ASSOCIATION BETWEEN HBA1C LEVEL AND RETINAL NERVE FIBER LAYER THICKNESS IN NON-PROLIFERATIVE DIABETIC RETINOPATHY

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ABSTRACT

Objective: To investigate the association between Hemoglobin A1c (HbA1c) and retinal nerve fiber layer (RNFL) thickness in patients with type 2 diabetes mellitus (DM) at the non-proliferative diabetic retinopathy stage, considering that retinal neurodegeneration is an early event in diabetic retinopathy (DR). **Methods:** This cross-sectional study included 50 patients with type 2 DM, categorized into without diabetic retinopathy (NDR, n=30) and non-proliferative diabetic retinopathy (NPDR, n=20) groups. Peripapillary RNFL thickness was measured using spectral-domain optical coherence tomography (SD-OCT). Systemic data, including HbA1c, blood pressure, BMI, and DM duration, were collected and analyzed for correlations. **Results:** The NPDR group exhibited a significantly longer DM duration, higher systolic blood pressure, and elevated HbA1c levels compared to the NDR group ($p<0.05$). Average RNFL thickness was significantly lower in the NPDR group for both the right (94.3 ± 5.53 µm vs. 100.77 ± 5.26 µm, $p<0.001$) and left eyes (95.0 ± 5.38 µm vs. 100.27 ± 6.65 µm, $p=0.005$). A significant negative correlation was found between average RNFL thickness and HbA1c levels, duration of DM, and systolic blood pressure. **Conclusion:** RNFL thinning is a significant structural change in early DR, strongly associated with poor glycemic control, longer disease duration, and elevated systolic blood pressure. These findings highlight the potential of RNFL thickness as a biomarker for early neurodegeneration and emphasize the importance of managing systemic risk factors.

Keywords: *Diabetic Retinopathy, Retinal Nerve Fiber Layer, HbA1c, Neurodegeneration, Optical Coherence Tomography, Type 2 Diabetes.*

I. INTRODUCTION

Diabetic retinopathy (DR) is one of the most common microvascular complications of diabetes mellitus (DM) and a leading cause of vision loss among the working-age population worldwide [2]. Traditionally, DR has been considered a microvascular disease, with clinical diagnosis primarily based on structural changes in retinal blood vessels observable through fundoscopy. However, once the disease progresses to the proliferative stage or involves macular edema, treatment efficacy is often significantly reduced. Therefore, finding new methods for earlier diagnosis and intervention is a critical need in clinical ophthalmology.

In recent years, mounting evidence suggests that retinal neurodegeneration is an early event in the pathogenesis of DR, potentially preceding clinically detectable microvascular abnormalities. Among the neural changes, the thinning of the retinal nerve fiber layer (RNFL) is considered one of the earliest lesions [3]. The advent of Optical Coherence Tomography (OCT) has provided an effective, non-invasive tool that allows for high-resolution cross-sectional imaging of the retina, enabling precise

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quantification of RNFL thickness [1]. This opens a new avenue for a better understanding of the neurodegenerative process at different stages of the disease.

Numerous studies have demonstrated the thinning of inner retinal layers, including the RNFL and ganglion cell layer (GCL), in patients with type 1 and 2 DM even without clinical manifestations of DR [4-8]. Peripapillary RNFL thickness has been shown to be inversely correlated with disease duration, severity, and Hemoglobin A1c (HbA1c) levels [4]. Visual function decline has also been found to accompany these structural changes. Furthermore, systemic risk factors such as duration of diabetes, blood pressure, and particularly glycemic control (via HbA1c) have been proven to have a significant impact on the formation and progression of microvascular lesions in DR. However, the role of these factors in retinal neurodegeneration has not been fully elucidated.

Although the link between risk factors and microvascular damage has been extensively studied, their role in the pathogenesis of retinal neurodegeneration remains unclear. Therefore, this study was conducted to investigate the association between HbA1c levels and retinal nerve fiber layer thickness in patients with non-proliferative type 2 diabetic retinopathy. The study will focus on clarifying the influence of systemic risk factors, especially glycemic control, on the retinal neurodegenerative process, thereby providing further evidence for the early diagnosis and timely intervention of this complication.

II. METHODS

1. Study Design

This was a descriptive cross-sectional study.

2. Study Population

- **Population and Venue:** The study population consisted of patients with type 2 diabetes mellitus attending outpatient consultations and treatment at the Department of Endocrinology, Le Van Thinh Hospital, Ho Chi Minh City. Data were collected from June 2022 to November 2022.
- **Sample Size:** The minimum required sample size was calculated to be 44 patients. A total of 50 patients who met the criteria were included in the study.
- **Inclusion Criteria:**
  - Patients diagnosed with type 2 diabetes with either normal retina (Without Diabetic Retinopathy, NDR) or mild non-proliferative diabetic retinopathy (NPDR).
  - Patients indicated for OCT scanning as per the hospital's routine procedures.
  - Patients who provided written informed consent to participate.
- **Exclusion Criteria:**
  - Patients with a diagnosis of glaucoma, a family history of glaucoma, or a clinical finding of a cup-to-disc (C/D) ratio > 0.5 or a C/D asymmetry between the two eyes > 0.2.
  - History of neuro-ophthalmic diseases, uveitis, or other retinal pathologies.
  - Patients with a spherical equivalent refractive error > 3 Diopters or an axial length > 25 mm.
  - History of refractive surgery, intraocular surgery, or retinal laser photocoagulation.

3. Study Procedure

Eligible patients were invited to participate after their routine HbA1c test results were available. After a thorough explanation of the study's purpose and procedures, consenting patients signed an informed consent form and underwent the following steps:

- **Collection of General Information and History:** Administrative information,

duration of diabetes, and history of other eye diseases were collected. Systemic parameters including HbA1c, blood pressure, height, and weight were obtained from existing outpatient medical records.

- **Comprehensive Eye Examination:** All patients were examined by the same ophthalmologist. The examination included visual acuity measurement, intraocular pressure measurement using a Schiotz tonometer, and anterior and posterior segment examination with a slit lamp and a Volk 90D lens after pupil dilation. Based on fundoscopy findings, patients were divided into two groups: the NDR group and the NPDR group.
- **Ocular Biometry:** Axial length was measured using an A-scan ultrasound device.
- **RNFL OCT Imaging:** The peripapillary retinal nerve fiber layer (RNFL) thickness was assessed using an SD-OCT machine (Optovue model RTVue XR Avanti). Data on the average thickness and the thickness in four quadrants (superior, inferior, nasal, temporal) were recorded for analysis.

4. Study Variables

The main variables collected included: age, gender, duration of DM, body mass index (BMI), systolic blood pressure, diastolic blood pressure, HbA1c level, and RNFL thickness (average and in four quadrants).

5. Statistical Analysis

Data were managed using Epidata 3.1 software and analyzed with SPSS 20.0.

- **Descriptive Statistics:** Categorical variables were presented as frequencies and percentages. Normally distributed quantitative variables were expressed as mean ± standard deviation; non-normally distributed quantitative variables were expressed as median and interquartile range.
- **Analytical Statistics:**
  - The Chi-square test (or Fisher's exact test) was used to compare categorical variables between the two groups.
  - The independent t-test or Mann-Whitney U test was used to compare quantitative variables between the two groups.
  - The Pearson correlation coefficient (for normally distributed data) and Spearman correlation coefficient (for non-normally distributed data) were used to assess the association between quantitative variables.
- A p-value of < 0.05 was considered statistically significant.

6. Ethical Considerations

The study was approved by the Institutional Review Boards of the University of Medicine and Pharmacy at Ho Chi Minh City, and Le Van Thinh Hospital. All personal patient information was coded and kept confidential. Participation was entirely voluntary and did not affect the patients' treatment.

III. RESULTS

Our study included 50 patients with type 2 diabetes, who were divided into two groups: Without diabetic retinopathy (NDR) group, comprising 30 patients (60%), and the non-proliferative diabetic retinopathy (NPDR) group, comprising 20 patients (40%).

1. General Characteristics of the Study Population

The baseline characteristics of the study participants are presented in Table 1. The NPDR group had a significantly longer duration of diabetes, higher systolic blood pressure, and higher HbA1c levels compared to the NDR group. There were no statistically significant differences in age, gender, BMI, or diastolic blood pressure between the two groups.

Table 1: ***Comparison of baseline characteristics between the two study groups***

Characteristic	NDR group (n=30)	NPDR group (n=20)	p-value
Age (years)	58.57 ± 7.79	64.75 ± 9.56	0.07
Gender (Female/Male)	17/13 (56.7%/43.3%)	11/9 (55%/45%)	0.907
Duration of DM (years)	7.9 ± 2.35	11.1 ± 2.22	< 0.001
BMI (kg/m²)	23.35 ± 1.25	23.44 ± 1.7	0.825
Systolic blood pressure (mmHg)	127.33 ± 6.79	132.7 ± 5.67	0.005
Diastolic blood pressure (mmHg)	77.93 ± 5.7	79.1 ± 4.7	0.55
HbA1c (%)	7.93 ± 1.6	9.95 ± 1.7	< 0.001
Data are presented as mean ± standard deviation or frequency (percentage).			

2. Comparison of Retinal Nerve Fiber Layer (RNFL) Thickness

The RNFL thickness in the NPDR group was statistically significantly thinner than in the NDR group across multiple locations, as detailed in Table 2. Notably, the average RNFL thickness in both eyes was considerably thinner in the NPDR group.

Table 2: ***Comparison of RNFL thickness (µm) between the NDR and NPDR groups***

Eye	RNFL Location	NDR group (n=30)	NPDR group (n=20)	p-value
Right Eye	Average	100.77 ± 5.26	94.3 ± 5.53	< 0.001
	Superior	121.63 ± 8.84	112.95 ± 13.35	0.008
	Inferior	126.8 ± 9.67	118.8 ± 9.64	0.006
	Nasal	77.17 ± 7.8	75.85 ± 8.6	0.58
	Temporal	78.2 ± 8.4	69.8 ± 8.98	< 0.001
Left Eye	Average	100.27 ± 6.65	95 ± 5.38	0.005
	Superior	123.43 ± 11.113	115.40 ± 11.44	0.017
	Inferior	127.1 ± 13.47	121.4 ± 12.75	0.14
	Nasal	75.27 ± 9.07	72.1 ± 8.8	0.046
	Temporal	75.23 ± 6.98	71.3 ± 8.68	0.083
Data are presented as mean ± standard deviation.				

3. Correlation between RNFL Thickness and Risk Factors

Correlation analysis revealed a negative association between RNFL thickness and HbA1c levels, duration of DM, and systolic blood pressure. No statistically significant correlation was found between RNFL thickness and BMI. Detailed results are presented in Table 3.

Table 3: ***Correlation between RNFL thickness and systemic risk factors***

Risk Factor	Eye	RNFL Location	Correlation Coefficient (r)	p-value
HbA1c (%)	Right	Average	-0.404	0.004
		Superior	-0.287	0.043
	Left	Average	-0.389	0.005
		Superior	-0.438	0.001
		Inferior	-0.303	0.033
Duration of DM (years)	Right	Average	-0.485	< 0.001
		Superior	-0.281	0.048
		Inferior	-0.313	0.027
	Left	Average	-0.395	0.004
		Superior	-0.329	0.02
		Inferior	-0.309	0.029
Systolic BP (mmHg)	Right	Average	-0.464	0.001
		Inferior	-0.433	0.002
		Nasal	-0.335	0.017
	Left	Average	-0.378	0.007
		Inferior	-0.382	0.006
BMI (kg/m²)	Right/Left	All locations	No significant correlation	> 0.05
Only statistically significant correlations (p < 0.05) are shown, except for BMI.				

IV. DISCUSSION

This study was based on the hypothesis that retinal neurodegeneration is an early manifestation in the pathogenesis of diabetic retinopathy (DR), potentially preceding clinically detectable microvascular changes. The primary objective was to investigate the association between the glycemic control indicator HbA1c, other systemic risk factors, and retinal nerve fiber layer (RNFL) thickness in type 2 diabetes mellitus (DM) patients with no or non-proliferative retinopathy.

The main findings of the study confirmed the initial hypothesis. The results revealed significant thinning of the RNFL in the non-proliferative diabetic retinopathy (NPDR) group compared to the group with no retinal complications (NDR). More importantly, the study identified a statistically significant negative correlation between RNFL thickness and key risk factors, including HbA1c levels, duration of DM, and systolic blood pressure. These results suggest that poor glycemic control and other systemic risk factors are directly associated with the extent of neural structural damage in the retina during the early stages of the disease.

Our results are consistent with the majority of published studies. Regarding sample characteristics, the duration of DM, systolic blood pressure, and HbA1c levels were all significantly higher in the NPDR group than in the NDR group, which is similar to the findings of studies by Zhong-Qi Wan (2021) [7], Huiyan Zhang (2014) [8], and Abd-Rashid (2018) [5], confirming these as important risk factors for disease progression.

In terms of retinal structural changes, the finding of RNFL thinning in the NPDR group compared to the NDR group is also consistent with the work of Zhong-Qi Wan (2021) [7] and Rui Shi (2018) [6]. Specifically, the average, superior, and inferior quadrant RNFL thicknesses were the most affected areas. This strengthens the evidence that neurodegeneration is an early process. However, the literature also reports inconsistencies, with some studies by Srinivasan et al. finding no significant difference in RNFL thickness, possibly due to differences in study populations and measurement methods.

The negative correlation between HbA1c and RNFL thickness that we found is also corroborated by studies from Zhong-Qi Wan (2021) [7] and Rui Shi (2018) [6], indicating that chronic hyperglycemia has a direct negative impact on neural structures. Similarly, the correlation between disease duration, systolic blood pressure, and RNFL thinning has been reported in previous studies, underscoring the multifactorial role in the pathogenesis of retinal neurodegeneration.

The results of this study can be explained within the framework of the model where “neurodegeneration” is a core and early component of DR. This hypothesis posits that damage to retinal neurons (particularly ganglion cells and their axons, which form the RNFL) occurs in parallel with or even before microvascular lesions.

The mechanism behind RNFL thinning is complex. Chronic hyperglycemia (reflected by high HbA1c levels) induces a cascade of metabolic disturbances, including oxidative stress, neuroinflammation, and glutamate-mediated excitotoxicity. These processes directly trigger apoptosis of nerve cells, leading to the irreversible loss of axons and thinning of the RNFL.

The association with disease duration and systolic blood pressure reinforces the concept of the "neurovascular unit" in which the function and survival of neurons and blood vessels are intricately linked. Prolonged disease duration and high blood pressure damage vascular endothelial cells, leading to reduced perfusion, local hypoxia, and exacerbation of oxidative stress, thereby causing secondary damage to adjacent nerve cells. Thus, neurodegeneration and microvascular pathology may be two mutually reinforcing processes in a pathological cycle.

The findings of this study have significant implications for clinical practice. First, it provides strong evidence that DR is not merely a microvascular disease but also a neurodegenerative condition.

Second, the study affirms the value of measuring RNFL thickness with OCT as a potential, non-invasive biomarker for the early detection of retinal neural damage, even before signs of DR are visible on fundoscopy. This opens up possibilities for earlier screening and intervention to preserve patients' visual function.

Finally, establishing a strong correlation between HbA1c, blood pressure, and RNFL thickness once again highlights the critical importance of tightly controlling systemic risk factors. This not only helps prevent known vascular complications but also plays a direct role in protecting the neural structure of the retina, slowing the neurodegenerative process in patients with DM.

The study has several notable strengths. The research design applied strict exclusion criteria, such as excluding patients with glaucoma, high refractive error, or hypertension, to minimize confounding factors that could affect RNFL thickness, thereby increasing the accuracy of assessing the impact of DM.

However, the study also has some limitations that should be considered. Its cross-sectional design only allows for the identification of associations at a single point in time and cannot establish causality. With 50 patients, the sample size is relatively small, which may limit the generalizability of the results to a larger population. The study focused on structural changes (RNFL thickness) but did not correlate them with functional visual deficits (e.g., visual fields), which would be an important direction for future research. The study did not analyze the history of DM medication use, which is a factor that could influence the results. Furthermore, subclinical cases of primary open-angle glaucoma cannot be entirely ruled out.

V. CONCLUSION

This study of 50 patients with type 2 diabetes demonstrated significant thinning of the retinal nerve fiber layer (RNFL) in the group with non-proliferative diabetic retinopathy (NPDR) compared to the group with no retinal complications (NDR). The results indicate a statistically significant negative correlation between RNFL thickness and HbA1c levels, duration of disease, and systolic blood pressure.

These findings confirm that RNFL thinning is an early structural change in diabetic retinopathy. Therefore, strict control of blood glucose and systolic blood pressure may be an effective strategy to prevent or slow retinal neurodegeneration in the early stages of diabetes.

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