plexus. OCT-A biomarkers can complement clinical examination and structural OCT for detection, staging, and monitoring of diabetic retinal microvascular injury. Device-specific thresholds and limited cross-platform comparability currently prevent universal clinical cutoffs; standardized acquisition and analysis, as well as external validation, are required before individualized risk models can be adopted routinely.

Keywords: diabetic retinopathy, optical coherence tomography angiography, vessel density, foveal avascular zone, fractal dimension, personalized ophthalmology

1. Introduction

Diabetic retinopathy (DR) is a common microvascular complication of diabetes and a major cause of preventable visual loss in working-age adults. A 2021 global meta-analysis estimated that 103.12 million adults had DR in 2020 and projected an increase to 160.50 million by 2045, underscoring the need for scalable methods that detect and quantify retinal injury early [1].

Fluorescein angiography remains valuable for demonstrating leakage, nonperfusion, intraretinal microvascular abnormalities, and neovascularization, but it is invasive and does not provide depth-resolved separation of the retinal capillary plexuses. Optical coherence tomography angiography (OCT-A) derives vascular contrast from the motion of erythrocytes, allowing noninvasive visualization of the superficial and deep retinal plexuses and repeated quantitative assessment. Unlike fluorescein

angiography, however, OCT-A does not directly depict leakage [2,3]. A normal macular capillary network is illustrated in Figure 1.

Quantitative OCT-A analysis includes foveal avascular zone (FAZ) area and morphology, area-based vascular or perfusion density, skeletonized vessel length density (VLD), and measures of vascular complexity such as fractal dimension (FD). These variables capture related but nonidentical aspects of capillary loss, remodeling, and flow impairment. Their clinical interpretation is influenced by retinal layer, scan field, signal strength, edema, segmentation, device software, and image-processing pipeline [2–4].

This narrative review summarizes evidence published from 2021 through 2025 on major OCT-A biomarkers in diabetes and DR. It focuses on the direction and magnitude of reported changes, diagnostic and longitudinal performance, methodological limitations, and the extent to which these biomarkers may support individualized clinical assessment.

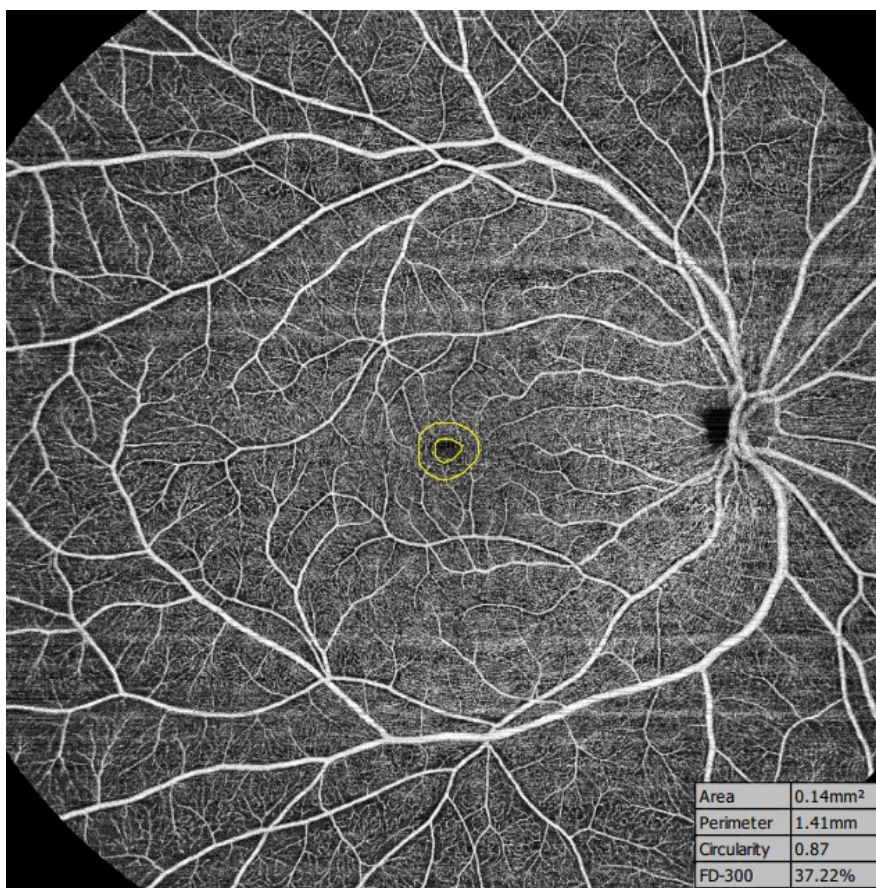


Figure 1. Normal macular OCT-A showing a well-defined foveal avascular zone and an intact capillary network. Image provided courtesy of TowardPi and reproduced with permission.

2. Materials and Methods

The literature search was last updated on September 10, 2026, in PubMed/MEDLINE and supplemented by screening the reference lists of relevant reviews. The publication window was restricted to January 1, 2021, through December 31, 2025, to summarize recent evidence.

Search concepts combined terms for diabetic retinopathy or diabetes with optical coherence tomography angiography or OCT-A and the following outcomes: foveal avascular zone, vessel density, perfusion density, vessel length density, fractal dimension, capillary nonperfusion, diagnostic accuracy, progression, reproducibility, and artificial intelligence.

Original English-language studies in humans, systematic reviews, and meta-analyses were eligible when they reported quantitative OCT-A findings in people with diabetes, with or without clinically apparent DR. Methodological studies were included when they directly examined device agreement, acquisition, segmentation, or image-processing effects relevant to biomarker interpretation. Case reports and articles without quantitative OCT-A outcomes were excluded.

Evidence was synthesized narratively by biomarker and clinical application. Because study populations, devices, scan sizes, segmentation boundaries, and processing algorithms were heterogeneous, no new pooled analysis was performed. Numerical results are reported from the cited studies or meta-analyses. Bibliographic details and DOIs were checked against PubMed records.

2.1. Ethical Approval

Not applicable. This narrative review used previously published, aggregate data and did not involve new human participants or identifiable patient information.

3. Results

3.1. Foveal Avascular Zone

The FAZ is the capillary-free central macular region. Enlargement and reduced circularity generally increase with DR severity, but findings before clinically visible retinopathy are not uniform. In a 2024 meta-analysis of 18 studies and 2,101 eyes, total FAZ area did not differ significantly between diabetic eyes without retinopathy and healthy eyes (weighted mean difference [WMD], 0.00 mm²; 95% confidence interval [CI], -0.02 to 0.01; $P = 0.84$), whereas mild nonproliferative DR was associated with a larger FAZ (WMD, 0.06 mm²; 95% CI, 0.01–0.11; $P = 0.03$) [5]. An earlier meta-analysis found FAZ enlargement in diabetes without retinopathy but noted variation by diabetes type [6]. In a 149-eye study, Temel and Batıoğlu found significant baseline FAZ differences between healthy eyes and both diabetic groups, although the DR group's quantitative measures did not change significantly over the 12-month follow-up [7]. In a prospective cohort of 268 participants, Oliverio et al. found larger superficial and deep FAZ areas in type 1 diabetes without DR than in controls and a correlation between diabetes duration and superficial FAZ area ($r = 0.44$; $P = 0.0001$) [8]. These results support FAZ morphology as a marker of established or evolving ischemia, but not as a stand-alone universal screening threshold. Representative FAZ enlargement and capillary dropout are shown in Figure 2.



Figure 2. OCT-A in diabetic retinopathy showing FAZ enlargement, capillary dropout, and reduced macular vessel density. Image provided courtesy of TowardPi and reproduced with permission.

3.2. Vessel Density and Perfusion Density

Vessel density (VD) and perfusion density (PD) quantify the proportion of a selected retinal area occupied by vascular or flow signal; definitions vary by instrument and software. The 2024 meta-analysis detected reductions in superficial VD (WMD, -1.34 ; 95% CI, -1.99 to -0.68), deep VD (WMD, -2.00 ; 95% CI, -2.95 to -1.04), and peripapillary VD (WMD, -1.07 ; 95% CI, -1.70 to -0.43) in diabetes without clinical retinopathy compared with healthy controls [5]. In mild nonproliferative DR, the corresponding reductions were larger for superficial VD (WMD, -6.11 ; 95% CI, -9.90 to -2.32) and deep VD (WMD, -4.26 ; 95% CI, -5.95 to -2.57) [5]. A separate meta-analysis of 45 cross-sectional studies (2,241 diabetic eyes without DR and 1,861 healthy eyes) similarly found lower macular PD in both superficial and deep plexuses, although results differed by diabetes type and retinal subfield [6].

3.3. Capillary Nonperfusion

Capillary nonperfusion may be expressed through reduced density metrics, extrafoveal avascular areas, or geometric perfusion deficits. OCT-A can localize nonperfusion by retinal slab and can be repeated without dye exposure, but slow flow below the detection threshold may mimic absent perfusion. Reviews therefore recommend inspection of co-registered structural B-scans and quality-controlled en face slabs before attributing a dark region to true capillary loss [2,3]. Wide-field OCT-A examples of retinal nonperfusion are shown in Figure 3.

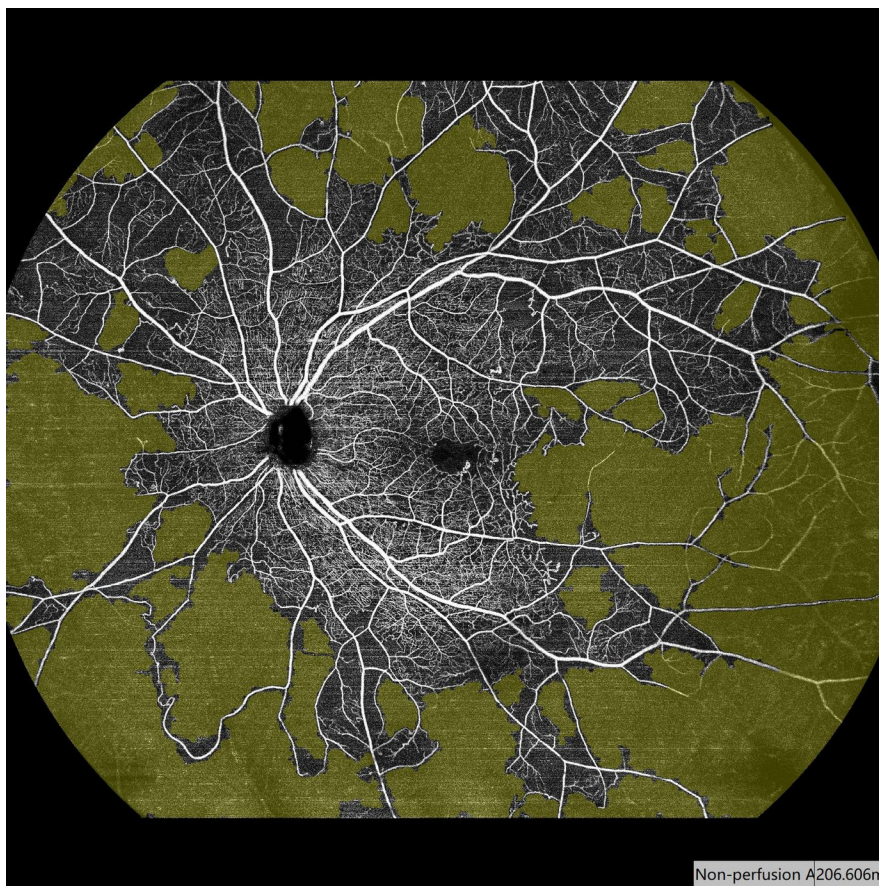


Figure 3. Wide-field OCT-A in diabetic retinopathy demonstrating extensive areas of capillary nonperfusion consistent with retinal ischemia. Image provided courtesy of TowardPi and reproduced with permission.

3.4. Vessel Length Density

VLD is calculated from a skeletonized vascular map and represents total perfused vessel length per unit area. In 119 eyes, Choi et al. reported inverse associations between DR severity and VLD in both superficial and deep capillary plexuses ($P < 0.001$ for both) [9]. Because skeletonization reduces the influence of vessel caliber, VLD may complement area-based density measures. However, its value remains sensitive to thresholding, skeletonization, scan resolution, and segmentation choices [9,10].

3.5. Fractal Dimension

FD summarizes the branching complexity of the perfused vascular network. In a study of 49 control eyes and 58 eyes with DR, deep-plexus FD was significantly lower in diabetic eyes, while reductions in the superficial plexus were most evident in severe nonproliferative and proliferative DR [11]. In a separate cohort of 136 eyes, Alam et al. found that combining FD with vessel complexity and tortuosity improved differentiation among controls, nonproliferative DR, and proliferative DR; FD alone was less sensitive for distinguishing the two retinopathy stages [12]. FD is therefore a potentially informative network-level biomarker, but not a device-independent severity index.

3.6. Diagnostic and Staging Performance

A diagnostic meta-analysis of 44 studies encompassing 4,284 eyes reported that OCT-A differentiated DR from diabetes without DR with 88% sensitivity (95% CI, 85%–92%) and 88% specificity (95% CI, 85%–91%). For proliferative versus nonproliferative DR, pooled sensitivity and specificity were both 91%. Sensitivity increased with scan size, from 85% for 3 × 3 mm scans to 96% for 12 × 12 mm scans, although larger fields generally trade spatial sampling density for coverage [13]. These pooled estimates describe OCT-A-based models and thresholds across heterogeneous studies and should not be interpreted as a single validated clinical test.

3.7. Longitudinal and Individualized Interpretation

Prospective longitudinal evidence suggests that biomarker performance depends on baseline severity and retinal layer. In a 1-year study of 320 eyes, deep-plexus geometric perfusion deficits had already increased at 6 months in referable DR, whereas the only significant change in nonreferable eyes was a reduction in superficial-plexus VD at 1 year [14]. This finding argues against a single universal progression metric and supports selecting the parameter, plexus, and scan protocol according to the disease stage and intended clinical question. The principal biomarkers are summarized in Table 1.

Table 1. Principal OCT-A biomarkers in diabetic retinopathy.

Biomarker	Evidence synthesized	Interpretation and principal limitation
FAZ area and shape	Often larger and less circular with increasing DR severity; preclinical findings are heterogeneous [5,6,8].	Reflects central capillary remodeling; influenced by axial scale, segmentation, and natural interindividual variability.
VD / PD	Reduced in superficial, deep, and peripapillary networks; abnormalities may precede visible DR [5,6].	Sensitive early marker; definitions and units differ among devices and software.
VLD	Lower superficial and deep VLD is associated with increasing DR severity [9].	Less dependent on vessel caliber than area density; strongly dependent on skeletonization and thresholding.
FD	Lower FD reflects vascular-network simplification and is most evident in more advanced DR [11,12].	Captures global complexity; varies with scan size, image quality, and processing method.
Perfusion deficits	Layer-specific deficits may detect longitudinal progression, especially in referable DR [14].	Promising for monitoring; slow flow and artifacts can mimic nonperfusion.

4. Discussion

The reviewed evidence supports OCT-A as a quantitative complement to dilated fundus examination, color photography, fluorescein angiography, and structural OCT. Across studies, loss of vascular or perfusion density is the most consistent abnormality, while FAZ, VLD, FD, and perfusion-deficit measures provide additional information about central ischemia, capillary rarefaction, network complexity, and spatial distribution [2–6,13].

The data also show why biomarker interpretation should be stage- and context-specific. In early diabetes, VD abnormalities may be detectable even when total FAZ area is unchanged [5]. In established or referable DR, deep-plexus perfusion deficits may identify progression earlier than conventional vessel-based metrics [14]. A personalized approach would therefore combine the patient's DR stage, diabetes duration,

visual function, structural OCT findings, and longitudinal change on the same device rather than rely on a single cross-sectional cutoff.

Important technical limitations currently prevent universal thresholds. In 38 patients imaged with different acquisition protocols and platforms, Crincoli et al. found good agreement for superficial-plexus parameters but only moderate-to-poor agreement for several deep-plexus and choriocapillaris measures; averaging and high-speed acquisition also changed quantitative values [15]. In 211 scans, Freedman et al. showed that preprocessing and binarization methods significantly affected VD, skeletonized VD, and FD values (all $P < 0.001$) and could alter which clinical covariates appeared significant [10]. Serial clinical assessment should therefore use the same device, scan size, segmentation strategy, and analysis pipeline whenever possible.

Image quality remains a clinical and research constraint. Motion, projection, blink, and segmentation artifacts; media opacity; poor fixation; edema-related boundary errors; and flow below the instrument's detection range may create false vascular loss or obscure true abnormalities. Quality grading, review of structural B-scans, correction of segmentation, and reimaging when necessary are essential before quantitative results are accepted [2,3].

Artificial intelligence may improve automated staging and extraction of spatially complex OCT-A features, but evidence is still largely retrospective and device-specific. In a study of 1,118 eyes, a convolutional neural network achieved 72.8% accuracy, 67.5% sensitivity, 94.4% specificity, and a quadratic weighted kappa of 0.908 for six-level DR staging; performance was better with 6×6 mm than with 3×3 mm images [16]. External, prospective validation across diverse populations and platforms is required before such models guide referral or treatment decisions. This review is limited by its narrative design, restriction to English-language publications from 2021 to 2025, and the heterogeneity of acquisition and analysis methods, which precluded direct comparison or new meta-analysis.

5. Conclusions

OCT-A provides repeatable, noninvasive visualization of diabetic retinal microvascular injury when image quality and segmentation are carefully controlled. VD and PD currently have the most consistent evidence across disease stages, while FAZ, VLD, FD, and spatial perfusion-deficit measures add complementary information.

The strongest near-term clinical use is longitudinal comparison on a consistent platform, integrated with examination and multimodal imaging. Device-independent cutoffs, standardized reporting, and externally validated predictive models are still needed before OCT-A biomarkers can support routine individualized risk stratification or treatment selection.

Funding: This research received no external funding.

Declaration of Generative AI and AI-Assisted Technologies: During the preparation of this manuscript, the authors used OpenAI ChatGPT for language editing, manuscript organization, and drafting support. The tool was not treated as a scientific source. The authors reviewed and revised the complete manuscript, verified all bibliographic details against PubMed and DOI metadata, and take full responsibility for the final content.

Conflict of Interest: The authors declare no conflict of interest.

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How to cite: Ceca S, Torreggiani A. OCT Angiography Biomarkers in Diabetic Retinopathy: Current Evidence and Future Perspectives for Personalized Ophthalmology. *Eur J Med Transl Biosci.* 2026;1(1):82–90.