META-ANALYSIS

The Role of OCTA in Evaluating Diabetic Retinopathy Progression: A Meta-Analysis

Lei Xi, MM; Minfang Fan, MM; Longhao Kuang, MM; Feng Zhao, MM

ABSTRACT

Background • Diabetic retinopathy (DR) substantially threatens ocular health, necessitating the accurate and prompt assessment of its onset and progression. Optical coherence tomography angiography (OCTA) is a valuable tool for evaluating periocular microvascular indicators, offering insights crucial for diagnosing and treating DR.

Objective • This meta-analysis aims to evaluate the progression of diabetic retinopathy (DR) by examining periocular microvascular indicators using optical coherence tomography angiography (OCTA). The objective is to provide substantive evidence for the future diagnosis and treatment of DR.

Methods • We analyzed the relevant research retrieved from PubMed and Web of Science until January 2023. The inclusion and exclusion criteria were carefully applied to select eligible studies. Quality assessment was performed using the Newcastle-Ottawa Scale, with studies scoring 4 or less excluded. Meta-analysis was conducted using Revman 5.3 software and focused on key indicators, including peripapillary vascular length density (pVLD) and peripapillary vascular density (pVD). Heterogeneity was assessed using I^2 and P-values, with effect sizes determined via fixed-effect or random-effects models based on heterogeneity levels.

Results • Six studies involving 839 DR-afflicted eyes and 3209 non-DR eyes were included after screening. All selected articles exhibited high reference value, with quality scores ranging from 5 to 8 points. The meta-analysis demonstrated that DR patients displayed significantly lower pVD and pVLD in the superficial (SCP) and deep capillary plexus (DCP) compared to non-DR patients ($P < 0.05$). These findings remained consistent across different effect models, reaffirming their validity.

Conclusions • Patients with DR exhibit reduced levels of pVD and pVLD in the SCP and DCP compared to non-DR individuals. OCTA examination of periocular microvascular indicators emerges as an effective tool for assessing the onset and progression of DR. (*Altern Ther Health Med.* [E-pub ahead of print.])

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INTRODUCTION

Diabetes mellitus (DM) is one of the most common chronic diseases in the world, especially among middle-aged and elderly individuals, with more than 300 million cumulative cases worldwide.[1] While DM itself doesn't cause significant pathological damage, it can lead to malignant lesions in various human body tissues and organs by continuously raising blood sugar.[2] Among these complications, diabetic retinopathy (DR) is notably prevalent in individuals with DM. In its early stages, DR typically lacks symptoms, but as it progresses, patients may experience symptoms such as floaters, blurred vision, the presence of shadows or blank areas in the visual field, and eventual loss of vision in advanced stages.

At present, DR stands as one of the foremost causes of blindness.[3] The pathogenesis of DR remains unclear, and consequently, no definitive clinical cure exists for this condition.[4] Therefore, early confirmation of DR's occurrence and timely intervention have become critically important in safeguarding patients' visual health. Ongoing research reveals that retinal microvascular injury and neurodegenerative changes associated with DR manifest much earlier than observable retinopathy detected in routine fundus

examinations.[5] Consequently, there is an urgent clinical need to develop more effective early diagnostic methods for DR.

Optical coherence tomography angiography (OCTA) is a relatively recent non-invasive imaging technique that detects blood cell movement within blood vessels by analyzing amplitude changes in reflected OCT signals. This technology allows for the visualization of the retinal plexus layer by layer, quantifying microvascular parameters and correlating these parameters with retinal function and morphology data. Its widespread utilization in clinical ophthalmology is attributed to several advantages, including the absence of the need for fluorescent dye injection, rapid inspection, and the provision of high-definition three-dimensional visualizations.[6,7]

OCTA serves as a valuable tool for both diagnosis, and the early identification of alterations in the retinal microvascular system and nerves during the initial stages of DR. OCTA enables quantitative analysis of blood flow density (vessel density, VD), foveal avascular area (FAZ) within each retinal layer, as well as area and circumference measurements. These capabilities have significantly advanced early DR diagnosis.[8] However, it is noteworthy that the current state of OCTA research primarily centers on assessing the occurrence of DR through metrics such as VD and FAZ, with few studies examining other potential applications.[9,10]

Zhang et al.[11] noted that variations in DM types and blood sugar levels can lead to discrepancies in the abovementioned indicators.[11] It further adds complexity to the OCTA diagnosis of DR. In recent years, researchers have begun to explore the use of OCTA to detect periocular microvascular parameters to achieve a more precise assessment of DR. However, a consensus in this regard has not yet been reached.

Therefore, we conducted this meta-analysis to assess the contribution of OCTA in appraising periocular microvascular indicators in DR. This study aims to provide a more robust foundation of evidence and direction for the future application of OCTA in the diagnosis and treatment of DR.

MATERIALS AND METHODS

Study Design

We employed a systematic and comprehensive approach to investigate the role of OCTA in evaluating periocular microvascular indicators in diabetic retinopathy. The relevant studies were retrieved from PubMed and Web of Science until January 2023 to compile a robust and up-to-date dataset. The inclusion and exclusion criteria were carefully applied to select eligible studies.

Inclusion and Exclusion Criteria

Inclusion criteria were as follows: (1) Studies in English; (2) studies involving diabetic retinopathy patients and individuals with uncomplicated DM as study participants who underwent OCTA examination; (3) availability of original data suitable for statistical analysis.

Exclusion criteria were as follows: (1) Uncontrolled studies that prevent the establishment of causal relationships; (2) review articles, animal experiments, or conference papers; (3) duplicated publications; (4) literature with evident research design flaws; (5) studies lacking detailed method descriptions; (6) literature showing potential selective reporting biases.

Literature Retrieval Strategy

Relevant research concerning OCTA in the diagnosis of DR was systematically gathered from the PubMed database (URL: https://www.ncbi.nlm.nih.gov/) and the Web of Science database (URL: http://www.webofscience.com) available from the establishment of these databases up to January 2023. Our retrieval strategy incorporated a combination of subject and free terms. The search keywords encompassed "diabetic," "diabetes," "diabetes mellitus," "DM," "optical coherence tomography angiography," "OCT angiography," "OCTA," "angio-OCT," "Diabetic Retinopathy," "microvascular," "superficial capillary plexus (SCP)," "peripapillary vascular length density (pVLD)," "peripapillary vascular density (pVD)," "deep capillary plexus (DCP)," "diagnosis," and "assessment."

Literature Screening and Extraction

Two researchers independently performed a comprehensive selection and screening process, adhering to predetermined inclusion and exclusion criteria. It thoroughly examined titles, abstracts, full texts, and raw data. The literature was considered for final analysis only when the selection results from both researchers were in agreement. In instances of disagreement, the two researchers engaged in further discussion or sought the opinion of a third researcher to reach a consensus. Relevant information related to the application of OCTA in diabetic retinopathy, including author(s), study period, research participants, pVD, pVLD, and other relevant data, was systematically extracted.

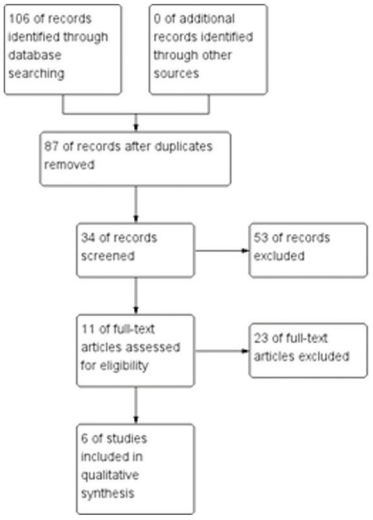
Literature Quality Evaluation

The quality of the articles was rigorously assessed by two researchers employing the Newcastle-Ottawa Scale (NOS),[12] considering the domains of cohort selection, comparability, and exposure/outcome. The NOS scale assigns a maximum score of 10, categorizing scores 1-3, 4-6, and 7-9 as low, medium, and high-quality indicators, respectively.

Statistical Analysis

We utilized Revman 5.3 software for statistical analysis in this meta-analysis. A significance level of $P < .05$ was applied for all analyses. Continuous variables were represented by the mean difference (MD) along with a 95% confidence interval (95% CI), while categorical variables were represented by the risk ratio (RR). To assess heterogeneity among the included articles, we examined both the I^2 and P values. Effect sizes were combined using fixed-effect models when heterogeneity was low ($I^2 < 50\%$), and a random-effects model was employed when heterogeneity was substantial ($I^2 \geq 50\%$).

Figure 1. Flowchart of Literature Retrieval



Note: This flowchart outlines the systematic document retrieval process used in this study to select relevant literature for analysis.

RESULTS

Study Selection and Participant Details

The initial keyword search yielded a total of 106 relevant studies. After a thorough screening process, six papers were selected for inclusion.[13-18] These studies included a total of 3109 cases and 4118 eyes, with 3209 eyes belonging to non-DR individuals and 839 eyes to those with diabetic retinopathy. For a visual representation of the literature screening process, refer to Figure 1.

Basic Characteristics and Quality Evaluation Results of Included Studies

The summary of important characteristics of included studies is presented in Table 1. Notably, 312 DR eyes and 1452 non-DR eyes were excluded from a study by Guo et al.[14] We also excluded 115 eyes with diabetic macular edema. The quality of the papers was assessed using the NOS, resulting in a score of 8 points for one paper, 7 points for two papers, 6 points for one paper, and 5 points for two papers. No paper scored below 4 points, demonstrating the overall high quality of the included studies.

Comparison of Superficial Capillary Plexus's Peripapillary Vascular Density (SCP's pVD)

All six studies investigated pVD within the SCP.[13-18] Notably, a substantial degree of heterogeneity was observed among these studies (I^2 = 100%), which prompted the application of a random effects model for analysis. The findings revealed a significant difference in SCP's pVD between DR patients and non-DR patients (P = .02), with DR patients exhibiting a lower pVD by approximately -0.11, refer to Figure 2.

Comparison of SCP's Peripapillary Vascular Length Density (pVLD)

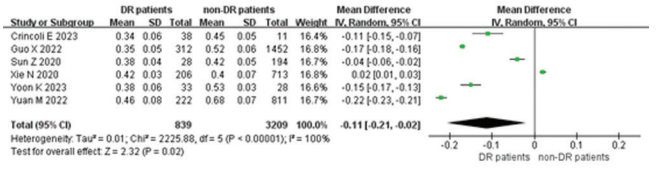
Only four studies[13,16-18] reported SCP's peripapillary vascular length density and a consistent degree of

Table 1. Basic Characteristics and Quality Evaluation Results of Literature

Authors And Years	Number of People	Number of Eyes	DR Eyes	Non-DR Eyes	Observed Indicators	NOS Score
Crincoli et al. (2023)[13]	49	49	38	11	①②③④	8
Guo et al. (2022)[14]	946	1879	312	1452	①③	6
Sun et al. (2020)[15]	129	205	28	194	①③	7
Xie et al. (2020)[16]	919	919	206	713	①②③④	7
Yoon el at. (2023)[17]	33	33	33	28	①②③④	5
Yuan et al. (2022)[18]	1033	1033	222	811	①②③④	5

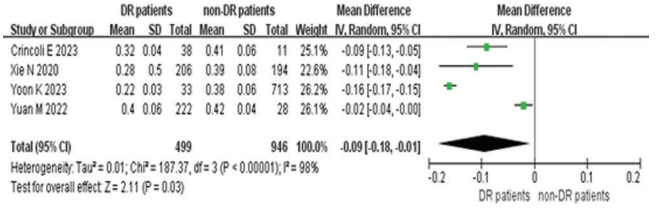
Note: ① peripapillary vascular density of superficial capillary plexus (SCP's pVD); ② peripapillary vascular length density of peripapillary vascular length density (SCP's pVLD); ③ peripapillary vascular density of deep capillary plexus (DCP's pVD); ④ peripapillary vascular length density of deep capillary plexus (DCP's pVLD).

Figure 2. Comparison of Peripapillary Vascular Density of Superficial Capillary Plexus (SCP's pVD).



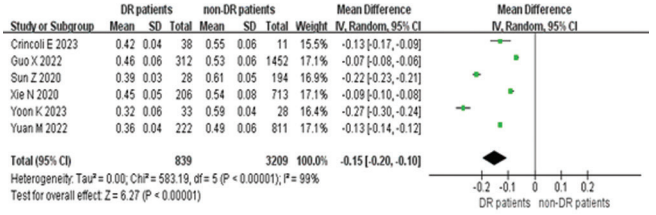
Note: In this forest plot, lines represent individual studies, squares signify their effect size estimates, and diamonds at the bottom summarize the overall effect. Lines depict the confidence intervals, squares show the study-specific effect sizes, and the diamond represents the combined effect size.

Figure 3. Forest Plot of Peripapillary Vascular Length Density (SCP's pVLD) Comparisons



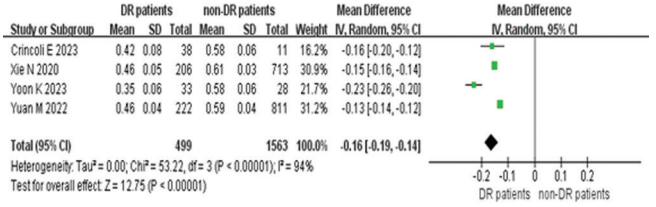
Note: Figure 3 presents a forest plot that illustrates the comparisons of peripapillary vascular length density (SCP's pVLD) across multiple studies. Each study is represented by a square, indicating its effect size estimate, and a horizontal line, representing the associated confidence interval. The diamond at the bottom summarizes the overall effect, providing a visual representation of individual study outcomes and the combined effect size.

Figure 4. Forest Plot of Peripapillary Vascular Density of Deep Capillary Plexus (DCP's pVD) Comparisons



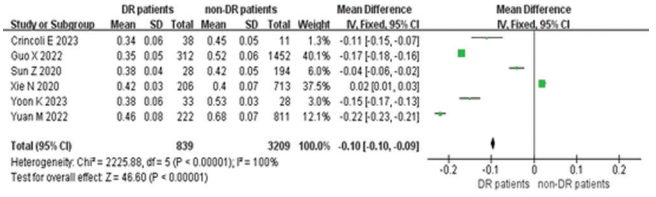
Note: In Figure 4, a forest plot displays comparisons of peripapillary vascular density in the deep capillary plexus (DCP's pVD) across multiple studies. Each study is represented by a square, indicating its effect size estimate, and a horizontal line, representing the associated confidence interval. The diamond at the bottom summarizes the overall effect, visually presenting individual study outcomes and the combined effect size for this specific parameter.

Figure 5. Forest Plot of Peripapillary Vascular Length Density of Deep Capillary Plexus (DCP's pVLD) Comparisons



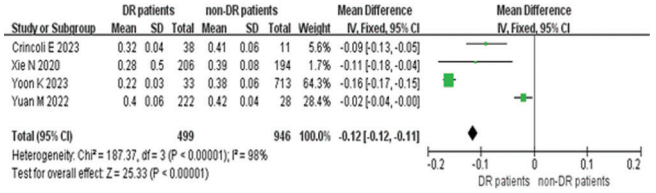
Note: Figure 5 outlines comparisons of peripapillary vascular length density (pVLD) within the deep capillary plexus (DCP) across various studies. Each study is depicted by a square, representing its effect size estimate, and a horizontal line signifying the confidence interval. The diamond at the bottom provides an overview of the overall effect, offering a visual representation of individual study results and the combined effect size for this specific parameter.

Figure 6. Fixed-Effects Model Analysis of Peripapillary Vascular Density of Superficial Capillary Plexus (SCP's pVD)



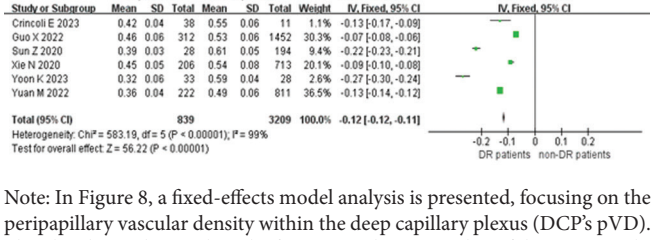
Note: In Figure 6, the fixed-effects model analysis of peripapillary vascular density within the superficial capillary plexus (SCP's pVD) is presented. The figure shows the combined effect size and its associated confidence intervals, reflecting the results of the analysis. This analysis helps provide insights into the SCP's pVD in diabetic retinopathy patients and non-diabetic retinopathy patients.

Figure 7. Fixed-Effects Model Analysis of Peripapillary Vascular Length Density of Superficial Capillary Plexus (SCP's pVLD).



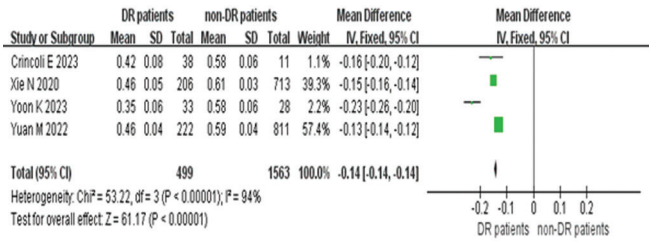
Note: Figure 7 displays the results of a fixed-effects model analysis regarding the peripapillary vascular length density (pVLD) within the superficial capillary plexus (SCP). The plot illustrates the combined effect size and its corresponding confidence intervals, offering insights into the SCP's pVLD among the studied parameters.

Figure 8. Fixed-Effects Model Analysis of Peripapillary Vascular Density of Deep Capillary Plexus (DCP's pVD)



Note: In Figure 8, a fixed-effects model analysis is presented, focusing on the peripapillary vascular density within the deep capillary plexus (DCP's pVD). The plot shows the combined effect size and associated confidence intervals, providing insights into the DCP's pVD as assessed in the included studies.

Figure 9. Fixed-Effects Model Analysis of Peripapillary Vascular Length Density of Deep Capillary Plexus (DCP's pVLD)



Note: Figure 9 showcases the results of a fixed-effects model analysis regarding the peripapillary vascular length density (pVLD) within the deep capillary plexus (DCP). The graph illustrates the combined effect size and its associated confidence intervals, offering insights into the DCP's pVLD as evaluated across the included studies.

heterogeneity was observed among these studies (I^2 = 98%). Utilizing a random effects model for analysis, the results indicated that SCP's pVLD was notably lower in DR patients compared to non-DR patients (P = .03, MD=-0.09, 95% CI=-0.18 to -0.01), with an approximate difference of -0.09 between the two groups, refer to Figure 3.

Comparison of DCP's Peripapillary Vascular Density (pVD)

All the included studies[13-18] reported data on the pVD within the deep capillary plexus (DCP) for both DR and non-DR patients. Notably, there was substantial heterogeneity among these studies (I^2 = 99%). An analysis utilizing a random effects model demonstrated a significant reduction of approximately 0.15 in DCP's pVD in DR patients compared to non-DR patients (P < .001, MD=-0.15, 95% CI=-0.20 to -0.10). Refer to Figure 4.

Comparison of DCP's Peripapillary Vascular Length Density (pVLD)

Only four studies[13,16-18] reported pVLD within the DCP), with noticeable heterogeneity among these papers (I^2 = 94%). The results of the analysis, conducted using a random effects model, revealed that DR patients exhibited significantly lower DCP's pVLD compared to non-DR patients (P < .001, MD=-0.16, 95% CI=-0.19 to -0.14), with an approximate difference of 0.16 between the two groups, refer to Figure 5.

Validation Analysis

A fixed-effects model analysis was conducted to confirm the reliability of the previously observed heterogeneous results. The results remained consistent, with DR patients consistently demonstrating lower values in the studied parameters. Specifically, DR patients exhibited lower SCP's pVD (MD=-0.10, 95% CI=-0.10 to -0.09), SCP's pVLD (MD=-0.12, 95% CI=-0.12 to -0.11), DCP's pVD (MD=-0.12, 95% CI=-0.12 to -0.11), and DCP's pVLD (MD=-0.14, 95% CI=-0.14 to -0.14) compared to non-DR patients, further validating the accuracy of the preceding experimental findings (all P < .001). Refer to Figures 6 to 9.

DISCUSSION

DR, a vascular neurological disease with the potential to cause vision loss, still lacks a comprehensive understanding of its pathogenesis. The current consensus suggests that its pathological progression primarily involves factors such as endothelial cell loss, thickening of the basement membrane, luminal constriction or blockage, neovascularization, and damage to the optic nerve.[19] Recent studies have revealed that retinal microvascular and neural damage manifest in the early stages of DR, sometimes preceding clinically observable retinal impairments.[20]

Hence, the early identification and quantification of vascular and neural alterations in DR patients have become areas of particular interest and challenge in current research. OCTA stands out as an innovative, non-invasive imaging technique. Utilizing its ability to analyze reflectivity and scattering variations resulting from the movement of red blood cells within lumens, OCTA enables quantitative assessment of several critical parameters. These parameters include the morphology and dimensions of the FAZ, VD of the macular region, and the thickness of the RNFL. Such capabilities offer new prospects for the early detection of microangiopathy and neural changes in DR patients.[21]

OCTA is predominantly employed for the examination of the macular area, allowing for the visualization of retinal blood flow within distinct layers.[22] Consequently, some researchers have employed OCTA to investigate the perfusion status of the macular region. Their findings indicate a statistically significant reduction in perfusion density within both superficial and deep retinal capillaries, as well as choroidal capillaries, at various stages of DR when compared to healthy eyes. Furthermore, linear model analysis has emphasized the substantial correlation between the levels of superficial and deep retinal capillaries and the severity of lesions.[23]

Moreover, there is evidence suggesting that microvascular damage induced by DM originates at an early stage within DR lesions and deteriorates with the duration of DM. This progression leads to impaired vascular autoregulation and diminished blood flow to the retina and optic nerve.[24] Consequently, the assessment of periocular microvascular changes may offer a more advantageous approach for the early evaluation of DR.

In this meta-analysis, we observed that despite the existence of numerous studies related to the use of OCTA in DR assessment, only six papers that concentrated on periocular microvascular parameters successfully met the inclusion criteria after rigorous screening. It becomes apparent that the current utilization of OCTA is predominantly centered on observing the FAZ and the macular area. This focus is believed to be a significant contributing factor to the existing controversy surrounding the effectiveness of evaluating periocular microvessels for DR.

This meta-analysis has identified a significant reduction in pVD and pVLD within both the SCP and DCP in DR patients when compared to non-DR individuals. This finding highlights the strong correlation between changes in the periocular microvasculature and the development of DR, consistent with past studies.[25,26] However, it is worth noting that some DR patients exhibited a lack of capillary perfusion in the studies mentioned above. This difference is attributed to strong neovascularization in the area, which leads to elevated local blood flow and can create the illusion of normal blood vessel density during OCTA assessments.

The reduction in retinal vascular density around the macular fovea is primarily attributed to the loss of retinal nerve tissue and functional impairment resulting from hypoxia and hyperglycemia.[27] Prolonged periods of ischemia and hypoxia within the peripheral capillary network can lead to the loss of autoregulation capacity, ultimately resulting in pathological capillary occlusion.[28] We believe this is a major contributing factor to the decrease in pVD and pVLD observed in DR patients. It is well-established that microvascular dysfunction or abnormal blood flow within the retinal capillary plexus can lead to impairment in retinal nerve function, including the retinal nerve fiber layer (RNFL) or ganglion cells.[6]

Monitoring pVD and pVLD holds considerable significance in DM and DR. These parameters provide valuable insights not only into the clinical evaluation of DR onset but also into the early detection of various visual impairments and disorders associated with DM. This proactive approach can prove instrumental in the future diagnosis and treatment of a wide range of ophthalmic conditions, including DR. Through validation analysis, the accuracy of such monitoring and its implications for patient care has been reaffirmed, highlighting the critical role of these assessments in ensuring the visual health and well-being of individuals with DM and those at risk of DR.

Our validation analysis has firmly established the accuracy of the preceding findings. Building upon the insights derived from this analysis, we assert that the examination of microvascular changes in the periocular region serves a dual purpose. It not only enables the precise detection of vascular data alterations in specific areas, offering a more nuanced understanding of their perfusion status, but also provides a clear visualization of the avascular zone within the macular fovea through the superficial retinal capillaries. This dual functionality is of critical importance for the future diagnosis and treatment of DR.

Study Limitations

It is important to recognize certain limitations in our research. The primary limitation was the limited availability of literature with a relatively small number of cases included. This limitation may introduce some bias into our analysis results. Additionally, the absence of large-scale cohort analyses further highlights the need for more extensive research to confirm the effectiveness of OCTA in assessing periocular microvessels for DR. Moreover, the lack of clinical controlled trials is a notable limitation that hinders the establishment of a more concrete evidence base. Despite these challenges, we believe that our study provides valuable insights and forms a stepping stone for future research in this field.

CONCLUSION

In conclusion, our meta-analysis underscores the substantial differences in peripapillary vascular density and peripapillary vascular length density within both the superficial capillary plexus and deep capillary plexus between diabetic retinopathy and non-DR patients. These findings signify the potential of optical coherence tomography angiography as a valuable tool for the precise and expedited evaluation of DR onset and progression through the assessment of periocular microvascular indicators. This research highlights the promising role of OCTA in enhancing the clinical understanding and management of diabetic retinopathy.

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None

CONFLICT OF INTERESTS

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AVAILABILITY OF DATA AND MATERIALS

The data supporting the findings of this study are available from the corresponding author upon request, subject to reasonable conditions.

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