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ORIGINAL RESEARCH

An Investigation of the Correlation Between Retinal Nerve Fiber Layer Thickness with Blood Biochemical Indices and Cognitive Dysfunction in Patients with Type 2 Diabetes Mellitus

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Objective: The study aimed to explore the correlation between retinal nerve fiber layer thickness (RNFLT) with blood biochemical indicators and cognitive dysfunction in patients with type 2 diabetes mellitus (T2DM) and the possible mechanism, thereby providing more theoretical basis for the occurrence and prevention of diabetes related complications.

Methods: Eighty T2DM patients treated in our hospital from March 2022 to September 2022 were selected as the study subjects, and the clinical data of the patients were retrospectively analyzed. All patients underwent fundus fluorescein angiography (FFA) to analyze the changes in retinal blood vessels. Patients who met the inclusion criteria were divided as the diabetic retinopathy (DR) group (n=46) and simple diabetes group (n=34). The RNFLT, blood biochemical indexes and changes in cognitive functions of the patients were detected. The correlation between RNFLT with blood biochemical indexes and cognitive dysfunction was analyzed.

Results: Compared with the simple diabetes group, patients in the DR group had much lower mean, nasal, inferior and superior thicknesses ($P<0.01$). There existed no significant difference in blood pressure, body mass index (BMI), blood lipids (triglycerides, cholesterol, low-density lipoprotein, high-density lipoprotein) between the two groups ($P>0.05$). Compared with the simple diabetes group, patients in the DR group had much higher fasting blood glucose (FBG), hemoglobin A1c (HbA1c), fasting insulin (FINS), insulin resistance (HOMA-IR) index, apolipoprotein B (ApoB)/apolipoprotein A1 (ApoA1) ($P<0.001$). Besides, the DR group had sharply lower scores on the Mini-Mental State Examination (MMSE) scale and higher levels of the Trail Making Test-A (TMT-A) and TMT-B ($P<0.001$). Spearman correlation analysis confirmed that the mean RNFLT was negatively correlated with the levels of FBG, HbA1c, HOMA-IR index, TMT-A and TMT-B ($P<0.05$), positively correlated with the score of mini-mental state examination (MMSE) ($P<0.05$), and was no significant correlation with FINS and ApoB/ApoA1 ($P>0.05$).

Conclusion: DR patients had significantly reduced RNFLT, elevated levels of blood glucose related indicators, and cognitive dysfunction. There existed a correlation between RNFLT and FBG, HbA1c, HOMA-IR index, TMT-A, TMT-B and MMSE.

Keywords: type 2 diabetes mellitus, retinal nerve fiber thickness, blood biochemical indicators, cognitive dysfunction, correlation

Introduction

Type 2 diabetes mellitus (T2DM) is a global health problem. According to statistics,[1,2] with the improvement of diet level and the change of lifestyle, the incidence rate of T2DM is increasing year by year, which may exceed 600 million by 2045. More than 2 million patients die each year due to complications of large blood vessels and micro-vasculature. Diabetes not only has a serious impact on the health of patients, but also brings a heavy economic burden to society. Some studies believe that,[3] increase in the incidence rate of T2DM may be related to the increase of diabetes retinopathy (DR). The thickness of the retinal nerve fiber layer is an important component of the visual system, which plays a role in transmitting visual information and regulating visual function. The study found that,[4] T2DM patients generally have

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changes in retinal nerve fiber layer thickness (RNFLT), and the changes in RNFLT are closely related to the course of diabetes, blood sugar control, diabetes complications and other factors. Therefore, it is of great significance to explore the changes of RNFLT in T2DM patients for evaluating the condition of diabetes and predicting the occurrence and development of complications.

DR is one of the common micro-vascular complications of T2DM, and it is also the main reason for blindness of the sick people worldwide.[5,6] Blood biochemical indicators are important parameters that reflect the physiological functions and metabolic status of the human body. In T2DM patients, abnormal blood biochemical indicators are a key factor in the progression of their condition.[7] Blood biochemical abnormalities such as hyperglycemia, hyperlipidemia and renal insufficiency not only accelerate the occurrence of complications of diabetes, but also may cause damage to multiple organ systems in the whole body.[8] Therefore, the monitoring and intervention of blood biochemical indicators in T2DM patients is an important part of the treatment of diabetes. The incidence rate of T2DM and related cognitive disorders is increasing year by year. However, there is still a lack of effective strategies for treating or delaying cognitive decline, so it is necessary to search for relevant indicators for early identification of cognitive decline.[9]

Based on this, by following up the changes of RNFLT and cognitive function in diabetes patients, this study aims to understand the early retinopathy in T2DM patients before the onset of symptoms and explore its relationship with cognitive function, thereby providing more theoretical basis for the occurrence and prevention of diabetes complications.

Materials and Methods

Clinical Materials

Eighty T2DM patients who received treatment in the Endocrinology Department of Yancheng Third People's Hospital from March 2022 to September 2022 were retrospectively selected as the study subjects. The clinical data and treatment status of patients were studied and analyzed. All patients underwent fundus fluorescein angiography (FFA) to analyze the changes in retinal blood vessels. Patients who met the inclusion criteria were divided as the DR group (n=46) and simple diabetes group (n=34). There were 26 males and 20 males aged 23–75 years old in the DR group, with an average age of (57.56 ± 4.39) years. Patients in DR group had a course of illness of (1–15) years, with an average course of illness of (5.22 ± 1.36) years. There were 21 males and 13 males aged 23–72 years old in the simple diabetes group, with an average age of (56.25±7.39) years. Patients in simple diabetes group had a course of illness of (1–15) years, with an average course of illness of (5.37±1.16) years. There existed no significant difference in clinical data between the two groups (P>0.05). Diagnostic criteria for DR: According to the results of FFA, Phase I showed a small amount of microvascular tumors visible in the macular region; Phase II presented with visible small bleeding in the retina, caused by microvascular tumors and hard exudates; In stage III, bleeding points, microvascular tumors, hard exudates, and cotton wool spots were visible in the retina, which were manifestations of retinal hypoxia.

Inclusion criteria: (1) Patients met the diagnostic and treatment criteria for T2DM,[10] with fasting blood glucose ≥ 7.0 mmol/L (126 mg/dl), and/or 2-hour blood glucose ≥ 11.1 mmol/L (200 mg/dl) in 75 g OGTT, and/or HbA1c ≥ 6.5%; (2) All research subjects had complete clinical data; (3) There was no history of neurological disorders and no history of cognitive impairment. Exclusion criteria: (1) Patients with concomitant eye diseases such as glaucoma; (2) Patients with combined liver and kidney function or cardiac dysfunction; (3) Patients with combined neurological disorders such as Parkinson's disease; (4) Patients with concomitant primary hypertension, liver injury, malignant tumors, and lupus erythematosus; (5) Patients with concomitant nephrotic syndrome, nephritis, and renal insufficiency; (6) Patients with other secretory diseases such as hyperthyroidism and hypothyroidism. This study was approved by the Ethics Committee of The Third Affiliated Hospital of Soochow University.

This study has been defined as a retrospective study. Thus, sample selection could be on behalf of the target population, and had enough statistical validity to detect differences in expectations or associated. Therefore, the inclusion of patients in this study was achieved with some accuracy and clarity.

Methods

RNFLT Detection

All cases underwent routine optical coherence tomography (OCT) examination to exclude other fundus diseases. All research subjects were measured for RNFLT using Zeiss frequency domain OCT by professionals in the case of dilated pupils. Two to four images were used for each eye to be studied. The segmentation line was delineated by the conventional OCT software in Spectralis SD-OCT, including the front and back RNFLT boundaries corresponding to the inner boundary membrane and inner plexus layer in circular scanning. A circular scan was performed around the center of the optic disc, with a diameter of 3.4 m. The measurement included the average thickness of retinal nerve fibers throughout the week and the average thickness of the nasal, temporal, lower, and upper quadrants. Each part of each eye was scanned at least five times. The three sets of images with the best signal and clearest image were saved, and the average value was taken for statistical processing. Ophthalmologists should check all OCT machine segmentation for possible segmentation errors and manually performed segmentation correction on B-scans. Subsequently, the RNFLT data from the corrected segmentation was recorded as "ground truth" data.

Detection of Blood Biochemical Indicators

The blood pressure [systolic blood pressure (SBP), diastolic blood pressure (DBP)] and body mass index (BMI) of all subjects were recorded. Elbow vein blood was extracted from patients after fasting for 8–10 hours. The levels of blood lipids (triglycerides, cholesterol, low-density lipoprotein (LDL) and high-density lipoprotein (HDL)) were measured by using an automatic biochemical analyzer. The hemoglobin A1c (HbA1c) level was measured using reverse phase cation exchange chromatography. The levels of fasting blood glucose (FBG) and fasting insulin (FINS) were measured by immunochemiluminescence method, and the homeostasis model assessment of insulin resistance (HOMA-IR) index was calculated based on the following formula: HOMA-IR = FBG×FINS/22.5. Apolipoprotein A1 (ApoA1) and apolipoprotein B (ApoB) were measured by multi-point calibration turbidimetry, and the ratio of ApoB and ApoA1 (ApoB/ ApoA1) was calculated.

Cognitive Function Assessment

All patients underwent cognitive function assessment, including the Mini-Mental State Examination (MMSE)[11] and the Trail Making Test (TMT), including TMT-A and TMT-B.

1. MMSE: All enrolled subjects were measured for their cognitive level by a dedicated person. The measurement included 7 items, including time orientation, memory, attention and computing power, recall ability, language ability, etc., with a total score of 30 points. The evaluation duration was approximately 5–10 minutes. According to the patient's educational level, the criteria for dividing cognitive impairment was listed as follows: general illiteracy ≤ 17 points, primary school education ≤ 20 points, and secondary school education ≤ 24 points. Being identified as having cognitive impairment below the standard score, who required further examination.
2. TMT: TMT-A and TMT-B were included. TMT-A required the participants to connect 25 randomly arranged numbers in order and at the fastest speed possible. Part B required participants to connect 13 numbers and 12 words in alternating order as quickly as possible. Practice was conducted before each section of the test, and the completion time was recorded during the test as the test score. It was believed that cognitive impairment existed when TMT-A>78 s and TMT-B>273 s.

The measuring tool used in this study was reliable and effective, which has been validated and widely accepted in the relevant fields. When data were collected through a questionnaire survey, the design of the questionnaire was reasonable, the questions were clear and easy to understand, the responses were comprehensive, the data collection methods were clearly described, and the factors that might lead to error or bias were small. Therefore, the assessment in this study had a certain degree of accuracy and clarity.

Statistical Analysis

SPSS 20.0 software was used to process data. Homogeneity of variance and normality distribution tests were performed on all data. Quantitative data that conformed to a normal distribution were represented by ($\bar{x}\pm$ s), and pairwise comparisons between groups were conducted using *t*-tests. Enumeration data were represented as (%), and inter-group comparisons were made using χ^2 test. The correlation was analyzed using Spearman correlation analysis. The difference was statistically significant with $P<0.05$.

Results

RNFLT Analysis Between Two Groups

There was no significant difference in temporal level between DR group and simple diabetes group ($P>0.05$); Compared with the simple diabetes group, patients in the DR group had much lower mean, nasal, inferior and superior thicknesses ($P<0.01$, Table 1).

Analysis of Blood Biochemical Indicators Between Two Groups

There existed no significant difference in blood pressure (SBP, DBP), BMI, blood lipids (triglycerides, cholesterol, low-density lipoprotein, high-density lipoprotein) between the two groups ($P>0.05$). Compared with the simple diabetes group, patients in the DR group had much higher FBG, HbA1c, FINS, HOMA-IR index and ApoB/ApoA1 ($P<0.001$, Table 2).

Table 1 RNFLT Analysis Between Two Groups ($\bar{x}\pm$ s)

Groups	DR group (n=46)	Simple diabetes group (n=34)	t	P
Mean thickness (μm)	102.09±10.45	110.64±11.96	3.402	0.001
Nasal (μm)	53.19±23.19	75.62±22.58	4.324	<0.001
Temporal (μm)	81.20±16.38	84.52±19.53	0.826	0.412
Inferior (μm)	99.15±13.94	124.87±28.63	5.309	<0.001
Superior (μm)	103.19±26.94	125.68±29.23	3.560	0.001

Notes: *t*: statistical value of *t* test; *P*: value of probability.
Abbreviations: RNFLT, retinal nerve fiber layer thickness; DR, diabetic retinopathy.

Table 2 Analysis of Blood Biochemical Indicators Between Two Groups ($\bar{x}\pm$ s)

Groups	DR group (n=46)	Simple diabetes group (n=34)	t	P
Blood pressure (mmHg)				
SBP	127.64±12.50	130.42±16.47	0.859	0.393
DBP	79.63±10.27	81.46±12.26	0.725	0.470
BMI (kg/m^2)	23.51±3.53	24.79±3.03	1.701	0.093
FBG (mmol/L)	11.26±0.56	7.85±1.73	12.534	<0.001
Blood lipids (mmol/L)				
Triglycerides	4.05±0.81	4.22±1.08	0.805	0.423
Cholesterol	1.80±0.72	17.83±0.80	0.176	0.861
LDL	2.79±0.45	2.91±0.46	1.168	0.246
HDL	2.20±0.44	2.18±0.46	0.197	0.844
HbA1c (%)	11.42±1.56	8.07±1.75	9.150	<0.001
FINS (mU/L)	13.52±2.01	11.80±1.74	4.002	<0.001
HOMA-IR index	7.62±0.97	5.11±0.58	13.408	<0.001
ApoB/ApoA1	0.96±0.28	0.81±0.33	2.195	0.031

Notes: *t*: statistical value of *t* test; *P*: value of probability.
Abbreviations: DR, diabetic retinopathy; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; FBG: fasting blood glucose; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HbA1c, hemoglobin A1c; FINS, fasting insulin; HOMA-IR index, insulin resistance index; ApoB/ApoA1, apolipoprotein B/apolipoprotein A1.

Table 3 Cognitive Function Analysis of Two Groups ($\bar{x}\pm s$)

Groups	Cases	MMSE (score)	TMT-A (s)	TMT-B (s)
DR group	46	21.14±3.69	90.39±15.68	280.96±49.47
Simple diabetes group	34	30.94±3.30	70.58±12.85	191.85±32.46
t		12.274	6.020	9.142
P		<0.001	<0.001	<0.001

Notes: *t*: statistical value of *t* test; *P*: value of probability.
Abbreviations: DR, diabetic retinopathy; MMSE, Mini-Mental State Examination; TMT-A, Trail Making Test-A; TMT-B, Trail Making Test-B.

Cognitive Function Analysis of Two Groups

The DR group had sharply lower scores on the MMSE scale and higher levels of the TMT-A and TMT-B ($P<0.001$, Table 3 and Figure 1).

The Relationship Between RNFLT with Blood Biochemical Indicators and Cognitive Impairment

Spearman correlation analysis confirmed that the mean RNFLT was negatively correlated with the levels of FBG, HbA1c, HOMA-IR index, TMT-A, and TMT-B (r=−0.272, −0.249, −0.224, −0.226, −0.309, $P<0.05$), positively correlated with the score of MMSE (r=0.223, $P<0.05$), and no significant correlation between FINS and ApoB/ApoA1 (r=−0.033, −0.066, $P>0.05$, Figure 2).

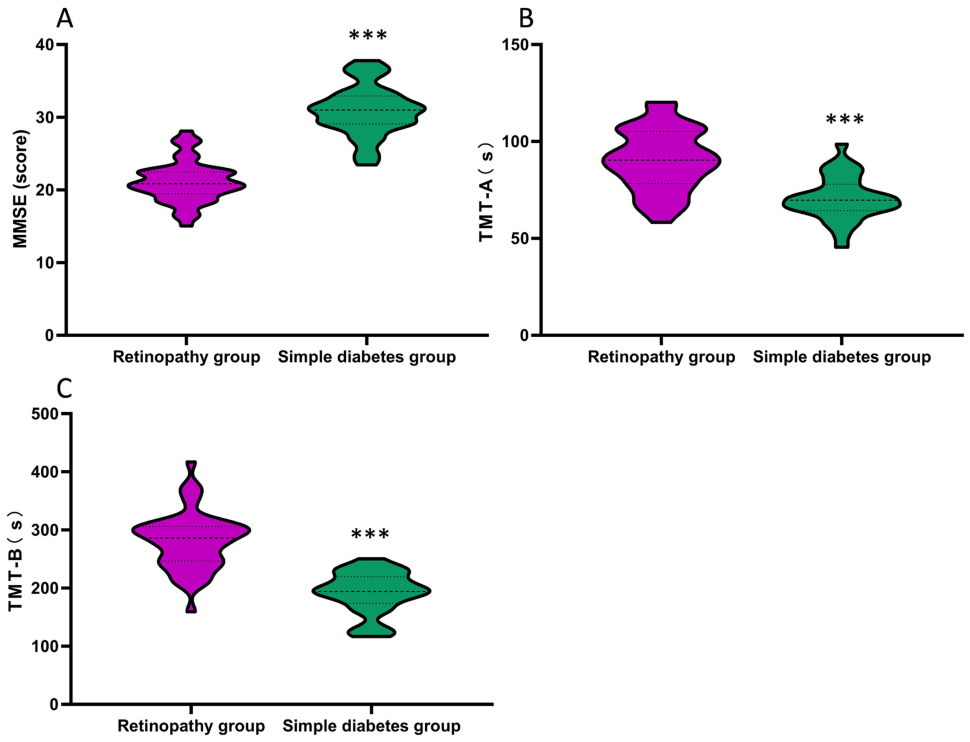

Figure 1 Cognitive function analysis of two groups. (**A**) Comparison of MMSE scores between two groups; (**B**) Comparison of TMT-A time between two groups; (**C**) Comparison of TMT-B time between two groups.
Notes: ***P<0.001 compared with DR group. P: value of probability.
Abbreviations: DR, diabetic retinopathy; MMSE, Mini-Mental State Examination; TMT-A, Trail Making Test-A; TMT-B, Trail Making Test-B.

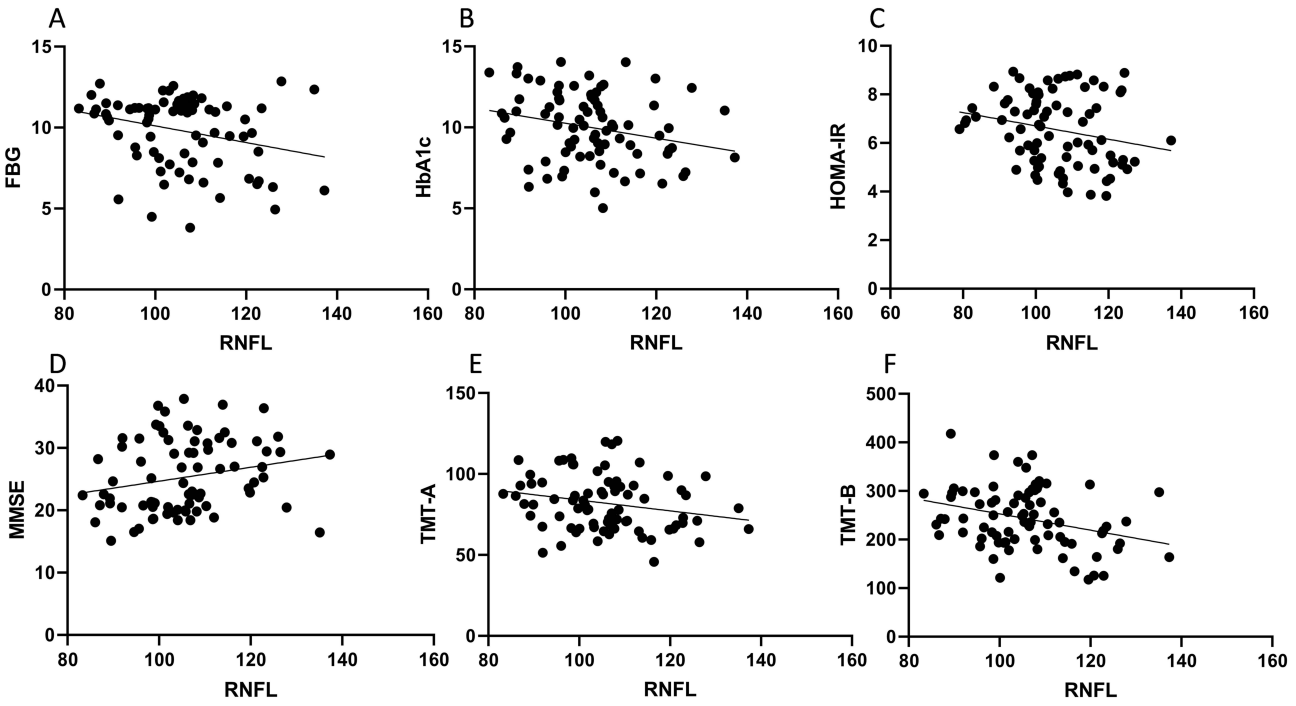

Figure 2 The relationship between RNFLT with blood biochemical indicators and cognitive impairment. (**A**) The correlation between RNFLT and FBG levels; (**B**) The correlation between RNFLT and HbA1c levels; (**C**) The correlation between RNFLT and HOMA-IR index; (**D**) The correlation between RNFLT and MMSE score; (**E**) The correlation between RNFLT and TMT-A time; (**F**) The correlation between ERNFLT and TMT-B time.

Abbreviations: RNFLT, retinal nerve fiber layer thickness; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; HOMA-IR index, insulin resistance index; MMSE, Mini-Mental State Examination; TMT-A, Trail Making Test-A; TMT-B, Trail Making Test-B.

Discussion

Diabetes is a chronic metabolic disease, which may result in increased blood glucose concentration due to hereditary and acquired deficiency in insulin production or ineffective reaction of human cells to insulin (insulin resistance).[12,13] At present, the etiology of this disease is not fully understood, and if not treated in a timely manner during the occurrence and development of T2DM, it may increase the risk of chronic complications such as macro-vascular disease and micro-vascular complications.[14] DR is a retinal complication of diabetes, which is the damage of retinal micro-vessels caused by long-term hyperglycemia, and it is also associated with retinal neuroglial network disease.[15] The fundus changes caused by diabetes retinopathy include micro-angioma, hard exudation, cotton wool spots, new blood vessels, vitreous proliferation, macular edema, and even retinal detachment, which can cause different degrees of vision loss, and is a chronic progressive blindness eye disease.[16] However, most patients have no clinical symptoms in the early stages. If not detected in a timely manner, diabetes retinopathy can seriously affect vision and even lead to blindness in the later stages. Therefore, timely evaluation and management are crucial for the prognosis of patients.

Retinal neuropathy in diabetes is one of the typical injuries in T2DM caused by neuronal apoptosis and glial activation.[17] In the retina, neurons, glial cells, and vascular cells are tightly connected in the neurovascular units to maintain the necessary balance for normal neuro-retinal function.[18] A study has found[19] that T2DM may have a certain relationship with the loss of RNFLT. Diabetes may cause retinal damage due to ischemic changes and neuronal deformation, thus leading to the reduction of RNFLT. At present, scholars believe[20] that diabetic neuropathy is the joint action of multiple factors such as metabolic disorders, vascular damage, neurotrophic factor deficiency, oxidative stress and immune damage, which can cause demyelination and degeneration of nerve fibers. RNFL, which is composed of ganglion cell axons, becomes thinner when nerve degeneration occurs, so RNFL thickness reflects ganglion cell survival. The reduction of RNFL thickness has a significant impact on the visual acuity of patients with T2DM. Diabetes mellitus can lead to retinal microcirculation disorder in the fundus due to high blood glucose, and this damage of small blood vessels will cause severe visual loss.[21] The results of this present study found that the average thickness, nasal, inferior and superior thickness of patients with DR were significantly reduced. Pearson analysis revealed a significant negative correlation between RNFLT and FBG, HbA1c and HOMA-IR index, indicating that the control of

indicators such as FBG, HbA1c and HOMA-IR index has a certain impact on RNFLT. It is speculated that as the condition worsens, blood sugar levels gradually increase. High blood sugar can induce apoptosis and dysfunction of retinal ganglion cells, leading to thinning of the retinal nerve fiber layer.[22] In addition, the increase in blood sugar can lead to oxidative stress and inflammatory reactions, which can also cause damage to the retinal nerve fiber layer.[23] It has been confirmed by previous studies[24] that the retina of T1DM or T2DM patients without retinopathy is thinner, involving the retinal nerve fiber layer, ganglion cell layer, and inner plexus layer. Moreover, RNFLT was revealed to be negatively correlated with HbA1c, the duration of diabetes and the severity of the patient's condition. The specific mechanism related to HbA1c and DR is still unclear. The possible mechanism is that low HbA1c promotes the occurrence and development of DR by reducing shear stress. In small blood vessels, shear stress can control vascular tension and angiogenesis.[25] In the retina, the reduction of shear stress affects the function and activity of retinal micro-vasculature, acting on endothelial cells and pericytes, which are important regulatory factors for vascular remodeling and tension. Shear stress dysfunction can promote the occurrence and development of DR.[26] The study has shown[27] that RNFL thickness gradually decreases with the increase in the degree of DR, indicating that changes in RNFL thickness are closely related to the severity of diabetes. In addition, some other study has pointed out[28] that HOMA-IR index, as an important indicator of insulin resistance, is related to the development of diabetes. These factors may all affect the thickness of RNFL. Further analysis showed that HOMA-IR index was positively correlated with the severity of DR, which meant that higher HOMA-IR index was associated with thinner RNFL thickness in diabetic patients, indicating more severe nerve damage.

Cognitive dysfunction refers to abnormalities in the brain's information processing ability, learning and memory, and cognitive judgment, manifested as symptoms such as lack of concentration, decreased memory, and delayed thinking.[29] T2DM patients are generally accompanied by cognitive impairment. Besides, the risk of cognitive impairment increases with the progression of T2DM. Cognitive dysfunction not only affects the quality of life of patients, but also may lead to difficulties in the treatment and management of diabetes.[30] Some studies have found that,[31] compared with non-diabetes patients, diabetes patients have poor cognitive ability and abnormal brain imaging. At present, studies have confirmed[32,33] that vascular risk factors, micro-vascular complications, and poor blood glucose control may all be risk factors for cognitive dysfunction in T2DM patients. However, the relationship between DR and cognitive dysfunction is still unclear. In this study, we analyzed the changes of cognitive function in patients with DR. The results showed that the MMSE score of patients with DR was significantly reduced, and the levels of TMT-A and TMT-B of patients with DR were significantly increased, indicating that the cognitive function of patients with DR was decreased. In addition, Pearson correlation analysis showed a significant correlation between RNFLT and levels of TMT-A, TMT-B and MMSE, suggesting that cognitive impairment may lead to a decrease in RNFLT to a certain extent. This may be related to micro-vascular disease in diabetes patients, which will lead to hypoxia and further dysfunction in the retinal nerve fiber layer.[34] In addition, cognitive dysfunction may also aggravate the metabolic disorder of diabetes patients, thus affecting RNFLT.[35] Other possible reasons are that there are major receptors in the retina associated with the muscle cell pathway associated with retinal nerve fibers, while in T2DM patients, there is dysfunction in the muscle cell pathway. The loss of primary visual cortex cells and changes in RNFLT may cause axonal changes that affect synaptic function, leading to a deterioration of cognitive function.[36]

This study provided new ideas for the treatment and prevention of T2DM. On the one hand, in view of the change of RNFLT, doctors should strengthen the monitoring of the retinal nerve fiber layer of patients during clinical diagnosis and treatment, thereby detecting the risk of DR timely. On the other hand, for patients with cognitive impairment, their cognitive function should be evaluated in a timely manner and corresponding intervention measures should be taken to reduce the impact of cognitive impairment on RNFLT. At the same time, in response to abnormalities in blood biochemical indicators, patients need to strengthen lifestyle improvements, such as controlling diet, increasing exercise, and taking medication on time, to slow down damage to the retinal nerve fiber layer.

In general, patients with DR had obviously decreased RNFLT, increased FBG and HbA1c levels, and some cognitive dysfunction. RNFLT had a certain correlation with FBG, HbA1c, TMT-A, TMT-B and MMSE. However, this study still has certain limitations. Due to time constraints, this study had not yet conducted visual function tests such as visual field testing and contrast testing. The relationship between visual function and T2DM retinopathy was not yet clear. This study was a retrospective study and lacked a long research period. In the future, large-scale and long-term observational studies will be conducted to increase the accuracy of the conclusion.

Innovations

1. The application of new technology: OCT technique provides the possibility for noninvasive measurement of RNFLT thickness, which helps to accurately assess diabetic retinal nerve fiber damage degree.
2. Exploration of biomarkers: Finding biomarkers related to RNFLT thickness, blood biochemical indicators and cognitive dysfunction in diabetic patients, thereby providing new targets for early diagnosis and treatment.
3. Research on intervention strategies: To explore effective intervention strategies, such as anti-oxidation, anti-inflammation, and improvement of vascular function, according to the mechanism of correlation between RNFLT thickness and blood biochemical indexes and cognitive dysfunction.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

All procedures performed in studies were in accordance with the ethical standards of the ethics committee of The Third Affiliated Hospital of Soochow University.

Consent for Publication

Written Informed consent was obtained from all individual participants included in the study. The patients participating in the study all agree to publish the research results.

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Disclosure

The authors declare that they have no competing interests.

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