ORIGINAL ARTICLE

Macular vessel density in patients with refractory diabetic macular edema in different stages of nonproliferative diabetic retinopathy

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Background: Macular vessel density can play a significant role in the prognosis of diabetic macular edema (DME). The aims of this study were to investigate macular vessel density using optical coherence tomography angiography (OCTA) in patients with refractory DME across different stages of nonproliferative diabetic retinopathy (NPDR) and explore its relationship with clinical parameters. **Material and Methods:** This was a cross sectional descriptive analytical study. Diabetic patients diagnosed with NPDR and refractory DME were included. OCTA imaging was performed to quantify vessel densities. Foveal avascular zone (FAZ), central macular thickness (CMT), and best corrected visual acuity (BCVA) were also measured. **Results:** Eighty nine eyes from 89 patients, including 53 males (59.6%), with a mean age of 60.17 ± 9.95 years were enrolled. The results revealed no significant differences in vessel densities and FAZ between different DR severity groups ($P > 0.05$). In addition, no significant correlations were observed between vessel density and CMT or most clinical variables, except for a negative correlation between deep capillary plexus (DCP) vessel density in the foveal region and BCVA ($r = -0.246$, $P = 0.019$). **Conclusion:** In patients with refractory DME, foveal DCP density was negatively correlated with visual acuity, suggesting its potential as a biomarker for visual prognosis and follow up of patients.

Key words: Diabetes, diabetic retinopathy, macular edema, optical coherence, tomography

How to cite this article: Salehi A, Malekahmadi M, Ghanbari H, Ghazi M. Macular vessel density in patients with refractory diabetic macular edema in different stages of nonproliferative diabetic retinopathy. J Res Med Sci 2025;30:13.

INTRODUCTION

Diabetic retinopathy (DR) is a leading cause of irreversible vision loss and blindness among adults worldwide.[1] Diabetic macular edema (DME), a serious vision-threatening complication of DR, is characterized by fluid accumulation in the macula due to increased vascular permeability and can occur at any stage of DR.[2]

The pathogenesis of DME involves a complex interaction of biochemical and physiological factors that ultimately lead to the leakage of plasma and its components from retinal vessels. Chronic hyperglycemia activates various biochemical pathways, including the polyol pathway, formation of advanced glycation end-products, and activation of protein kinase C.[3] These pathways lead to pericyte damage, disruption of endothelial cell junctions, and ultimately breakdown of the blood–retinal barrier, increased vascular permeability, and subsequent fluid accumulation in the retina.[4,5]

Despite the widespread use of various treatments, including antivascular endothelial growth factor (anti-VEGF) agents such as bevacizumab, a significant portion of patients (up to 50%) show less response or resistance to treatment.[6,7] The persistence of macular edema despite treatment poses a major challenge in the management of DME, as ongoing or worsening edema can lead to irreversible vision impairment and negatively impact these patients' quality of life and independence.

Access this article online

Quick Response Code:

Website: https://journals.lww.com/jrms

DOI: 10.4103/jrms.jrms_656_24

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Submitted: 19-Nov-2024; **Revised:** 21-Dec-2024; **Accepted:** 07-Jan-2025; **Published:** 28-Feb-2025

The underlying mechanisms contributing to refractory DME are complex and multifactorial, with factors such as genetic predisposition, disease duration, and comorbidities such as hypertension and hyperlipidemia potentially playing a role.[7,8] However, the role of vascular changes in the retina, particularly vessel density, largely remains unknown.[9,10]

Optical coherence tomography angiography (OCTA) is a novel, noninvasive imaging technique that provides high-resolution images of the retinal and choriocapillaris vasculature without the need for dye injection.[11] By providing depth-resolved images of the retinal vascular networks, OCTA offers a unique opportunity to study vessel density in different retinal layers and its potential association with refractory DME.[11,12]

The primary objective of this study was to investigate macular vessel density using OCTA in patients with refractory DME across different stages of nonproliferative DR (NPDR). By examining the relationship between macular vessel density and various clinical parameters such as foveal avascular zone (FAZ) area, central macular thickness (CMT), and visual acuity, we aimed to gain insights into the potential role of vascular changes in the pathogenesis and progression of refractory DME.

SUBJECTS AND METHODS

Ethics

This study was approved by the Ethics Committee of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1400.682), and informed consent was obtained from all participants before enrollment. Participants' personal and medical information was collected and stored with strict confidentiality and was only accessible to the research team. No information was disclosed without the participants' consent. All aspects of the research, including study design, data collection methods, and informed consent process, were reviewed and approved by the ethics committee.

Study design

This cross-sectional, descriptive-analytical study utilized OCTA to investigate macular vessel density in diabetic patients with refractory DME. The study was conducted at Feiz Hospital in Isfahan, Iran. Patients were included based on the following criteria: (1) diagnosed with type 1 or 2 diabetes and refractory DME (defined as those that received at least three intravitreal bevacizumab injections over the past 3 months, showing no improvement in best-corrected visual acuity (BCVA) and/or less than a 10% reduction in CMT,[12] (2) age over 18 years, (3) diagnosed as NPDR based on dilated fundoscopy, (4) no history of cataract surgery within the past 3 months, (5) no history of vitreoretinal surgery or retinal laser treatment, and (6) absence of any other retinal conditions that could cause macular edema, including vascular occlusive diseases, uveitis, or pseudophakic macular edema. Exclusion criteria included participants' unwillingness to continue participating in the study or the occurrence of any ocular comorbidity that could influence our results, such as retinal vein occlusion, glaucoma, or trauma.

After identifying eligible participants, demographic information, medical history, and treatment data were collected. Dilated fundoscopy was performed, and the patient was categorized according to Early Treatment Diabetic Retinopathy Study criteria as mild, moderate, and severe nonproliferative DR.[1] OCTA images were obtained for each patient to assess macular vessel density. OCTA images were acquired using the Optovue OCTA machine (the RTVue-XR, Optovue, Canada). The macular region was scanned, and vessel density was automatically calculated for the superficial capillary plexus (SCP) and deep capillary plexus (DCP) in the whole image, fovea, parafovea, and perifovea regions.

The primary outcome measures were macular vessel density in the SCP and DCP in different macular regions, assessed using OCTA. Secondary outcome measures included CMT and BCVA. The relationship between vessel density and DR severity, as well as other clinical parameters such as CMT and BCVA, were also investigated.

Statistics

The data were stored and analyzed using statistical analysis was performed using IBM SPSS Statistics for Windows, version 23 (IBM Corp., Armonk, N.Y., USA). Descriptive statistics, including mean, standard deviation, median, range, frequency, and percentage, were used to summarize the data. Analysis of variance (ANOVA) was employed for normally distributed data, whereas the Kruskal–Wallis test was used for nonnormally distributed data. $P < 0.05$ was considered statistically significant.

RESULTS

The study included 89 eyes from 89 participants, consisting of 36 females (40.44%) and 53 males (59.56%). The demographic and other data are presented in Table 1.

Macular thickness and the FAZ area were evaluated across different stages of retinopathy (mild, moderate, and severe). The Kruskal–Wallis test revealed no statistically significant differences in macular thickness between the groups in the whole macula, fovea, parafovea, and perifoveal regions ($P > 0.05$ for all comparisons). Similarly,

the FAZ area showed no significant differences between the groups ($P > 0.05$ for all comparisons) [Table 2].

The SCP and DCP vessel density was analyzed in different macular regions across the retinopathy stages. The ANOVA test revealed no significant differences between the groups in the whole macula, foveal, parafoveal, and perifoveal regions ($P > 0.05$ for all comparisons) [Table 3].

Pearson correlation tests were conducted to investigate the relationship between clinical variables (blood pressure, blood sugar, intraocular pressure, and BCVA) and retinal imaging parameters (retinal thickness and vascular density) in different macular regions. The results showed weak and nonsignificant correlations for most variables, except for a significant negative correlation between BCVA and DCP vessel density in the foveal region (r = −0.246, $P = 0.019$), indicating that better visual acuity was associated with higher DCP vessel density in the fovea [Table 4].

Table 1: Demographic information of all participants

Parameters	Statistical values
Gender	
Female	40.44% (36 individuals)
Male	59.56% (53 individuals)
Stage of DR (total)	89
Mild	16
Moderate	20
Severe	53
Age (mean±SD)	60.17±9.95
Blood pressure (mmHg) (mean±SD)	12.84±1.50
Blood sugar (mg/dL)* (mean±SD)	114.13±9.62
Visual acuity (LogMAR) (mean±SD)	0.773±0.16
IOP (mmHg) (mean±SD)	18.66±4.22

*Random (nonfasting) blood sugar. SD=Standard deviation; DR=Diabetic retinopathy; IOP=Intraocular pressure

DISCUSSION

The present study investigated the relationship between macular vessel density, as measured by OCTA, and various clinical parameters in patients with refractory DME. Our results did not demonstrate a significant difference in macular vessel density across different stages of NPDR in both the SCP and DCP. Furthermore, we found no significant correlation between vessel density and CMT or visual acuity, except for the correlation between DCP vessel density in the foveal region and visual acuity.

These findings contrast with some previous studies that have reported decreased vessel density in eyes with more advanced stages of DR.[9,13] Several factors may contribute to this discrepancy. First, our study's specific focus on refractory DME may influence the results. The pathophysiology of refractory DME is complex and multifactorial, involving not only VEGF-mediated pathways but also other mechanisms such as inflammation, oxidative stress, and neurodegeneration.[2,14] The inflammatory hypothesis has gained increasing attention in recent years, with multiple studies suggesting that persistent, low-grade inflammation may play a key role in the development and progression of DME, particularly in cases resistant to anti-VEGF therapy.[6,15] Given our findings, it is possible that in refractory DME, inflammatory pathways may play a significant role alongside vascular changes across different

Table 2: Comparative analysis of retinal thickness and foveal avascular zone area by severity level of diabetic retinopathy

Stage of retinopathy measurement	Mild (*n*=16), mean±SD	Moderate (*n*=20), mean±SD	Severe (*n*=53), mean±SD	Total (*n*=89), mean±SD	*P*¶
Whole thickness (μm)	349.69±27.53	358.3±34.63	378.52±140.54	368.9±110.88	0.407
Foveal thickness (μm)	369.56±53.08	394.40±94.34	395.67±158.40	390.74±131.96	0.787
Parafoveal thickness (μm)	371.31±50.99	396.0±58.29	402.61±151.52	395.58±122.35	0.197
Perifovea thickness (μm)	321.31±39.85	335.95±44.34	364.59±147.33	339.73±117.07	0.324
FAZ area (mm)	0.369±0.18	0.25±0.13	0.29±50.32	0.29±0.27	0.824

¶Result from Kruskal–Wallis test. SD=Standard deviation; FAZ=Foveal avascular zone

Table 3: Comparison of macular superficial and deep vessel density by stages of diabetic retinopathy

Stage of retinopathy measurement	Mild (*n*=16), mean±SD	Moderate (*n*=20), mean±SD	Severe (*n*=53), mean±SD	Total (*n*=89), mean±SD	*P*¶
Whole SVD (%)	43.53±5.52	44.65±4.52	44.22±3.91	44.18±4.33	0.758
Whole DVD (%)	40.92±6.27	41.75±4.69	43.13±5.33	42.43±5.39	0.824
Foveal SVD (%)	22.93±7.10	20.96±8.30	23.52±11.05	22.85±9.85	0.617
Foveal DVD (%)	35.58±8.04	35.26±11.1	36.45±12.37	36.03±11.34	0.874
Parafoveal SVD (%)	43.41±5.50	42.45±6.79	43.11±7.29	43.01±6.83	0.908
Parafovea DVD (%)	45.49±4.52	44.84±5.49	45.47±7.55	45.34±6.63	0.738
Perifoveal SVD (%)	44.92±5.27	46.78±4.51	46.02±4.45	45.99±4.60	0.486
Perifovea DVD (%)	41.78±6.54	42.99±5.05	44.60±5.64	43.74±5.73	0.535

¶Result from Kruskal–Wallis test. SVD=Superficial vessel density; DVD=Deep vessel density; SD=Standard deviation

Table 4: Pearson correlation results between clinical variables and retinal imaging parameters in different areas

Parameter/area	Whole	Fovea	Parafovea	Perifovea
Blood pressure and retinal thickness	0.074–0.615	0.003–0.981	0.149–0.312	0.244–0.095
Blood sugar and retinal thickness	0.209–0.153	0.053–0.719	0.183–0.214	0.186–0.206
IOP and retinal thickness	0.045–0.680	−0.054–0.615	−0.023–0.830	−0.021–0.848
LOGMAR and retinal thickness	0.005–0.966	−0.068–0.525	−0.018–0.865	0.030–0.782
Blood pressure and SVD	0.152–0.301	−0.092–0.534	0.091–0.536	0.172–0.242
Blood sugar and SVD	−0.032–0.828	−0.075–0.614	−0.153–0.298	0.107–0.469
IOP and SVD	−0.089–0.409	−0.115–0.284	0.004–0.968	−0.144–0.180
LOGMAR and SVD	−0.104–0.329	−0.131–0.217	−0.019–0.856	−0.055–0.608
Blood pressure and DVD	0.066–0.656	−0.096–0.516	0.062–0.676	0.077–0.604
Blood sugar and DVD	−0.119–0.420	−0.147–0.320	−0.199–0.174	−0.029–0.847
IOP and DVD	−0.075–0.485	−0.125–0.247	0.038–0.725	−0.054–0.615
LOGMAR and DVD	−0.192–0.069	−0.246–0.019	−0.048–0.653	−0.186–0.079

The results of Pearson correlation tests analyzing the relationships between clinical variables and retinal imaging parameters across different areas. Each row corresponds to a specific aspect of the statistical analysis, such as the correlation between blood pressure, blood sugar, IOP, and visual acuity (LOGMAR) with retinal thickness and vessel density (superficial and deep). Each value in the columns represents the correlation coefficient and statistical significance (*P*), providing deeper insight into clinical relationships for further research. IOP=Intraocular pressure; DVD=Deep vessel density; SVD=Superficial vessel density

stages of NPDR. Further research is needed to elucidate the complex interactions between these factors in the pathogenesis of refractory DME. Second, the distribution of patients across different DR severity groups in our study may affect the results. Our study did not include patients with proliferative DR (PDR) or very severe NPDR, which are associated with more pronounced microvascular changes.[16] The absence of these more advanced stages of DR may limit the ability to detect significant differences in vessel density among the different DR categories.

Racial differences in the pathophysiology of DR and DME may contribute to the discrepancies between our findings and those of previous studies. The prevalence, severity, and susceptibility to complications of diabetes and its related eye diseases vary among racial and ethnic groups. These differences may be influenced by genetic, environmental, and socioeconomic factors.[17] In refractory DME, racial differences may impact the underlying pathophysiological mechanisms and lead to variations in microvascular changes detected by OCTA, such as differences in angiogenic and inflammatory mediator expression and genetic polymorphisms associated with DR and DME susceptibility.[18,19] The racial composition of our study population may have influenced the observed relationships between macular vessel density, DR severity, and treatment response, potentially explaining the discrepancies with previous studies.

Another crucial factor to consider when interpreting the results of this study is the potential impact of anti-VEGF agents on the vessel density of the macula. All patients in this study underwent evaluation of their vessel density after receiving treatment with anti-VEGF injections. As previous researches have demonstrated, these injections can significantly change the vessel density of the macula.[20,21] Consequently, the lack of significant differences in vessel density across various stages and severities of the disease may be attributed to the effects of the medication rather than the inherent pathophysiology of the disease. This potential confounding factor should be carefully considered when drawing conclusions from the current study's findings, as the results may reflect the influence of the anti-VEGF treatment on the vessel density rather than the disease process itself.

The significant negative correlation between BCVA and DCP vessel density in the foveal region ($r = -0.246$, $P = 0.019$) suggests that better visual acuity, as indicated by lower LogMAR values, is associated with higher DCP vessel density in the fovea. This finding is consistent with previous studies that have demonstrated the importance of the DCP in maintaining visual function, particularly in the foveal region.[22,23] Several mechanisms may explain the association between higher DCP vessel density and better visual acuity in refractory DME. First, the DCP is responsible for providing oxygen and nutrients to the photoreceptors, which are critical for visual function.[24] Preservation of DCP vessel density in the foveal region may ensure an adequate supply of oxygen and nutrients to the photoreceptors, thus maintaining their integrity and function. Second, the DCP has been shown to play a role in the removal of metabolic waste products from the retina.[25] Efficient removal of waste products may prevent the accumulation of toxins that could damage the photoreceptors and impair visual acuity. Furthermore, the DCP has been implicated in the regulation of retinal pigment epithelium (RPE) function.[26] The RPE is essential for maintaining the health and function of photoreceptors, and its dysfunction has been associated with the development of DME.[27] Higher DCP vessel density in the foveal region may support RPE function, thus indirectly contributing to the preservation of visual acuity in refractory DME. The lack of significant correlations between BCVA and vessel density in other macular

regions (parafovea and perifovea) may be attributed to the unique anatomical and functional characteristics of the fovea. The fovea, which is responsible for central vision and visual acuity, has the highest concentration of cone photoreceptors and is avascular in nature. The parafovea and perifovea, on the other hand, have a lower density of photoreceptors and are primarily supplied by the SCP.[28] As a result, vascular changes in these regions may have a less direct impact on visual acuity compared to the fovea. The significant correlation between BCVA and DCP vessel density in the foveal region highlights the potential of OCTA as a noninvasive tool for assessing the relationship between microvascular changes and visual function in refractory DME. Future research should investigate the longitudinal changes in DCP vessel density and their association with visual acuity in refractory DME, as well as explore the potential of DCP vessel density as a biomarker for predicting treatment response and guiding personalized management strategies.

Despite the lack of significant association between vessel density and DR severity or clinical parameters in our study, it is essential to recognize the potential utility of OCTA in assessing and managing refractory DME. OCTA provides high-resolution, depth-resolved images of retinal microvasculature, allowing for visualization of capillary dropout, microaneurysms, and vascular remodeling.

The main limitation of our research is the small sample size and the absence of a control group. Future research is necessary to address these shortcomings.

CONCLUSION

This study provides valuable insights into the relationship between macular vessel density and clinical parameters in refractory DME. The significant negative correlation between visual acuity and DCP vessel density in the foveal region suggests that foveal DCP density may serve as a potential biomarker for determining visual prognosis in patients with refractory DME. Preserving the integrity of the foveal DCP appears to be crucial for maintaining visual function in these patients.

Authors' contribution

AS contributed in the conception of the work, conducting the study, revising the draft, and approval of the final version of the manuscript and agreed for all aspects of the work.

MM contributed in the conception of the work, conducting the study, gathering the data, revising the draft, and approval of the final version of the manuscript and agreed for all aspects of the work.

HG contributed in the conception of the work, conducting the study, and approval of the final version of the manuscript and agreed for all aspects of the work.

MG contributed in the searching of literature, acquisition and analysis of data, preparation of draft, and approval of the final version of the manuscript and agreed for all aspects of the work.

Acknowledgments

This study was approved by the Ethics Committee of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1400.682).

Financial support and sponsorship

This study was financially supported by the Isfahan University of Medical Sciences.

Conflicts of interest

There are no conflicts of interest.

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