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Original Article

Dyslipidemia and reduced retinal layer thicknesses in mild to moderate non-proliferative diabetic retinopathy

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Abstract: Objective: To investigate the changes in ganglion cell layer-inner plexiform layer (GCL-IPL) thickness and its association with peripheral blood indices in non-proliferative diabetic retinopathy (NPDR). Methods: In this cross-sectional study, 132 participants were categorized into three groups: 30 healthy volunteers (control group), 50 diabetic patients with non-diabetic retinopathy (NDR group), and 52 patients with NPDR. Optical coherence tomography (OCT) was used to measure the retinal nerve fiber layer (RNFL) and GCL-IPL thicknesses in the macula. The associations between RNFL loss and systemic risk factors for DR, such as diabetes duration, triglyceride (TG), total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and hemoglobin A1c (HbA1c) were evaluated. Results: The average, superior, and nasal thicknesses in the NDR and NPDR groups were significantly thinner compared to the control group (P=0.002, 0.020, 0.090, respectively). Similarly, GCL-IPL thicknesses in the 3 mm and 6 mm zones of the NDR and NPDR groups were thinner than those in the control group (P=0.040, 0.022, 0.037, respectively). Temporal thicknesses in the 3 mm range of the NDR and NPDR groups were also thinner than in the control group (P=0.010). Superior RNFL thickness was positively correlated with HbA1c (r=0.200, P=0.044), and negatively correlated with HDL (r=-0.198, P=0.047). The average inferior and nasal GCL-IPL thicknesses were negatively correlated with TC across the 3 mm zone (r=-0.211, P=0.033; r=-0.224, P=0.023; r=-0.227, P=0.022). Additionally, the average thickness of GCL-IPL in the 6-mm range were positively correlated with the duration of diabetes (r=0.196, P=0.048). Conclusion: This study demonstrates that dyslipidemia in diabetic patients correlates with reductions in RNFL and GCL-IPL thicknesses, suggesting a role in the pathogenesis of diabetic retinopathy.

Keywords: Diabetic retinopathy, retinal nerve fiber layer, retinal ganglion cells, risk factors

Introduction

With ongoing social and economic changes and increased dietary diversity, diabetes mellitus (DM), characterized by chronic hyperglycemia, has emerged as a global health issue significantly affecting life in the 21st century. According to recent statistics from the International Diabetes Federation, the number of individuals aged 20-79 with diabetes in 220 countries and regions is projected to rise from 415 million in 2015 (an 8.8% prevalence rate) to 642 million by 2040 (a 10.4% prevalence rate), with about 75% residing in developing countries [1]. Diabetic retinopathy (DR), affecting up to 53% of individuals with diabetes, is a significant microvascular complication [2].

Historically, DR has primarily been regarded as a vascular disorder. However, extensive research into the pathogenesis of retinal microangiopathy reveals that abnormal glucose levels disrupt retinal microcirculation. Key pathologic processes include early blood-retinal barrier disruption, capillary basement membrane thickening, and retinal cell loss [3]. Advanced stages involve neovascularization with clinical manifestations such as retinal microaneurysms, hard exudates, and small hemorrhages [4].

Recent animal and histopathologic studies have indicated that neuronal damage in DR precedes vascular changes [5]. This damage includes neuronal apoptosis, loss of retinal ganglion cells (RGCs), macrophage-mediated inflammation, and thinning of the inner retina [5]. The neurodegenerative aspect of DR primarily involves RGC damage, detectable in the retinal

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nerve fiber layer (RNFL), ganglion cell layer (GCL), and inner plexiform layer (IPL), collectively known as the ganglion cell complex. Optical coherence tomography (OCT) measures the thickness of these layers to assess RGC loss [6]. The nerve fibers run parallel to the retinal surface, spread across the retina outside the fovea, and converge at the optic disc to form the optic nerve. Loss of ganglion cells thus leads to RNFL thinning [7].

Consequently, DR should be considered not only as a microvascular disease but also as a neurodegenerative disorder. Spectral-domain OCT (SD-OCT) is a non-invasive, non-contact method that clearly delineates the ten-layer retinal structure of the macula, essential for early DR diagnosis [8]. Recent advancements in OCT image analysis algorithms now allow for objective quantification of inner retinal RGC loss [9].

Several factors, including blood lipid levels and body mass index, can accelerate the progression of DR [10, 11]. Dyslipidemia has been recognized as an independent risk factor for DR since 2002 [12]. Recent studies have also linked hypercholesterolemia and hypertriglyceridemia with DR [13]. These risk factors may contribute to the neurodegenerative changes observed in the retinas of patients with DR. Recent research highlights the lipid-lowering drug Norbert as a promising treatment for reducing retinal cell death [14].

This study utilized SD-OCT to examine changes in the thickness of the optic nerve fiber layer and the GCL-IPL in diabetic patients, both before and after the onset of retinopathy. By investigating factors associated with mild to moderate DR and their effects on retinal neurodegeneration, this paper provides a new perspective for understanding the pathogenesis of DR's neurodegenerative changes and for advancing early clinical diagnosis and treatment.

Materials and methods

Case selection and ethic approval statement

This retrospective cohort study was approved by the ethics committee of Ningde Municipal Hospital of Ningde Normal University (approval number: 201611008). Using the electronic medical record system, we identified 102 patients (102 eyes) diagnosed with non-proliferative diabetic retinopathy (NPDR) (52 eyes) and diabetic patients with non-diabetic retinopathy (NDR) (50 eyes) from July 2017 to July 2018. Patients were diagnosed based on the International Classification of Diabetic Retinopathy criteria, which relies on postnatal ophthalmoscopy findings (**Table 1**) [15]. 30 healthy volunteers (30 eyes) were included as a control group.

Inclusion criteria for NPDR and NDR groups: 1) Corrected visual acuity ≥4.6 (standard logarithmic visual acuity chart); 2) Spherical equivalent between -6.00D and +3.00D; 3) Intraocular pressure between 10 mmHg and 21 mmHg, with no previous history of high intraocular pressure and an eye pressure difference <5 mmHg; 4) Diagnosis of type 2 diabetes according to the WHO's 1999 criteria; 5) Availability of high-quality and complete data.

Additionally, 30 healthy volunteers (30 eyes) were included as the control group, with the following criteria: 1) Corrected visual acuity ≥4.9 (standard logarithmic visual acuity chart); 2) Spherical equivalent between -6.00D and +3.00D; 3) Intraocular pressure between 10 mmHg and 21 mmHg; 4) with no previous history of high intraocular pressure, an eye pressure difference <5 mmHg, and no DR or other fundus diseases.

Exclusion Criteria for all groups: 1) History of internal eye surgery, laser treatment, or trauma; 2) Refractive media opacities affecting fundus examination or other conditions precluding stable fixation; 3) Other fundus diseases such as age-related macular degeneration, macular edema, high myopia, glaucoma, hypertensive retinopathy, ischemic optic neuropathy, and central serous chorioretinopathy; 4) Systemic diseases such as hypertension and renal insufficiency; 5) Ocular surface diseases such as keratitis, corneal scars, and iris adhesions; 6) Incomplete data.

Data extraction

Subjects underwent vision and intraocular pressure examinations, slit lamp microscopy of the anterior segment, and fundus examinations including direct ophthalmoscopy, examination with a +90D lens, indirect ophthalmoscopy, and fundus photography. Fluorescein

Table 1. International clinical non-proliferative diabetic retinopathy grading

Severe condition	Post-delivery ophthalmoscopy
No diabetic retinopathy	Normal
Mild non-proliferative diabetic retinopathy	Only microangioma
Moderate non-proliferative diabetic retinopathy	Not only microangioma but also less extensive lesions compared to those observed in the severe non-proliferative phase
Severe non-proliferative diabetic retinopathy	One or more of the following criteria: more than 20 intraretinal hemorrhages in any of the four quadrants; venous beading in more than two quadrants; evident intraretinal microvascular abnormalities in at least one quadrant, alongside other signs of non-proliferative diabetic retinopathy

angiography was performed to assess retinal lesions.

Patient data included gender, age, weight, duration of diabetes, and levels of glycosylated hemoglobin (HbA1c), high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol (TC), and triglycerides (TG).

Outcome measures

The primary outcomes were inner retinal thickness values and optic disc parameters between diabetic and healthy eyes. The secondary outcomes were the correlations of HbA1c levels, biochemical indicators, and diabetes duration with the various ocular parameters in diabetic eyes.

Blood samples were collected after a 6-8 hour overnight fast, and HbA1c levels were measured using a BIO-RAD glycated hemoglobin analyzer (VARIANT II TURBO). Other lipid-related profiles were assessed using a Roche automatic biochemical analyzer (Cobas 800).

The Heidelberg Spectralis SD-OCT was used to analyze the optic disc with a 200×200 cube feature. RNFL thickness was measured using the RNFL fast scan mode, which involved a circular scan with a 3.46 mm diameter around the optic disc, covering all 360°, including the four quadrants. The scan settings were adjusted to ensure optimal signal selection, and the sharpest image was maintained for analysis. The RNFL thickness was automatically computed by the system's analysis software.

Statistical analysis

Statistical analysis was conducted using SPSS version 21.0. All measured data were expressed as mean ± standard deviation ($\bar{x}$ ± sd). The analysis included one-way analysis of variance (ANOVA), chi-square tests, t-tests, and Kruskal-Wallis H tests for non-parametric data. ANOVA was specifically applied to assess differences in RNFL and GCL-IPL thicknesses across the study groups. Post-hoc tests, including the LSD test for homogeneous variances and Dunnett's T3 test for heterogeneous variances, were utilized as appropriate. Spearman's correlation analysis was employed to examine the relationships among the variables. A *P*-value of <0.05 was regarded as a significant.

Results

Comparison of general data

The basic clinical and laboratory characteristics of the three groups are presented in **Table 2**. There were no significant differences in gender, age, TC, LDL, BCVA, IOP, or SE among the three groups (all P>0.050). The DM course presented significant variations between the NDR and NPDR groups (P<0.001). Compared to the control group, TG, HDL, and HbA1c levels in the NDR group and NPDR group differed significantly (P=0.029, P=0.015, P<0.001).

Comparison of the thickness of RNFL

The overall RNFL thickness was significantly reduced in both the NDR and NPDR groups compared to the control group. Significant differences were observed in the average, superior, and nasal thicknesses (P=0.002, 0.020, 0.009; **Table 3**). Comparisons between the NDR group and the control group revealed significant differences in average, superior, and nasal thicknesses (P=0.002, 0.033, 0.030; **Table 3**), while comparisons between the NPDR group and the control group also showed sig-

Table 2. Comparison of baseline data among three groups

	NDR	NPDR	Control	χ^2/F/t/H	P
Gender (n)				2.101	>0.05
Male	27	29	12		
Female	23	23	18		
Age (year)	55.90±8.06	56.08±8.81	54.27±8.17	0.495	0.661
DM course (year)	6.30±4.34	11.42±7.00	0.00±0.00	9.147	<0.001[a]
HbA1c (%)	7.92±2.01	9.24±2.96	5.50±0.46	26.347	<0.001
TC (mg/dl)	4.89±1.10	4.82±1.48	4.87±0.83	0.262	0.958*
TG (mg/dl)	1.58±1.29	1.80±1.08	1.12±0.69	14.138	0.029*
HDL (mg/dl)	1.21±0.35	1.14±0.43	1.41±0.40	4.332	0.015
LDL (mg/dl)	2.90±0.92	2.84±1.28	2.87±0.77	0.666	0.958*
BCVA (logMAR)	0.08±0.07	0.09±0.08	0.06±0.05	5.321	0.050*
IOP (mmHg)	13.43±2.14	14.16±2.91	13.29±2.42	1.526	0.221
SE (j/D)	1.05±0.59	1.03±0.54	0.92±0.53	0.534	0.588

DM: Diabetes Mellitus; HbA1c: glycosylated hemoglobin; TG: triglyceride; TC: total cholesterol; HDL: high-density lipoprotein; LDL: low-density lipoprotein; BCVA: Best corrected visual acuity; IOP: Intraocular pressure; SE: Spherical equivalent; NDR: diabetic normal retina; NPDR: non-proliferative diabetic retina. Compared with each other by t test, a; *compared with each other by Kruskal-Wallis H rank sum test.

Table 3. Comparison of one-way analysis of variance between RNFL among three groups

	NDR	NPDR	Control	F	P	P1	P2	P3
G	105±7.23	104.70±10.34	111.26±6.86	6.565	0.002	0.002	0.001	0.860
S	131.26±10.34	129.10±17.60	138.87±14.16	4.007	0.020	0.033	0.006	0.477
N	74.84±10.34	72.73±13.73	80.97±12.90	4.837	0.009	0.030	0.002	0.310
I	136.14±16.90	136.04±20.18	143.53±12.17	2.123	0.124	0.068	0.063	0.977
T	77.76±10.47	81.27±13.48	81.67±11.81	1.443	0.240	0.162	0.886	0.143

G: Average; S: Superior; N: Nasal; I: Inferior; T: Temporal; NDR: diabetic normal retina; NPDR: non-proliferative diabetic retina. P1: NDR vs. Normal, P2: NPDR vs. Normal group; P3: NDR vs. NPDR.

nificant reductions (P<0.001, 0.006, 0.002; **Table 4**).

Comparison of the thickness of GCL-IPL in the macular area

In the 3 mm and 6 mm zones, and the overall average of the eye, the GCL-IPL thicknesses in both the NDR and NPDR groups were significantly thinner than in the control group (P=0.040, 0.022). Within the 3 mm zone, the superior and temporal thicknesses of the NDR and NPDR groups were significantly thinner compared to the control group (P=0.010, 0.037; **Table 4**). When comparing the NDR group to the control group, significant differences were noted in the average thickness and quadrants of the NPDR group (P=0.012, 0.012, 0.031, 0.035, 0.006). There were also significant differences between the NDR and NPDR groups (P=0.35; **Table 5**).

In the 6 mm range, the superior quadrant showed significant thinning in both the NDR and NPDR groups compared to the control group (P=0.037; **Table 4**). Comparisons among the groups indicated significant differences in the superior quadrant (P=0.035, 0.014; **Table 6**).

Correlation between clinical factors and diabetic group optic disc RNFL, macular GCL-ILP

The superior RNFL thickness at the optic disc area was positively correlated with HbA1c levels, whereas HDL showed a negative correlation; no significant correlations were observed with other factors (**Table 6**). Additionally, in the 3 mm range, the overall average, lower, and nasal thicknesses of the GCL-IPL were negatively correlated with TC, as shown in **Table 7**. The average thickness of GCL-IPL in the 6 mm

Table 4. Comparison of one-way analysis of variance between GCL-IPL thickness among three groups of macular areas

	NDR	NPDR	Control	F	P	P1	P2	P3
G	77.47±4.86	76.11±4.86	79.07±5.72	3.296	0.040	0.175	0.012	0.176
3 mm								
S	90.56±7.38	87.10±8.79	91.90±8.43	3.937	0.022	0.480	0.012	0.035
N	87.00±9.74	85.71±12.02	90.90±8.13	2.425	0.093	0.107	0.031	0.532
I	88.06±9.16	85.89±10.41	90.43±7.19	2.327	0.102	0.271	0.035	0.239
T	84.38±9.69	79.96±13.16	87.37±7.88	4.803	0.010	0.355*	0.006*	0.157*
6 mm								
S	65.90±5.11	65.44±5.36	68.73±7.28	3.384	0.037	0.035	0.014	0.688
N	72.82±6.97	72.21±7.11	74.30±8.48	0.767	0.467	0.387	0.220	0.678
I	62.00±6.65	62.63±7.53	62.63±5.92	0.133	0.876	0.69	0.999	0.641
T	69.06±7.11	69.90±6.99	66.2±11.61	1.882	0.156	0.556*	0.328*	0.906*

Note: G: Average; S: Superior; N: Nasal; I: Inferior; T: Temporal; NDR: diabetic normal retina; NPDR: non-proliferative diabetic retina; GCL: ganglion cell layer; IPL: inner plexiform layer. Compared with each other by Dunnett T3 test, *P<0.05; the remainder was LSD test. P1: NDR *vs.* Normal, P2: NPDR *vs.* Normal, P3: NDR *vs.* NPDR.

Table 5. Results of Spearman correlation analysis of RNFL in optic disc area in the NDR and NPDR groups

	S	N	I	T	G
Age (year)					
r value	-0.012	0.060	-0.292	0.167	-0.077
P	0.905	0.552	0.003	0.094	0.442
DM course (year)					
r value	-0.058	0.063	-0.021	0.067	0.009
P	0.566	0.529	0.835	0.506	0.931
HbA1c (%)					
r value	0.200	-0.079	0.078	0.065	0.023
P	0.044	0.429	0.434	0.515	0.816
TC (mg/dl)					
r value	-0.059	-0.002	0.009	0.089	-0.031
P	0.556	0.986	0.927	0.374	0.757
TG (mg/dl)					
r value	0.058	-0.054	0.115	0.077	0.021
P	-0.561	0.59	0.251	0.441	0.833
HDL (mg/dl)					
r value	-0.198	0.011	-0.193	0.002	-0.188
P	0.047	0.910	0.052	0.984	0.058
LDL (mg/dl)					
r value	-0.062	-0.079	0.078	0.065	0.023
P	0.538	0.429	0.434	0.515	0.816

Note: DM: Diabetes Mellitus; HbA1c: glycosylated hemoglobin; TG: triglyceride; TC: total cholesterol; HDL: high-density lipoprotein; LDL: low-density lipoprotein; G: Average; S: Superior; N: Nasal; I: Inferior; T: Temporal; NDR: diabetic normal retina; NPDR: non-proliferative diabetic retina; GCL: ganglion cell layer; IPL: inner plexiform layer.

macular range was positively correlated with the duration of DM (**Tables 6** and **7**).

Discussion

Diabetic retinopathy (DR), a leading cause of vision loss and blindness among working-age adults globally, has seen a rising incidence. The pathogenesis of DR is not yet fully understood. Historically, DR was considered primarily a disease of the retinal microvasculature caused by impaired glucose tolerance. However, contemporary research has expanded this perspective, demonstrating that DR also exhibits characteristics of a neurodegenerative disease [16]. Unlike glaucoma, a distinct and prevalent optic nerve degenerative disease within ophthalmology [17], DR in its early stages can manifest characteristic optic nerve damage. This damage is similar to that seen in multiple sclerosis and other neurodegenerative diseases like Alzheimer's disease [18, 19]. The degeneration in DR predominantly involves apoptosis of RGCs, located within the layers of the RNFL, GCL, and IPL, collectively termed the ganglion cell complex [20]. Currently, the loss of RGCs is primarily assessed using SD-OCT. SD-OCT has been increas-

Table 6. Results of Spearman correlation analysis of GCL-IPL in the 3 mm range of the macular area of the NDR and NPDR groups

	S	N	I	T	G
Age (year)					
r value	0.068	0.070	0.077	0.034	0.084
P	0.494	0.482	0.441	0.735	0.401
DM course (year)					
r value	0.089	-0.025	-0.002	-0.024	0.046
P	0.373	0.800	0.988	0.813	0.649
HbA1c (%)					
r value	0.017	0.103	-0.053	-0.004	0.032
P	0.865	0.304	0.599	0.970	0.752
TC (mg/dl)					
r value	-0.135	-0.152	-0.211	-0.224	-0.227
P	0.176	0.107	0.033	0.023	0.022
TG (mg/dl)					
r value	-0.105	-0.035	-0.074	-0.121	-0.105
P	0.292	0.725	0.459	0.225	0.294
HDL (mg/dl)					
r value	0.039	-0.009	-0.014	-0.091	-0.034
P	0.701	0.926	0.893	0.365	0.731
LDL (mg/dl)					
r value	-0.1039	-0.146	-0.157	-0.093	-0.136
P	0.301	0.144	0.115	0.353	0.173

Note: DM: Diabetes Mellitus; HbA1c: glycosylated hemoglobin; TG: triglyceride; TC: total cholesterol; HDL: high-density lipoprotein; LDL: low-density lipoprotein; G: Average; S: Superior; N: Nasal; I: Inferior; T: Temporal; NDR: diabetic normal retina; NPDR: non-proliferative diabetic retina; GCL: ganglion cell layer; IPL: inner plexiform layer.

ingly utilized for its high resolution and reproducibility, accurately analyzing the GCL as an advanced retinal imaging technology [21, 22]. This study investigated the associations between GCL-IPL and RNFL thickness and diabetes-related risk factors in patients with mild to moderate NPDR [23].

In this study, SD-OCT was employed to detect thinning of the RNFL and GCL-IPL in diabetic patients. Notably, thinning of the RNFL and GCL-IPL was observed even in the NDR group. The RNFL was thinner in both the NDR and NPDR groups compared to the control group, with significant differences observed in the superior and nasal quadrants. However, there was no significant difference between the NDR and NPDR groups, aligning with findings by Carpineto and Picconi [20, 23-25]. These studies suggest that early RNFL thinning in DR may precede microvascular changes, indicating an early neurodegenerative lesion of DR.

Moreover, the superior and nasal RNFL were thinner than other sites, consistent with Carpinto and Lope's findings that microaneurysms and acellular capillaries are more prevalent in these regions [23, 26]. The obstruction and degradation of small blood vessel basement membranes, exacerbated by high blood glucose, may directly damage retinal nerve cells, particularly in the superior optic and macular regions, leading to heightened susceptibility to damage [27]. Barber et al. noted an increase in retinal neuronal apoptosis in diabetic rats and patients, attributed to various factors including axonal degeneration due to neurofilament accumulation, Müller cell dysfunction, extracellular glutamate excitotoxicity, an imbalance of neurotrophic factors, and microglial activation causing inner retinal inflammation [28-31]. Our results largely concur with those of Carpineto, but we noted that the GCL-IPL thickness differences between the NDR group and the control group were statistically significant except in the 6 mm range [23]. The directional thickness variation was not significant, which may be due to regional and ethnic differences and an insufficient sample size. The increased permeability of the internal retinal vascular network, accompanied by slight thickening and edema of the retinal neuroepithelial surface, may also contribute to edema in the ganglion cells, thereby countering the thinning induced by RGC loss [21]. This study highlights the complex interplay between neurodegenerative and microvascular changes in diabetic patients, underscoring the importance of early detection and management strategies for DR.

In this study, SD-OCT was used to measure the thickness of the RNFL and GCL-IPL in the macula of diabetic patients. The superior RNFL of the diabetic group showed a positive correla-

Table 7. Results of Spearman correlation analysis of GCL-IPL in the 6 mm range of the macular area of the NDR and NPDR groups

	S	N	I	T	G
Age (year)					
r value	0.077	-0.090	-0.177	-0.051	-0.069
P	0.443	0.368	0.075	0.609	0.490
DM course (year)					
r value	0.048	0.054	0.146	0.196	0.123
P	0.633	0.591	0.143	0.048	0.217
HbA1c (%)					
r value	0.091	0.063	0.102	-0.008	0.053
P	0.362	0.531	0.307	0.938	0.594
TC (mg/dl)					
r value	0.011	-0.089	0.043	0.034	0.005
P	0.912	0.375	0.670	0.734	0.956
TG (mg/dl)					
r value	0.162	0.004	0.011	0.138	0.101
P	0.104	0.970	0.916	0.168	0.311
HDL (mg/dl)					
r value	-0.131	-0.049	-0.074	-0.127	-0.116
P	0.190	0.623	0.462	0.203	0.247
LDL (mg/dl)					
r value	-0.020	-0.015	0.126	0.031	0.041
P	0.845	0.882	0.207	0.759	0.680

Note: DM: Diabetes Mellitus; HbA1c: glycosylated hemoglobin; TG: triglyceride; TC: total cholesterol; HDL: high-density lipoprotein; LDL: low-density lipoprotein; G: Average; S: Superior; N: Nasal; I: Inferior; T: Temporal; NDR: diabetic normal retina; NPDR: non-proliferative diabetic retina; GCL: ganglion cell layer; IPL: inner plexiform layer.

tion with HbA1c levels, whereas the GCL-IPL of the temporal side in the macular 6 mm range positively correlated with the duration of DM. This result contrasts with studies by Shi et al., which reported a negative correlation between upper RNFL thickness, DM duration, and HbA1c levels [32]. Current consensus acknowledges that hyperglycemia promotes the progression of DR, yet the specific role of HbA1c remains to be fully elucidated [25]. Carpineto et al. suggested that HbA1c levels positively correlate with average RNFL thickness, noting variability in correlations based on the duration of diabetes and glycemic control [24]. Van Dijk has demonstrated a positive correlation between GCL thickness and the duration of DM [33], reflecting the complex nature of diabetic pathology in patients. The timing of diabetes diagnosis varies, and some patients might have pre-existing glucose metabolism impairments years before an official diagnosis, complicating the relationship between diabetic duration, GCL-IPL, and RNFL changes. Further basic research is needed to clarify these relationships [23].

Recent studies emphasize that DR progression is closely linked to systemic risk factors such as blood lipid levels and glucose. Although the relationship between lipid levels and DR progression remains ambiguous, lipid-lowering medications have shown promise in delaying DR progression and reducing the need for retinal laser therapy [34]. Potential mechanisms include the upregulation of apolipoproteins, enhancing reverse cholesterol transport within the retina, and reducing lipid-mediated oxidative stress [35]. Kim et al. and Yan et al. have found positive correlations between lipid-lowering drugs, high-fat diets, and the thickness of the GCL-IPL, indicating that elevated plasma saturated fatty acids may contribute to insulin resistance and subsequent DR development [36, 37]. Elevated levels of saturated fatty acids, recognized as a significant metabolic risk factor for DM, have been linked to increased apoptosis of RGCs during the onset of DR. These lipid levels are also implicated in various ocular conditions, including age-related macular degeneration, where the composition of drusen deposits in the retina bears resemblance to that of atherosclerosis. Additionally, individuals with Smith-Lemli-Opitz syndrome are unable to convert cholesterol due to a deficiency of 7-dehydrocholesterol, resulting in reduced levels of cholesterol and the accumulation of precursor products from toxic cholesterol pathways, leading to abnormalities in the optic nerve and retina [38, 39].

Our investigation revealed a significant negative association between TC and GCL-IPL thickness beneath the fovea, as well as a weak inverse association between HDL and RNFL

thickness, aligning with findings from other studies [32]. The involvement of liver X receptor signaling in the retina, which affects cholesterol transport proteins and pathways, suggests that elevated serum lipids may impair endothelial function and provoke inflammatory responses, exacerbating neurodegenerative changes in the retina [40, 41]. Additionally, a correlation between serum 25-hydroxyvitamin D levels and RNFL thickness has been observed, linking dyslipidemia and vitamin D deficiency with retinal thinning [42]. Nevertheless, the manner in which lipid levels influence the pathological process of retinal thickness in diabetic patients, and whether lipid-regulating drugs can contribute to reversing this early pathologic process remain uncertain. Further research is required.

In conclusion, specific lipid metabolic disturbances in diabetic patients might play a role in the observed changes in RNFL and GCL-IPL thickness, potentially contributing to the pathogenesis of DR. The effect of lipid levels on retinal thickening and the potential therapeutic benefits of lipid-lowering medications warrant further comprehensive study. This research provides valuable insight for the early diagnosis and longitudinal monitoring of DR development.

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Disclosure of conflict of interest

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References

[1] Ogurtsova K, da Rocha Fernandes JD, Huang Y, Linnenkamp U, Guariguata L, Cho NH, Cavan D, Shaw JE and Makaroff LE. IDF diabetes atlas: global estimates for the prevalence of diabetes for 2015 and 2040. Diabetes Res Clin Pract 2017; 128: 40-50.

[2] Wadhwani M, Bali S, Bhartiya S, Mahabir M, Upadhaya A, Dada T, Sharma A and Mishra SK. Long term effect of panretinal photocoagulation on retinal nerve fiber layer parameters in patients with proliferative diabetic retinopathy. Oman J Ophthalmol 2019; 12: 181-185.

[3] Hafner J, Prager S, Lammer J, Kriechbaum K, Scholda C, Pablik E and Schmidt-Erfurth U. Comparison of ganglion cell inner plexiform layer thickness by cirrus and spectralis optical coherence tomography in diabetic macular edema. Retina 2018; 38: 820-827.

[4] Sachdeva MM. Retinal Neurodegeneration in diabetes: an emerging concept in diabetic retinopathy. Curr Diab Rep 2021; 21: 65.

[5] Chhablani J, Sharma A, Goud A, Peguda HK, Rao HL, Begum VU and Barteselli G. Neurodegeneration in type 2 diabetes: evidence from spectral-domain optical coherence tomography. Invest Ophthalmol Vis Sci 2015; 56: 6333-6338.

[6] van de Kreeke JA, Darma S, Chan Pin Yin JMPL, Tan HS, Abramoff MD, Twisk JWR and Verbraak FD. The spatial relation of diabetic retinal neurodegeneration with diabetic retinopathy. PLoS One 2020; 15: e0231552.

[7] Lee MW, Lee WH, Ryu CK, Lee YM, Lee YH and Kim JY. Peripapillary retinal nerve fiber layer and microvasculature in prolonged type 2 diabetes patients without clinical diabetic retinopathy. Invest Ophthalmol Vis Sci 2021; 62: 9.

[8] Tavares Ferreira J, Proença R, Alves M, Dias-Santos A, Santos BO, Cunha JP, Papoila AL and Abegão Pinto L. Retina and choroid of diabetic patients without observed retinal vascular changes: a longitudinal study. Am J Ophthalmol 2017; 176: 15-25.

[9] Mwanza JC, Oakley JD, Budenz DL, Chang RT, Knight OJ and Feuer WJ. Macular ganglion cell-inner plexiform layer: automated detection and thickness reproducibility with spectral domain-optical coherence tomography in glaucoma. Invest Ophthalmol Vis Sci 2011; 52: 8323-8239.

[10] Nguyen TT, Wang JJ and Wong TY. Retinal vascular changes in pre-diabetes and prehypertension: new findings and their research and clinical implications. Diabetes Care 2007; 30: 2708-2715.

[11] Joussen AM, Poulaki V, Le ML, Koizumi K, Esser C, Janicki H, Schraermeyer U, Kociok N, Fauser S, Kirchhof B, Kern TS and Adamis AP. A central role for inflammation in the pathogenesis of diabetic retinopathy. Faseb J 2004; 18: 1450-1452.

[12] Chowdhury TA, Hopkins D, Dodson PM and Vafidis GC. The role of serum lipids in exudative diabetic maculopathy: is there a place for lipid lowering therapy? Eye (Lond) 2002; 16: 689-693.

[13] Uçgun NI, Yildirim Z, Kiliç N and Gürsel E. The importance of serum lipids in exudative diabetic macular edema in type 2 diabetic patients. Ann N Y Acad Sci 2007; 1100: 213-217.
[14] Deng G, Moran EP, Cheng R, Matlock G, Zhou K, Moran D, Chen D, Yu Q and Ma JX. Therapeutic effects of a novel agonist of peroxisome proliferator-activated receptor alpha for the treatment of diabetic retinopathy. Invest Ophthalmol Vis Sci 2017; 58: 5030-5042.
[15] Wilkinson CP, Ferris FL 3rd, Klein RE, Lee PP, Agardh CD, Davis M, Dills D, Kampik A, Pararajasegaram R and Verdaguer JT. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Ophthalmology 2003; 110: 1677-1682.
[16] Ebrahimi M, Thompson P, Lauer AK, Sivaprasad S and Perry G. The retina-brain axis and diabetic retinopathy. Eur J Ophthalmol 2023; 33: 2079-2095.
[17] Rao HL, Yadav RK, Addepalli UK, Begum VU, Senthil S, Choudhari NS and Garudadri CS. Comparing spectral-domain optical coherence tomography and standard automated perimetry to diagnose glaucomatous optic neuropathy. J Glaucoma 2015; 24: e69-74.
[18] Uro M, Beauchet O, Cherif M, Graffe A, Milea D and Annweiler C. Age-related vitamin D deficiency is associated with reduced macular ganglion cell complex: a cross-sectional high-definition optical coherence tomography study. PLoS One 2015; 10: e0130879.
[19] Polo V, Rodrigo MJ, Garcia-Martin E, Otin S, Larrosa JM, Fuertes MI, Bambo MP, Pablo LE and Satue M. Visual dysfunction and its correlation with retinal changes in patients with Alzheimer's disease. Eye (Lond) 2017; 31: 1034-1041.
[20] van Dijk HW, Verbraak FD, Kok PH, Stehouwer M, Garvin MK, Sonka M, DeVries JH, Schlingemann RO and Abràmoff MD. Early neurodegeneration in the retina of type 2 diabetic patients. Invest Ophthalmol Vis Sci 2012; 53: 2715-2719.
[21] Shen PY, Chen WL, Xian WG, Shi YY, Chen HB and Zhong XW. Evaluation of early diabetic macular morphology changes using SD-OCT. Recent Adv Ophthalmol 2017; 37: 42-45.
[22] Garvin MK, Lee K, Burns TL, Abràmoff MD, Sonka M and Kwon YH. Reproducibility of SD-OCT-based ganglion cell-layer thickness in glaucoma using two different segmentation algorithms. Invest Ophthalmol Vis Sci 2013; 54: 6998-7004.
[23] Carpineto P, Toto L, Aloia R, Ciciarelli V, Borrelli E, Vitacolonna E, Di Nicola M, Di Antonio L and Mastropasqua R. Neuroretinal alterations in the early stages of diabetic retinopathy in patients with type 2 diabetes mellitus. Eye (Lond) 2016; 30: 673-679.
[24] Carpineto P, Nubile M, Agnifili L, Toto L, Aharrh-Gnama A, Mastropasqua R, Di Antonio L, Fasanella V and Mastropasqua A. Reproducibility and repeatability of Cirrus™ HD-OCT peripapillary retinal nerve fibre layer thickness measurements in young normal subjects. Ophthalmologica 2012; 227: 139-145.
[25] Picconi F, Parravano M, Ylli D, Pasqualetti P, Coluzzi S, Giordani I, Malandrucco I, Lauro D, Scarinci F, Giorno P, Varano M and Frontoni S. Retinal neurodegeneration in patients with type 1 diabetes mellitus: the role of glycemic variability. Acta Diabetol 2017; 54: 489-497.
[26] Lopes de Faria JM, Russ H and Costa VP. Retinal nerve fibre layer loss in patients with type 1 diabetes mellitus without retinopathy. Br J Ophthalmol 2002; 86: 725-728.
[27] Sugimoto M, Sasoh M, Ido M, Wakitani Y, Takahashi C and Uji Y. Detection of early diabetic change with optical coherence tomography in type 2 diabetes mellitus patients without retinopathy. Ophthalmologica 2005; 219: 379-385.
[28] Barber AJ, Lieth E, Khin SA, Antonetti DA, Buchanan AG and Gardner TW. Neural apoptosis in the retina during experimental and human diabetes. Early onset and effect of insulin. J Clin Invest 1998; 102: 783-791.
[29] Gastinger MJ, Kunselman AR, Conboy EE, Bronson SK and Barber AJ. Dendrite remodeling and other abnormalities in the retinal ganglion cells of Ins2 Akita diabetic mice. Invest Ophthalmol Vis Sci 2008; 49: 2635-2642.
[30] Al-Gayyar MM, Mysona BA, Matragoon S, Abdelsaid MA, El-Azab MF, Shanab AY, Ha Y, Smith SB, Bollinger KE and El-Remessy AB. Diabetes and overexpression of proNGF cause retinal neurodegeneration via activation of RhoA pathway. PLoS One 2013; 8: e54692.
[31] Antonetti DA, Klein R and Gardner TW. Diabetic retinopathy. N Engl J Med 2012; 366: 1227-1239.
[32] Shi R, Guo Z, Wang F, Li R, Zhao L and Lin R. Alterations in retinal nerve fiber layer thickness in early stages of diabetic retinopathy and potential risk factors. Curr Eye Res 2018; 43: 244-253.
[33] van Dijk HW, Verbraak FD, Kok PH, Garvin MK, Sonka M, Lee K, Devries JH, Michels RP, van Velthoven ME, Schlingemann RO and Abràmoff MD. Decreased retinal ganglion cell layer thickness in patients with type 1 diabetes. Invest Ophthalmol Vis Sci 2010; 51: 3660-3665.
[34] Singh RP, Habbu K, Ehlers JP, Lansang MC, Hill L and Stoilov I. The impact of systemic factors on clinical response to ranibizumab for diabetic macular edema. Ophthalmology 2016; 123: 1581-1587.
[35] Noonan JE, Jenkins AJ, Ma JX, Keech AC, Wang JJ and Lamoureux EL. An update on the mo-

lecular actions of fenofibrate and its clinical effects on diabetic retinopathy and other microvascular end points in patients with diabetes. Diabetes 2013; 62: 3968-3975.
[36] Kim K, Kim ES, Rhee SY, Chon S, Woo JT and Yu SY. Clinical characteristics and risk factors for retinal diabetic neurodegeneration in type 2 diabetes. Acta Diabetol 2017; 54: 993-999.
[37] Yan PS, Tang S, Zhang HF, Guo YY, Zeng ZW and Wen Q. Nerve growth factor protects against palmitic acid-induced injury in retinal ganglion cells. Neural Regen Res 2016; 11: 1851-1856.
[38] Mullins RF, Russell SR, Anderson DH and Hageman GS. Drusen associated with aging and age-related macular degeneration contain proteins common to extracellular deposits associated with atherosclerosis, elastosis, amyloidosis, and dense deposit disease. FASEB J 2000; 14: 835-846.
[39] DeBarber AE, Eroglu Y, Merkens LS, Pappu AS and Steiner RD. Smith-lemli-opitz syndrome. Expert Rev Mol Med 2011; 13: e24.
[40] Hammer SS, Beli E, Kady N, Wang Q, Wood K, Lydic TA, Malek G, Saban DR, Wang XX, Hazra S, Levi M, Busik JV and Grant MB. The mechanism of diabetic retinopathy pathogenesis unifying key lipid regulators, sirtuin 1 and liver x receptor. EBioMedicine 2017; 22: 181-190.
[41] Mazereeuw G, Herrmann N, Bennett SA, Swardfager W, Xu H, Valenzuela N, Fai S and Lanctôt KL. Platelet activating factors in depression and coronary artery disease: a potential biomarker related to inflammatory mechanisms and neurodegeneration. Neurosci Biobehav Rev 2013; 37: 1611-1621.
[42] Gungor A, Ates O, Bilen H and Kocer I. Retinal nerve fiber layer thickness in early-stage diabetic retinopathy with vitamin D deficiency. Invest Ophthalmol Vis Sci 2015; 56: 6433-6437.