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Correlation of Macular Vessel Density with Hemoglobin A1C in Non-Proliferative Diabetic Retinopathy

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Abstract

Purpose: This study aimed to investigate the correlation between glycosylated hemoglobin (HbA1c) and variations in macular vessel density (VD) in non-proliferative diabetic retinopathy (NPDR) using optical coherence tomography angiography (OCTA). **Methods:** This prospective cross-sectional observational study included 30 eyes of 18 Egyptian patients with NPDR selected from Ophthalmology Department at Benha University. All studied cases were subjected to full ophthalmological examination, OCTA scans were captured using specify OCTA device model (e.g., "RTVue XR Avanti"), and HBA1C was recorded for each patient. **Results:** Multivariate analysis, adjusted for age, gender, and DM duration revealed that HBA1C was a significant predictor of superficial VD in the parafoveal, temp parafoveal, and sup parafoveal regions. Univariate and multivariate linear regression analyses were performed for HBA1C to predict deep VD. The regression analyses were limited to the significant correlations. Multivariate analysis, adjusted for age, gender, and DM duration revealed that HBA1C was a significant predictor of deep VD in the temporal parafoveal and temporal perifoveal regions. **Conclusion:** HbA1C levels are significantly correlated with changes in macular VD and retinal thickness in patients with NPDR, as assessed by OCTA. Strong negative correlations between HbA1C levels and both superficial and deep VD in the parafoveal and perifoveal regions, highlighting HbA1C as a robust predictor of vascular alterations in these areas.

Keywords: Hemoglobin A1C, Macular Vessel Density, Non-Proliferative Diabetic Retinopathy, Optical Coherence Tomography Angiography.

Introduction

In developed countries, diabetic retinopathy (DR) the leading cause of vision loss" (stronger impact) among patients with diabetes [1]. In DR, visual impairment may be the result of vascular mutations in the retina's numerous layers. Recent research has suggested that the presence and progression of DR may be influenced by the alteration of retinal microvasculature, particularly in the macula, despite the fact that the pathogenesis of DR is not adequately studied [2, 3].

Vascular leakage or blood by the blood vessels is the hallmark of non-proliferative DR (NPDR), an early stage of DR. Exudates and hemorrhage are the results of the fluids and blood that have been expelled. Development of DR disease is indicated by the distribution, volumes, and diameters of exudates and hemorrhages [4]. When considering the pathophysiology of DR, hyperlipidemia and the level of glycemic control play crucial roles in the onset and development of diabetic complications. When it comes to monitoring glycemic control in diabetic patients, the measurement of glycosylated hemoglobin (HbA1c) is now considered the gold standard.This statistic represents glucose levels over a span of two to three months [5].

Tissue hypoxia is induced by the presence of blood vessel abnormalities in the retina, such as occlusion or narrowing, which subsequently leads to elevated levels of vascular endothelial growth factor. This, in turn, results in diabetic macular edema, a critical component of diabetic retinopathy (DR). Diabetic macular edema (DME) and its individual complications can lead to vision loss (DMI)[6]. Diagnostic tools such as optical coherence tomography (OCT) and fluorescein angiography (FA) are used to examine diabetic retinopathy (DR) in its different stages, as well as macular edema and ischemia. Recent years have seen the rise of optic coherence tomography angiography (OCTA) as a non-invasive, time-saving substitute for focal angiography (FA) for imaging the retinal vascular layers inside the macular region [7].

The objective of this study was to examine the relationship between alterations in macular vessel density in NPDR by OCTA and their impact on HbA1c .

Patients and methods

This prospective cross-sectional study included 30 eyes of 18 patients with NPDR. The study was carried out at Department of Ophthalmology, Benha University Hospital. The fieldwork will be carried out during the period from 1st June 2024 to 31st May 2025. (12 months). All participants provided written consent that is informed. An explanation of the study's purpose was provided to each patient, along with a

secret code number. After receiving approval from the Research Ethics Committee of the Faculty of Medicine at Benha University, the investigation was implemented. Based on the principles of the Declaration of Helsinki, the investigation was implemented.

Approval code: MS 34-6-2023

Inclusion criteria included patients with type 2 diabetes mellitus (NPDR) who were 35–65 years old, had diabetes with ≥5 years diabetes duration, and had a clear view of their retina

Exclusion criteria eyes with high myopia, optic neuropathy, advanced cataract, and cloudy media were excluded from the study. Additionally, DRs with a history of vitreoretinal surgery and laser surgery, retinopathy due to hypertension or other vascular retinal diseases, and poor fixation that resulted in poor ocular imaging all were excluded.

All studied cases were subjected to the following: detailed history taking; including duration of diabetes and history of any ocular and systemic diseases . Clinical examination included: Best corrected visual acuity (BCVA) measurement using Snellen chart. If vision is less than 3 meters then vision will be assessed at 2 meters distance, 1 meter distance and then 50 cm distance. BCVA was then converted from Snellen acuity into logarithm of minimum angle of resolution (LogMAR). The anterior segment examination was performed using slit lamp (Nidek Technologies, Japan). The pupil was dilated using 1% tropicamide and phenylephrine for fundus examination and OCTA Scanning. Examination of fundus was performed using slit lamp bio microscopy with +90Diopter lens and indirect ophthalmoscopy using 20+ diopter lens. Patients with NPDR of any stage were subjected to blood testing and OCTA scanning. Blood test was performed for recent evaluation of HBA1CHbA1c.

OCTA imaging protocol:

Three repeated scans performed per eye. An impressive rate of 70,000 A-scans/second was achieved during the execution of OCTA using the RTvue OCT (Optovue, Inc., Fremont, CA, USA). The split-spectrum amplitude decorrelation angiography (SSADA) algorithm improves the visualization of the macular vasculature and allow for the acquisition of OCTA images. The system's light source has a bandwidth of 50 nm and a focal point at 840 nm wavelength. The AngioVue retina scans allows for scan size of either 3x3, 6x6 or 8x8 mm. The smaller the scan size, the higher the image quality, since all are acquired with 304x304 A-scan per volume. The 6x6 mm scans were utilized for microvascular and FAZ evaluation in our study. All individuals had their fovea-centered images captured using a 6 x 6 mm cube. The inner and outer retinal layers were used to create frontal images of the retinal vasculature. As a means of quantifying the RPE from

the ILM, we employed optical coherence tomography (OCT). The three circular regions denoted by θ=1, θ=3, and θ=6 mm are the fovea, parafoveal, and perifoveal, respectively. The foveal avascular zone (FAZ) area, macular vein surface and profundity, and macular vein depth were all subjected to quantitative analyses.

The inherent software was used to automatically compute the parafoveal vascular density (PVD) of the deep and superficial capillary plexuses. A vessel's PVD is its total area divided by the percentage of its area that shows blood flow. The four quadrant PVDs (front, back, nasal, and temporal) were rendered using a two-ring ETDRS grid overlay.

This seasoned investigator obtained and analyzed all of the scans. For this reason, we did not include scans whose quality was lower than 5 out of 10 or whose projection or motion artefacts affected more than one of the 9 color-coded VD map regions.

The scans were analyzed into:

The ETDRS grid overlay was used to measure the superficial and deep capillary plexuses of both layers. Afterwards, the vessel densities of the superficial capillary plexus (SCP) and deep capillary plexus (DCP) were computed automatically by the software system. These densities are shown as a percentage, which is perfused vascular area divided by the total area of interest. The findings were displayed in tables with quantitative data and in color-coded vessel density maps with qualitative data; regions of severe ischemia were indicated by dark blue areas. The vessel density was recorded for the entire scanned area, as well as for the peri and parafoveal regions.

The software can also automatically calculate the area and demarcate the FAZ area. The user can achieve an average of the FAZ area over the thickness of the inner retinal layers of the fovea, which is defined as an area without flow, by using this method. In cases where the area was severely distorted, leading to inaccurate automatic delineation, manual outlining and subsequent calculation of the FAZ area were required. Automatic calculation of central macular thickness was performed from ILM to RPE for the purpose of analyzing foveal and parafoveal retinal thickness. To measure the thickness of the retina, a three-millimeter-diameter circle was used. In addition to the one millimeter-diameter foveal, parafoveal, and perifoveal areas, this region also encompassed the superior, nasal, inferior, and temporal quadrants. This area revolved around the FAZ.

In The current study we used OCTA integrated automated algorithms to examine changes of macular VD in NPDR and its relationship with HbA1c.

Statistical analysis

All statistical analysis and data administration were performed using

version SPSS 28 (IBM, Armonk, New York, United States). By using direct data visualization tools and the Shapiro-Wilk test, we were able to verify that the quantitative data was normal. Medians and ranges, or means and standard deviations, were used to describe quantitative data in line with normalcy. The categorical data was summarized using percentages and numbers. In order to examine the correlations, we used either Pearson's or Spearman's correlation (strong: $|r| > 0.6$, moderate: 0.4-0.6 and weak: <0.4). In both univariate and multivariate linear regression experiments, the researchers used HbA1c as a predictor of retinal thickness, superficial VD, plus deep VD. We calculated the coefficients of regression and supplied 95% confidence intervals. A two-sided statistical test was used. A p-value less than 0.05 was considered statistically significant [8].

Case presentation:

Case one:

Female patient, 48 years old, patient has type two diabetes for 15 years and HbA1c 8.5. BCVA: OD: 0.8 and OS: 0.9. We observed areas of decreased vascular density and capillary dropout areas in superficial retinal layer. Whole image VD 47.0, parafoveal VD 49.5 and perifoveal VD 48.6. In this patient the deep retinal layer was much less affected. Whole image VD 52.2, parafoveal VD 55.8 and perifoveal VD 55.0. Slightly enlarged Auto FAZ area 0.478 mm^2. **Figure 1**

Case Two:

Female patient, 52 years old, patient has type two diabetes for 10 years and HbA1c 6.5. BCVA: OD: 0.9 and OS: 0.9. We observed areas of decreased vascular density in SRL. Whole image VD 42.4, parafoveal VD 47.4 and perifoveal VD 42.7. In this patient the deep retinal layer was much less affected. Whole image VD 50.5, parafoveal VD 57.8 and perifoveal VD 50.8. Within normal Auto FAZ area 0.132mm^2. **Figure 2**

Results

A total of 30 eyes from 18 patients were included in the study. The general characteristics, superficial and deep vascular density, and OCT retinal thickness measurements of the studied patients are summarized in Table 1. The mean age of participants was 51.0 ± 8.0 years, with 11 of the eyes being left eyes and 19 right eyes. Baseline examination showed that gender distribution was predominantly female, 83.3% female (15/18 patients) compared to 16.7% of males (n=3). The mean Best Corrected Visual Acuity (BCVA) was 0.7, with a standard deviation of 0.2. The duration of diabetes mellitus (DM) among the participants had a median of 10 years, ranging from 6 to 18 years. The mean Hemoglobin A1c (HbA1c) level was 7.7% with a standard deviation of 1%. In analyzing the correlation between retinal thickness, as measured by OCT

from the ILM to the RPE, and the duration of diabetes mellitus (DM), no significant associations (all P>0.05) were found across the various retinal regions. The foveal region exhibited a weak positive correlation (r = 0.204) with DM duration, but this was not statistically significant. Similarly, no significant correlations were observed in all parafoveal regions, including the temporal, superior, nasal, and inferior parafoveal areas. The perifoveal regions followed the same trend, with no significant correlation in the temporal, superior, nasal, and inferior perifoveal regions. In contrast, significant moderate negative correlations were observed between superficial vessel density (VD) and the duration of DM in the temporal parafoveal (r = -0.441, P = 0.015) and superior parafoveal (r = -0.409, P = 0.025) regions. However, other areas, did not demonstrate statistically significant correlations with DM duration. Similarly, for deep VD, a significant weak negative correlation was found in the temporal parafoveal region (r = -0.382, P = 0.037), while other retinal regions did not exhibit significant associations with DM duration. Furthermore, no significant correlations were observed between FAZ and either DM duration or HbA1c levels. **Figure 3**

When evaluating the correlation between OCT thickness measurements and HbA1c levels, significant correlations were observed in multiple parafoveal and perifoveal regions. Moderate to strong positive correlations were detected in the temporal parafoveal (r = 0.542, P = 0.002), superior parafoveal (r = 0.572, P = 0.001), nasal parafoveal (r = 0.513, P = 0.004), and inferior parafoveal (r = 0.479, P = 0.007) regions. Similarly, strong positive correlations were also observed in the temporal perifoveal (r = 0.541, P = 0.002), superior perifoveal (r = 0.596, P = 0.001), nasal perifoveal (r = 0.511, P = 0.004), and inferior perifoveal (r = 0.469, P = 0.009) regions. In contrast, the correlation in the foveal region was not statistically significant (P = 0.056). **Figure 4**

Regarding the correlation between superficial VD and HbA1c levels, significant negative correlations were observed in specific regions. A strong negative correlation was found in the superior parafoveal region (r = -0.602, P < 0.001), with moderate negative correlations noted in the parafoveal (r = -0.493, P = 0.006) and temporal parafoveal (r = -0.506, P = 0.004) regions. Additionally, a mild negative correlation was observed in the temporal perifoveal region (r = -0.404, P = 0.027). Other retinal areas, did not show significant correlations. Similarly, deep VD exhibited strong negative correlations with HbA1c levels in the temporal parafoveal (r = -0.485, P = 0.007), superior parafoveal (r = -0.474, P = 0.008), and temporal perifoveal (r = -0.498, P = 0.005) regions. A moderate negative correlation was also observed in the parafoveal region (r = -0.441, P = 0.015). However, no significant

correlations were found in other areas. **Figure 5**

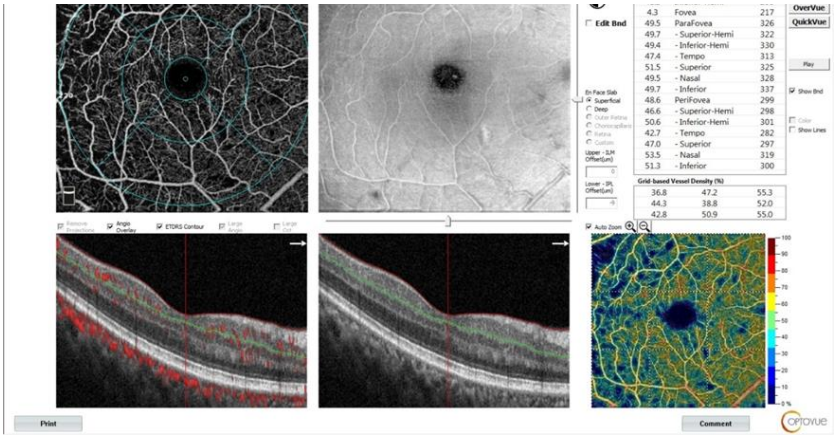
Univariate and multivariate linear regression analyses were conducted to examine HbA1c as a predictor of retinal thickness. The regression analyses were restricted to the significant correlations identified previously. Multivariate analysis, adjusted for age, gender, and diabetes duration, demonstrated that HbA1c was a significant predictor of retinal thickness in the temporal parafoveal, superior parafoveal, nasal parafoveal, inferior parafoveal, temporal perifoveal, nasal perifoveal, and inferior perifoveal regions. Similarly, univariate and multivariate linear regression analyses were performed to assess HbA1c as a predictor of superficial VD, focusing only on the previously identified significant correlations. After adjusting for age, gender, and DM duration, HbA1c remained a significant predictor of superficial VD in the parafoveal, temporal parafoveal, and superior parafoveal regions. Additionally, regression analyses were conducted to evaluate HbA1c as a predictor of deep VD, revealing that it was a significant predictor in the temporal parafoveal and temporal perifoveal regions after adjusting for confounding variables.

Table 1: General characteristics, superficial vascular density, OCT retinal thickness, Deep vascular density of the studied patients

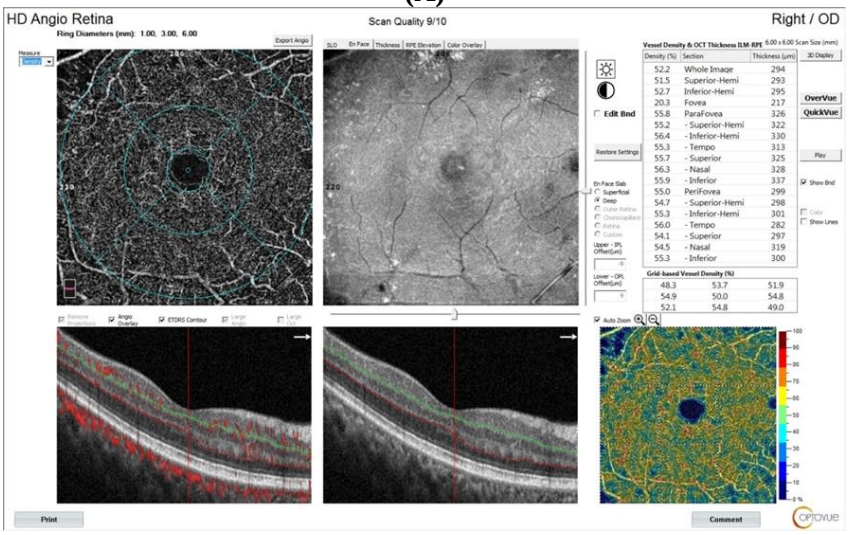
General characteristics			
Age (years)	**Mean ±SD**	51 ±8	
Sex Males	**n (%)**	3 (16.7)	
Females	**n (%)**	15 (83.3)	
BCVA	**Mean ±SD**	0.7 ±0.2	
DM duration (years)	**Median (range)**	10 (6 - 18)	
HbA1c	**Mean ±SD**	7.7 ±1	
	OCTA Superficial Vascular Density		**Deep vascular density**
Fovea	**Median (range)**	18.1 (4.3 - 34.4)	32.7 (10.6 - 48.7)
Parafovea	**Mean ±SD**	47.5 ±5.3	54.3 ±3.9
Temp para	**Mean ±SD**	46.3 ±6.4	54.5 ±3.5
Sup para	**Mean ±SD**	48.6 ±6.3	55.3 ±5.1
Nasal para	**Mean ±SD**	47.6 ±5.7	55.3 ±4.1
Inf para	**Mean ±SD**	47.6 ±5.5	52.1 ±5.4
Peri fovea	**Mean ±SD**	46.5 ±3.7	48.6 ±5.1
Temp peri	**Mean ±SD**	42.5 ±4.9	51.5 ±5.4
Sup peri	**Mean ±SD**	46.1 ±4.9	47.2 ±6.5
Nasal peri	**Mean ±SD**	50.8 ±3.9	47.5 ±6.2
Inf peri	**Mean ±SD**	46.7 ±3.9	48.1 ±6.5
FAZ	**Median (range)**		0.331 (0.073 - 0.81)
	OCT Thickness ILM- RPE		
Fovea		252 ±38	
Temp para		311 ±25	
Sup para		323 ±21	
Nasal para		322 ±24	
Inf para		324 ±30	
Temp peri		272 ±34	
Sup peri		285 ±28	
Nasal peri		294 ±20	

Inf peri	276 ±32

OCT: Optical coherence tomography; ILM: Inner limiting membrane; RPE: Retinal pigment epithelium; SD: Standard deviation; Temp: Temporal; Sup: Superior; Nasal; Inf: Inferior; Para: Parafoveal; Peri: Perifoveal.; n: Number; %: Percent; BCVA: Best corrected visual acuity; DM: Diabetes mellitus; HBA1C: Hemoglobin A1c; NPDR: Non-proliferative diabetic retinopathy



(A)



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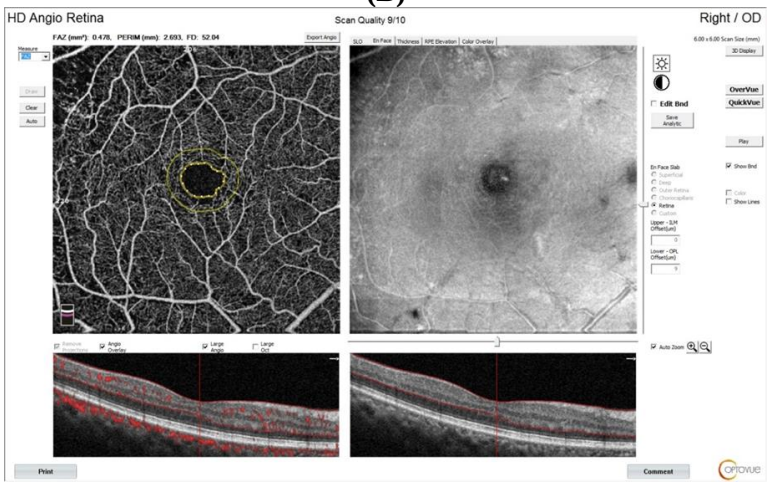
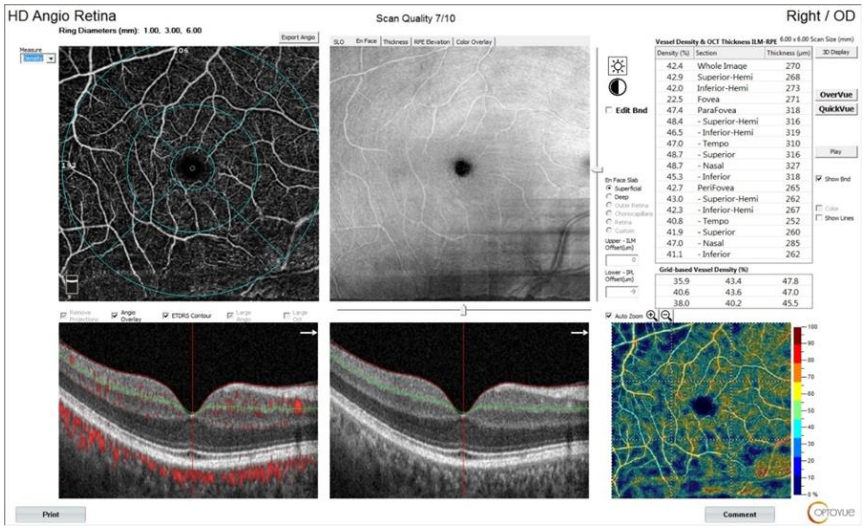


(C)

Figure 1: (A) RT eye sup VD, (B) RT eye deep VD, (C): RT eye Auto FAZ



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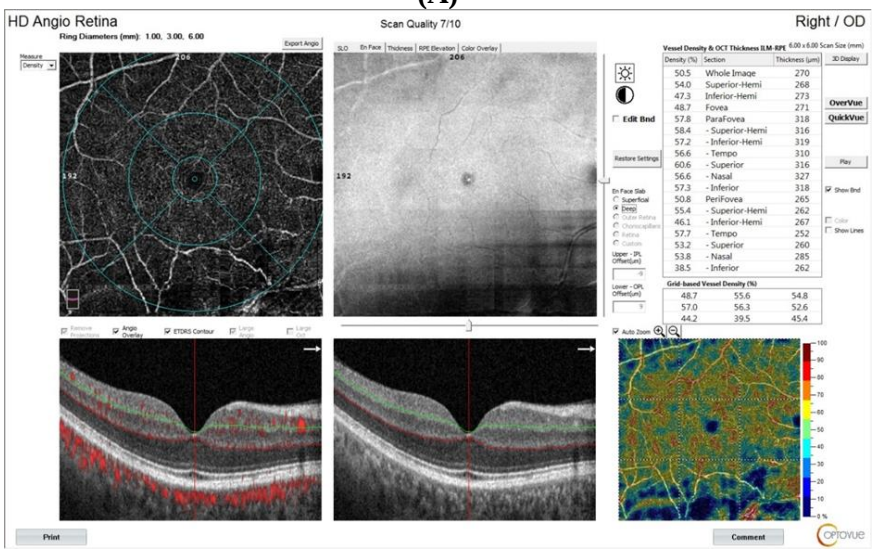

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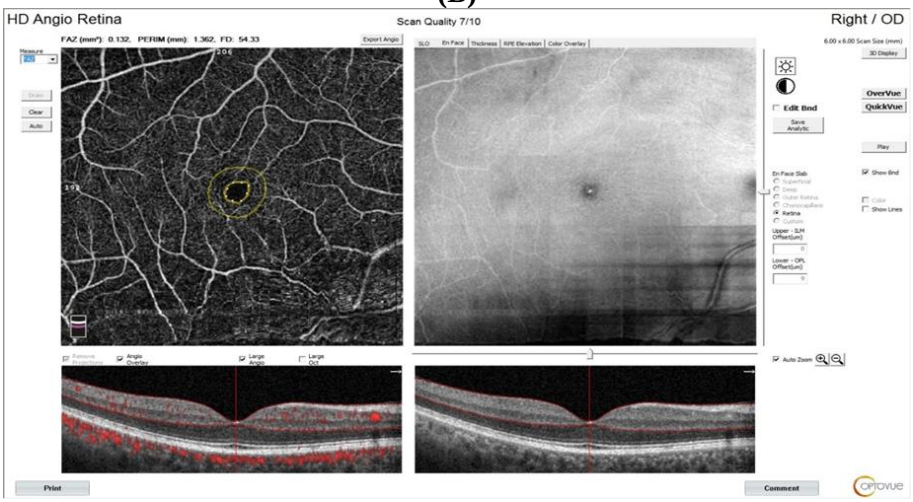

(C)

Figure 2: (A) RT eye sup VD, (B) RT eye deep VD, (C) RT eye Auto FAZ

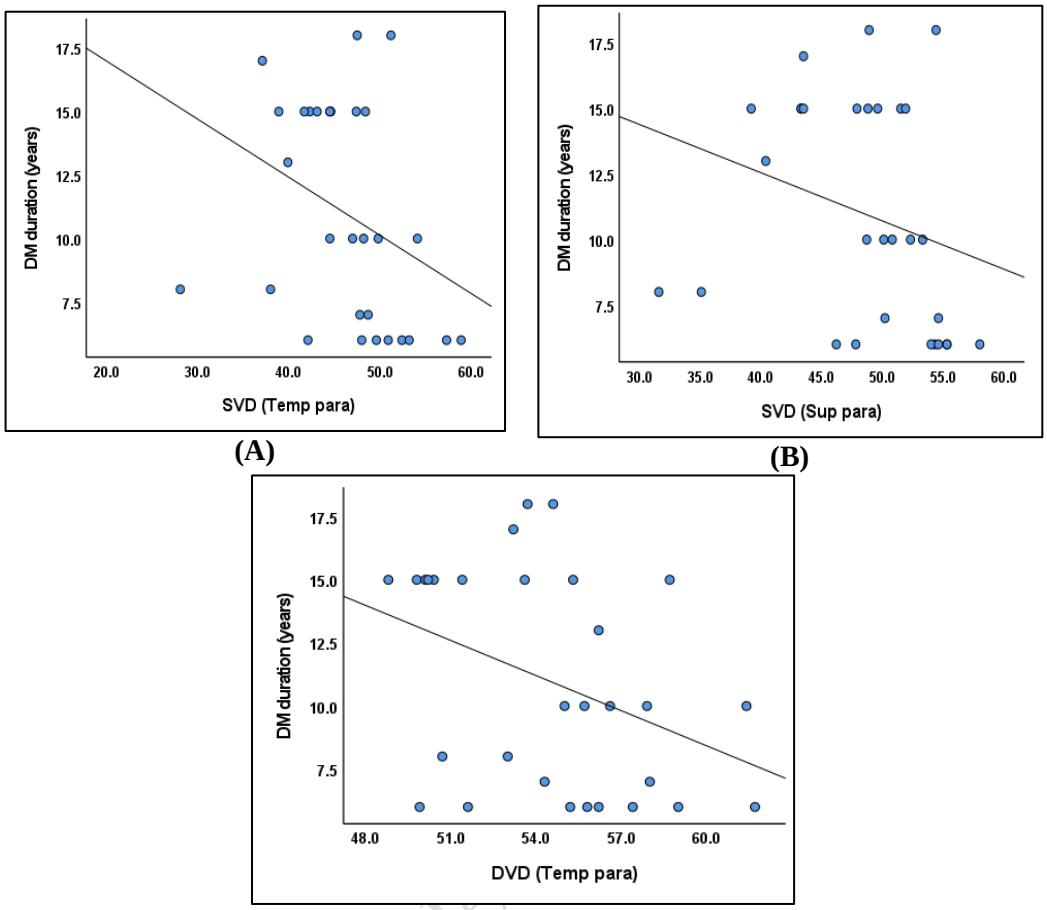

Figure 3: (A): Correlation between DM duration and superficial vascular density (Temp para), (B): Correlation between DM duration and superficial vascular density (Sup para), (C): Correlation between DM duration and deep vascular density (Temp para)

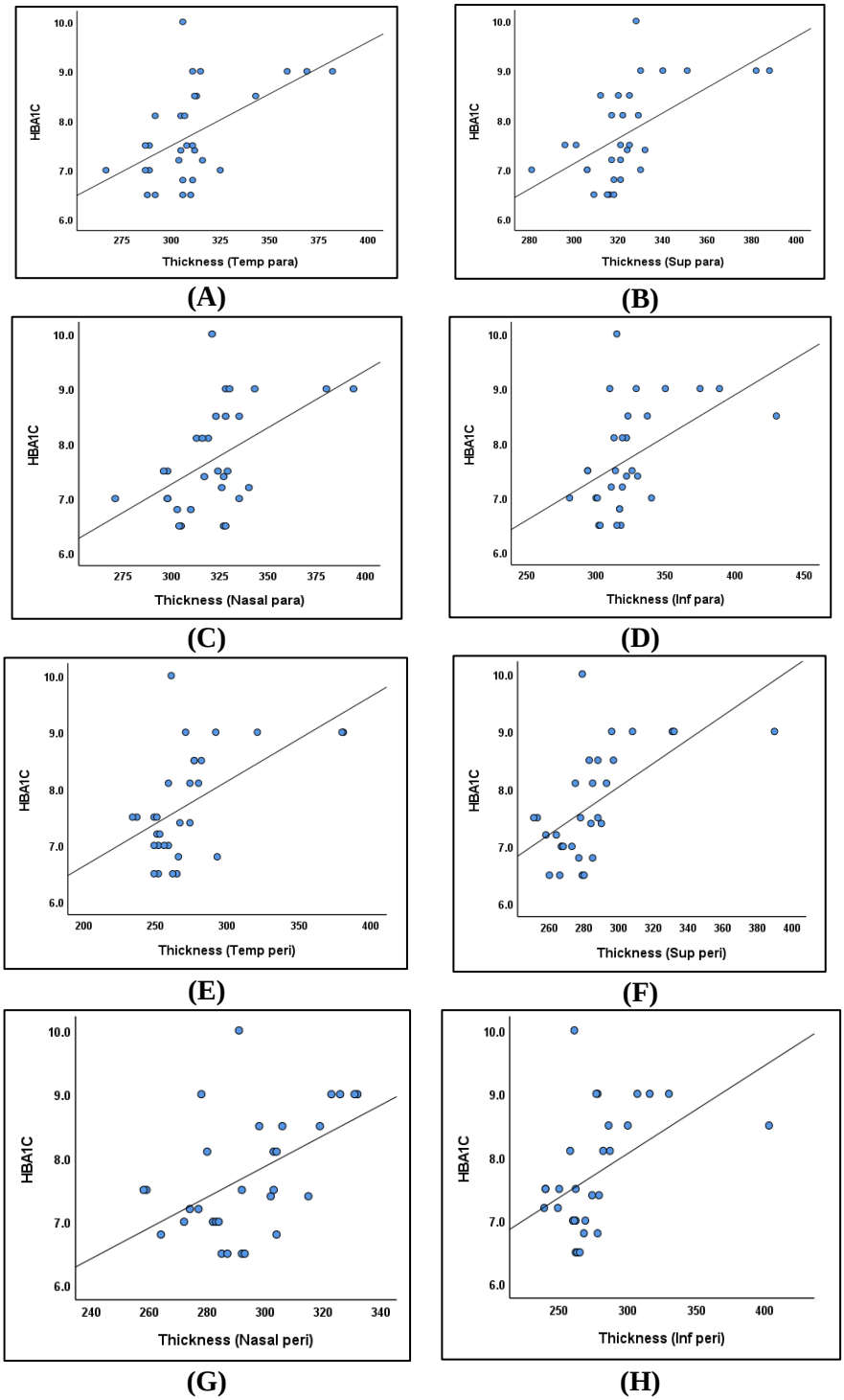

Figure 4: (A): Correlation between HbA1c and retinal thickness (Temp para), (B): Correlation between HbA1c and retinal thickness (Sup para), (C): Correlation between HbA1c and retinal thickness, (D): Correlation between HbA1c and retinal thickness (inf para), (E): Correlation between HbA1c and retinal thickness (Temp peri), (F): Correlation between HbA1c and retinal thickness (Sup peri), (G): Correlation between HbA1c and retinal thickness (Nasal peri), (H): Correlation between HbA1c and retinal thickness (Inf peri)

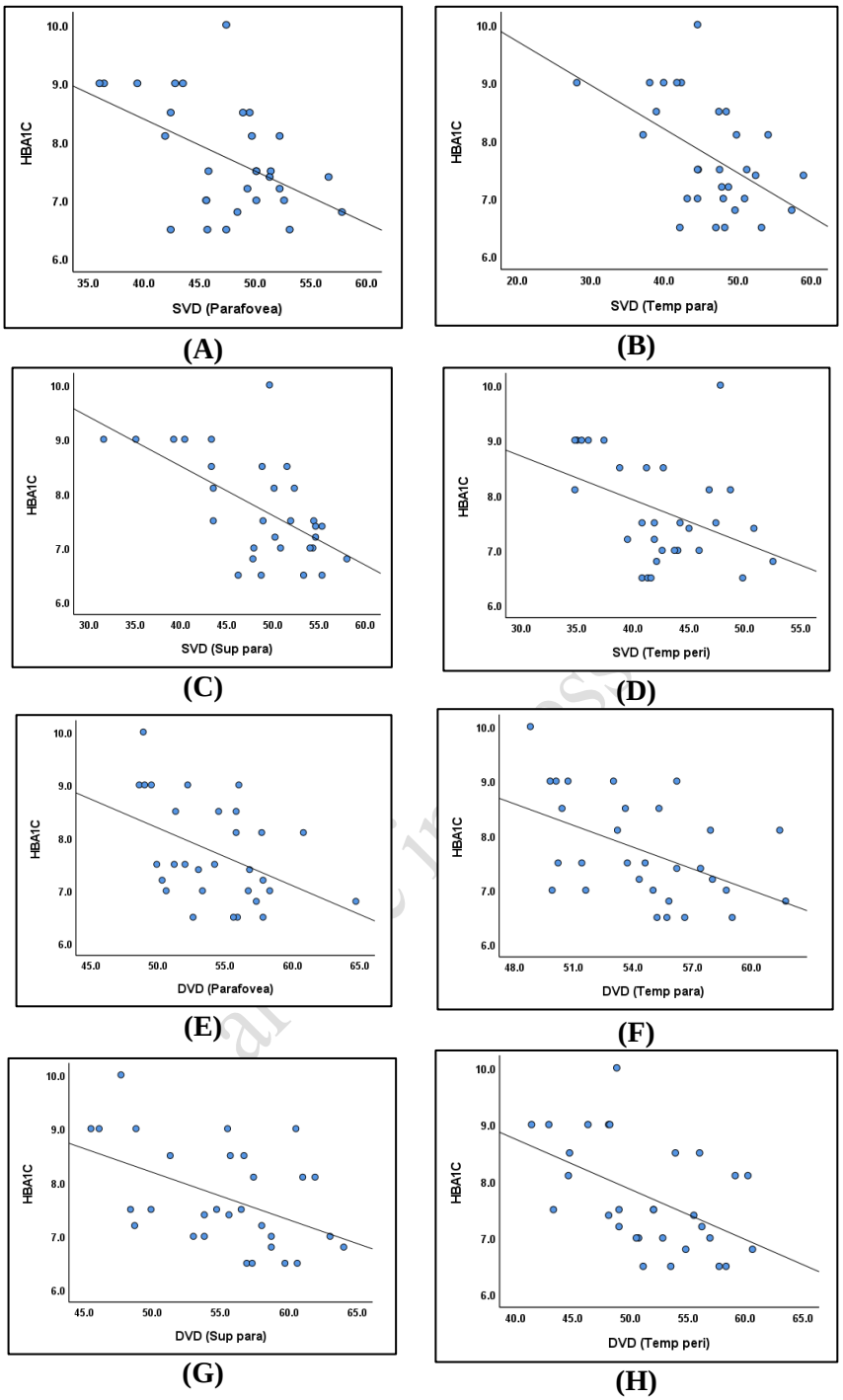

Figure 5: (A): Correlation between HbA1c and superficial vascular density (Parafovea), (B): Correlation between HbA1c and superficial vascular density (Temp para), (C): Correlation between HbA1c and superficial vascular density (Sup para), (D): Correlation between HbA1c and superficial vascular density (Temp peri), (E):Correlation between HbA1c and deep vascular density (Parafovea), (F): Correlation between HbA1c and deep vascular density (Temp para), (G): Correlation between HbA1c and deep vascular density (Sup para), (H): Correlation between HbA1c and deep vascular density

Discussion

Using OCTA, this research looked at how macular vessel density correlated with HbA1c levels in NPDR patients from Egypt. In particular, we found that parafoveal and perifoveal microvascular alterations in the retina are significantly associated with glycemic control. Further evidence for the role of hyperglycemia in the structural and vascular alterations of the retina in diabetic retinopathy is provided by these results.

Our analysis revealed significant negative correlations between superficial and deep vascular density (VD) and the duration of diabetes mellitus, particularly in the temporal parafoveal region. These findings suggest that longer disease duration is associated with progressive capillary dropout and reduced perfusion in this specific region. The temporal parafovea may be particularly vulnerable due to its high metabolic demand and blood flow, making it more susceptible to the effects of prolonged hyperglycemia, which can lead to microvascular occlusions and endothelial dysfunction [(9)].

Our findings are consistent with prior studies reporting a progressive decline in retinal vessel density with increasing DM duration. Li et al. [(10)] demonstrated that both superficial and deep capillary plexus vessel density (SVD and DVD) were significantly negatively correlated with DM duration and visual acuity, indicating that microvascular changes occur early in diabetic retinopathy and may contribute to functional vision loss. Similarly, Ghassemi et al. [(11)] found that vessel density decreases as diabetic retinopathy progresses, particularly in the deep capillary plexus, reinforcing the vulnerability of deeper retinal layers to chronic hyperglycemia.

A significant positive correlation was observed between HbA1c levels and retinal thickness in multiple parafoveal and perifoveal regions, suggesting that poor glycemic control contributes to structural retinal changes. The accumulation of extracellular fluid and early diabetic macular edema (DME) may explain this increase in thickness, as chronic hyperglycemia leads to vascular leakage and blood-retinal barrier dysfunction [(12)]. In contrast, no significant correlation was found in the foveal region, likely due to its avascular nature and distinct metabolic regulation, which makes it less prone to early vascular compromise [(13)].

These findings align with previous studies linking HbA1c levels to macular thickness. Wong et al. (2020) proved that reduced hemoglobin A1c levels, indicative of improved glycemic control, are linked to a more favorable anti-VEFG therapy response in diabetic macular edema (DME), implying that hemoglobin A1c affects retinal thickness and treatment results. Similarly, Teberik et al. [(14)] highlighted the importance of glycemic control in structural retinal changes by finding a significant

correlation between HbA1c and macular thickness in diabetic patients.

However, some studies have reported conflicting results. Lobo et al. [15] although they identified that hemoglobin A1c increased the likelihood of blood-retinal barrier disruption, they were unable to establish a causal relationship between the two variables in people with type 2 diabetes. Possible explanations for this variation include differences in research methodology, sample size, or individual variability in glycemic response and microvascular damage.

Significant negative correlations were observed between HbA1c levels and superficial VD in the superior parafoveal and temporal parafoveal regions, while no significant correlations were found in the foveal or other perifoveal regions. These results suggest that hyperglycemia preferentially affects specific vascular regions, possibly due to differences in regional blood flow and susceptibility to metabolic stress [16].

Chronic hyperglycemia is known to induce microvascular damage through endothelial dysfunction, capillary dropout, and impaired autoregulation, leading to a reduction in superficial vessel density [17]. Studies have shown that elevated HbA1c levels correlate with reduced vascular density, with the most pronounced changes occurring in the parafoveal regions as diabetic retinopathy progresses [18].The observed regional variability may be attributed to the differing metabolic demands and structural characteristics of retinal vascular networks, with some areas demonstrating greater resilience to glycemic stress [19].

Deep VD was also significantly negatively correlated with HbA1c in the temporal parafoveal and perifoveal regions, reinforcing the notion that prolonged hyperglycemia leads to microvascular rarefaction in metabolically active areas of the retina. Ischemic injury can cause serious problems for the deep capillary plexus because of the intricate system of vessels that it uses to ensure sufficient blood flow. Endothelial dysfunction, decreased capillary blood flow, hypoxia, and vascular degeneration are all consequences of chronic hyperglycemia, which causes glycation of vascular proteins and the production of advanced glycation end-products (AGEs) [20].

Our results align with findings from Ghassemi et al. [21] , who reported significant reductions in deep capillary plexus VD as diabetic retinopathy severity increased. Li et al. [10] further demonstrated that parafoveal vessel density in the deep retinal vascular layer was negatively correlated with fasting blood glucose, supporting the link between metabolic control and vascular deterioration. These findings highlight the importance of monitoring deep vascular changes as early indicators of diabetic microangiopathy.

Multivariate regression analysis confirmed that HbA1c is a significant

predictor of both retinal thickness and vascular density, particularly in parafoveal and perifoveal regions, even after adjusting for age, gender, and DM duration. This emphasizes the role of glycemic control as a key determinant of retinal microvascular health.

Our findings are consistent with Chua et al. [22], who demonstrated that HbA1c levels were strongly associated with retinal layer thickness in diabetic patients, supporting the hypothesis that diabetic retinal neurodegeneration begins before overt clinical signs of diabetic retinopathy. Similarly, Lavia et al. [23] found that diabetic patients had much lower levels of superficial and deep vascular density compared to healthy controls, and that there were strong correlations between better control of blood sugar and lower levels of vascular density.

Clinically, these results underscore the potential of OCTA-derived metrics as valuable biomarkers for detecting early diabetic retinopathy changes before visual impairment occurs. The predictive value of HbA1c for retinal vascular and structural changes highlights its utility in risk stratification and early intervention. Monitoring HbA1c levels, alongside OCTA assessments, may improve screening and management strategies for diabetic retinopathy, ultimately reducing the burden of vision-threatening complications**.**

Conclusion

This study demonstrates via OCTA that glycemic control, as indicated by HbA1c levels, is significantly associated with macular thickness and vascular density in NPDR patients. The strongest correlations were observed in the parafoveal and perifoveal regions, particularly in the temporal and superior quadrants. These findings align with previous research, reinforcing the role of chronic hyperglycemia in retinal microvascular compromise. Given the predictive value of HbA1c in retinal changes, integrating OCTA assessments into routine diabetic retinopathy screening could enhance early detection and targeted management strategies. Further longitudinal studies are needed to evaluate the long-term impact of glycemic control on retinal microvascular integrity and visual function.

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