Int J Clin Exp Med 2020;13(12):9727-9732
www.ijcem.com /ISSN:1940-5901/IJCEM0116115

Original Article

Observation of changes in retinal nerve fiber layer thickness in early diabetic retinopathy by optical coherence tomography

Hongwen Jiang

Department of Ophthalmology, The First People's Hospital of Kashgar, Kashgar, Xinjiang Uygur Autonomous Region, China

Received June 12, 2020; Accepted September 10, 2020; Epub December 15, 2020; Published December 30, 2020

Abstract: Objective: To explore the effectiveness and safety of measuring macular retinal nerve fiber layer (RFNL) thickness in early stages of diabetes retinopathy (DR) using optical coherence tomography (OCT). Methods: A total of 149 DR patients admitted from December 2018 to December 2019 were divided into non-diabetic retinopathy (NDR) group (56 cases, 110 eyes) and mild NPDR (non-proliferative DR) group (51 cases, 99 eyes) and moderate NPDR group (48 cases, 89 eyes). 46 healthy subjects (92 eyes) were included in the control group. All participants were subjected to OCT to measure RFNL thickness, including the quadrants of the optic disc (thickness, superior quadrant, inferior quadrant, and temporal quadrant), mean macular thickness (MMT), and foveal thickness. Results: Moderate NPDR group showed smaller thickness of superior quadrant, inferior quadrant and temporal quadrant than the control group ($P < 0.05$); temporal quadrant and inferior quadrant thickness in NDR group were not statistically different from control group ($P > 0.05$). However, its superior quadrant thickness is significantly smaller ($P < 0.05$); in contrast to NDP group, mild NPDR group showed similar thickness of superior quadrant and temporal quadrant, and smaller thickness of inferior quadrant ($P < 0.05$); the thickness of superior quadrant, inferior quadrant and temporal quadrant in the control group were greater than those of the mild NPDR, NDP and moderate NPDR groups ($P < 0.05$). The foveal thickness and MMT of the mild to moderate DR groups were significantly greater than those of the NDP and the control groups ($P < 0.05$); the macular RNFL thickness of each quadrant in NDR group was significantly thinner than that of the control group ($P < 0.001$), and it was significantly thicker in moderate NPDR group than that of NDR and mild NPDR groups ($P < 0.001$). Conclusion: The RNFL has thickened significantly before retinal vascular changes in DM patients. The thickness of RNFL can be used as the diagnostic indicator for evaluating the severity of DR disease.

Keywords: Diabetes, retinal nerve fiber layer, optical coherence tomography, safety analysis

Introduction

Diabetic retinopathy (DR) is a disease caused by diabetes that could lead to blindness. 60% patients with 20 years of diabetes will develop DR [1]. When DR advances into proliferative DR (PDR), it will cause blindness and seriously affect the normal life of patients [2]. The incidence of DR increases with the course of diabetes, which has reached 43.1% in China [3]. Some patients with hidden complications often did not take much attention, which eventually incur severe DR. Therefore, diabetes should be treated as soon as possible to prevent DR [4]. At present, a series of instruments can be used to quantitatively detect the papillary structure and the thickness of RNF. Among them, optical coherence tomography (OCT) is a non-contact, non-invasive, high-resolution imaging technology of biological tissue structure. In recent years, with the application of Fourier technology and broadband light source technology, a new generation of frequency domain OCT has brought higher-speed and higher-resolution OCT images than time domain OCT. RTVue OCT, manufactured by Optovue in the United States, is one of the frequency range OCT instruments currently used in ophthalmology clinical applications, which has an acquisition speed of 26,000 A scans per

second and a resolution of up to 5 m. Studies have pointed out that when DR occurs, the thickness of RNFL will change, and the specific change pattern has not been explored in detail [5].

In this study, OCT scanning and RNFL thickness detection were used to observe the changes and discuss possible mechanism of early RNFL changes.

Materials and methods

Baseline data

149 DR patients admitted from December 2018 to December 2019 were enrolled. On the basis of DR international staging [5] standard, 56 patients (110 eyes) were divided into NDR group, including 29 men and 27 women, aged 28-76 years, average 48.46 ± 9.76 years old, course of disease 10-28 years; 51 patients (99 eyes) in mild NPDR group, including 26 males and 25 females, aged 25-74 years, average 46.46 ± 8.76 years old, course of disease 11-27 years; 48 patients (89 eyes) in the moderate NPDR group, including 23 men and 25 women, aged 23-73 years, average 47.42 ± 8.96 years, course of disease 11-21 years; 45 healthy persons (90 eyes) were enrolled as the control group, including 22 males and 24 females, aged 21-77 years, with an average age of 50.16 ± 7.26 years.

Inclusion criteria: All patients were diagnosed as DR by ophthalmology specialists [6]. The clinical symptoms included vascular degeneration, lint spots, bleeding, retinal hypoxia and edema. There was no significant difference in baseline data such as gender and age among three groups ($P > 0.05$), which were comparable. None of the enrollees had congenital visual impairment, and all enrollees or their families had signed informed consent. This study has been approved by the Ethics Committee of First People's Hospital of Kashgar.

Outcome measurement

Optovue Fourier domain optical coherence tomography scanner (RTVUE-100, axial resolution 5 μm, scanning rate 26,000 times/s) was applied. Before examination, compound topicamide was used to enlarge the pupils. During the examination, the subject took the sitting position, placed their lower jaw on the bracket, and adopted internal fixation. The center point of the optic disc was taken as the center of the circle, and the optic disc was scanned in a circle with a diameter of 3.45 mm. The same eye was scanned for 3 times. The computer image analysis system was used to measure the RNFL thickness. The measurement parameters included average RNFL thickness around optic disc, temporal, superior, nasal and inferior RNFL thickness. The average value of the three measurements was taken as the RNFL thickness of the subject eye. Then, macular fovea was taken as the center, and linear scanning was performed along the horizontal and vertical meridians, and in the temporal-superior, temporal-inferior, nasal-superior and nasal-inferior directions, respectively. The thickness of macular fovea and average retinal thickness (the area around the fovea with a diameter of 1000 μm) were recorded. Macular topographic map software was used for analysis and measurement. All subjects were measured by the same technician.

Statistical analysis

SPSS19.0 was used for data analysis. Measurement data were expressed by mean ± standard deviation ($x \pm sd$), and t test was used for examination. The count data were tested by chi-square X^2 test, $P < 0.05$ was considered statistically significant.

Results

Comparison of general data

There was no statistically significant difference in gender, age, course of disease and number of included eyes among the four groups ($P > 0.05$). Except for the control group without course of disease data, there was no significant difference in other clinical data compared with each group ($P > 0.05$, **Table 1**).

Comparison of optic disc quadrants and RNFL thickness

Moderate NPDR group showed smaller thickness of quadrants and RNFL thickness than the control group ($P < 0.05$); NDP, NPDR (mild, moderate) groups showed smaller thickness of superior quadrant, inferior quadrant, and temporal quadrant than the control group ($P < 0.05$, **Table 2**; **Figure 1**).

Table 1. Comparison of general data

General data	NDR group	Mild NPDR	Moderate NPDR	Control group
Age (year)	48.46 ± 9.76	46.46 ± 8.76	47.42 ± 8.96	50.16 ± 7.26
Gender (M/F)	29/27	26/25	23/25	22/24
Course of disease (year)	10-28	11-27	11-21	-
Eye (number)	110	99	89	90

Table 2. The quadrants and RNFL thickness (x ± sd)

Group	Eyes	Thickness	superior quadrant	inferior quadrant	temporal quadrant
Control group	90	107.83 ± 8.36	132.92 ± 14.22	135.32 ± 17.32	78.29 ± 9.28
NDR group	110	105.22 ± 9.82	125.27 ± 16.28*	133.38 ± 12.32	77.27 ± 10.24
Mild NPDR	99	103.09 ± 8.02	123.98 ± 13.72*	127.82 ± 14.21*	77.01 ± 8.24
Moderate NPDR	89	101.28 ± 7.25*	118.28 ± 11.21*	120.38 ± 9.28*	72.1 ± 9.18*
t		7.03	7.16	7.29	7.06
P		< 0.05	< 0.05	< 0.05	< 0.05

Note: *Compared with the control group, P < 0.05.

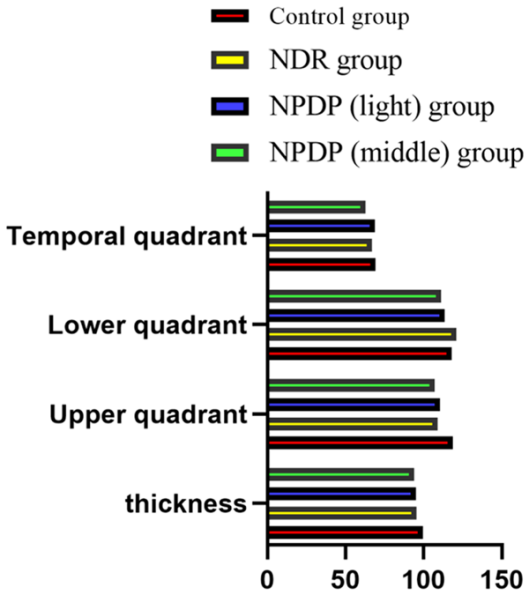

Figure 1. Thickness of quadrants and RNFL in the 4 groups. The RNFL, inferior quadrant and temporal quadrant thickness of the control group were different from those of the NDR group, mild NPDR and moderate NPDR groups (P < 0.05).

Macular RNFL thickness in each group

The macular RNFL thickness in NDR group was significantly thinner than that of the control group (P < 0.001). Moderate NPDR group showed smaller RNFL thickness than NDR and mild NPDR groups (P < 0.001, **Table 3**; **Figure 2**).

Comparison of MMT and fovea thickness in macular area

The MMT and foveal thickness of NPDR group (mild and moderate) were significantly greater than that of control group (P < 0.05); MMT of NDP and NPDR (mild and moderate) groups was greater than that of the control group (P < 0.05, **Table 4**; **Figure 3**).

Discussion

Diabetic retinopathy is the ocular complication of diabetes and its risk will increase over the course of diabetes [7]. Therefore, early prevention and diagnosis of DR can effectively avoid the occurrence and reduce the severity [8, 9]. Studies have shown that the early symptom of DR is the change in RNFL thickness resulted from damage to the optic nerve and abnormal retinal blood vessels [10, 11]. If the RNFL thickness is monitored and appropriate therapy is given in time, rate of blindness in DR patients will be greatly improved. Retinal thickness is an important index to evaluate macular disease. Previous studies have confirmed that there are differences in the thickness of the retina in different regions of the macula, and the macular fovea is the thinnest in normal people and the thickest in the 3 mm inner ring area, suggesting that DR may start with diffuse tissue edema and vascular leakage, while mild NPDR begins to show retinal sponge-like thickening, indicating that with the aggravation

Table 3. The thickness of RNFL in each quadrant of macular retina in 4 groups (x ± sd)

Group	eyes	Superior nasal	Superior temporal	Lateral temporal	Inferior temporal	Inferior nasal	Lateral nasal
Control group	90	47.76 ± 5.15	36.59 ± 3.11	28.26 ± 2.36	39.27 ± 4.13	44.53 ± 4.27	40.35 ± 2.93
NDR group	110	39.16 ± 5.49*	31.14 ± 3.45*	24.01 ± 2.18*	34.36 ± 4.19*	39.78 ± 5.61*	36.29 ± 4.64*
Mild NPDR	99	44.32 ± 6.85*	34.39 ± 3.34*	25.70 ± 3.09*	37.36 ± 4.32*	43.62 ± 5.43*	40.33 ± 6.36*
Moderate NPDR	89	45.46 ± 5.77*	35.23 ± 4.11*	26.74 ± 2.88*	38.56 ± 4.27*	44.87 ± 4.25*	41.76 ± 5.28*
F		17.809	15.207	12.149	21.543	9.883	5.218
P		< 0.001	< 0.001	< 0.001	< 0.001	0.001	0.003

Note: *Compared with the control group, P < 0.05.

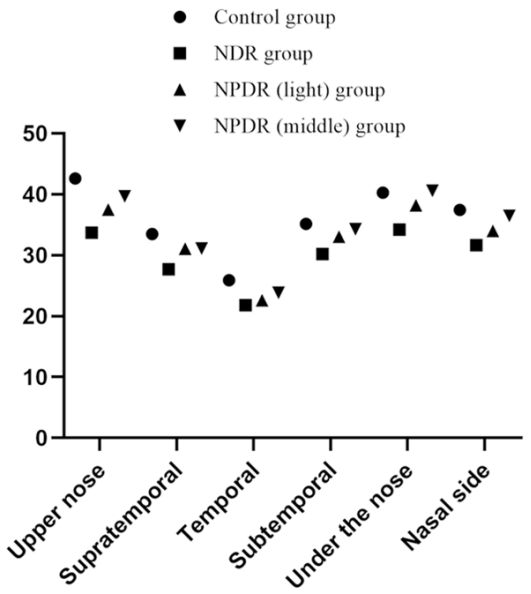

Figure 2. RNFL thickness in each quadrant of the macular retina in four groups. The thickness of RNFL and all quadrants in the control group were significantly higher than those of the NDR, mild NPDR and moderate NPDR groups (P < 0.05).

of the lesion, vascular permeability gradually increases [12]. This study analyzes the correlation between the thickness change of RNFL and the severity of DR, and formulates corresponding treatment measures. Some researchers have found that GCL or GCC becomes thinner in the macular area of patients with mild DR and without DR [13]. Due to the limitations of the instruments in this study, the thickness of GCL or GCC in the macular area could not be directly measured. As the axons of ganglion cells, the changes of RNFL could indirectly reflect the changes of GCL.

In this study, the thickness of the superior quadrant, inferior quadrant, and temporal quadrant of the control group were significantly higher than those of other three groups (P < 0.05), indicating that DR will increase the RNFL thickness, namely, the superior quadrant thickness of the optic disc is indicative of DR lesions [14, 15]. This study found that the thickness of superior quadrant is more sensitive and can be directly used as the main indicator for DR. In moderate NPDR group, the optic disc quadrants and RNFL thickness were significantly smaller than those in the control group (P < 0.05), indicating that the change of RFNL thickness in patients with moderate DR was significantly greater than that in the NDP and mild NPDR groups. Thickness of each quadrant may be related to the severity of DR [16-18].

The MMT and foveal thickness in the mild and moderate NPDR groups were significantly thicker than those in the control group (P < 0.05), indicating that DR affects MMT and foveal thickness, which can be used as an indicator for DR condition. The MMT of NDP and NPDR groups was significantly greater than that of the control group (P < 0.05), indicating that DR has a significant effect on retinal thickness and can be used in diagnosis of DR [19-22].

Since RNFL thickness can reflect the severity of DR, this study formulated treatment measures on the basis of above results. Specifically, if the retinal neovascularization is located 1.2 to 2.5 mm outside the optic disc, without protruding into vitreous cavity, the patients with NPDR should receive regular inspections and strict blood sugar control, and follow the doctor's instructions to take the medicine on time. When bleeding occurs in the retina, patients should do strenuous exercise, and should not intake high-sugar food, tobacco and alcohol to prevent hypoxia [23-25].

In summary, the thickness of RNFL canaccurately reflect the condition of DR. DR can be detected by observing changes in RNFL and

Table 4. MMT and foveal thickness (x ± sd, μm)

Group	Eyes	Foveal thickness	Mean RT
Control group	90	174.83 ± 26.36	212.92 ± 29.22
NDR group	110	186.22 ± 24.82	262.27 ± 31.28*
Mild NPDR	99	213.09 ± 32.02*	284.98 ± 30.72*
Moderate NPDR	89	221.28 ± 30.25*	296.28 ± 33.21*
t		7.11	7.34
P		< 0.05	< 0.05

Note: *Compared with the control group, P < 0.05.

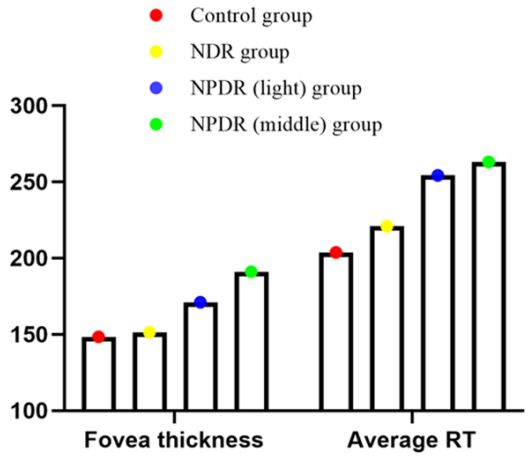

Figure 3. MMT and foveal thickness of the four groups. The MMT and foveal thickness did not differ between moderate and mild NPDR groups (P > 0.05). MMT in NDR group is different from mild and moderate NPDR groups (P < 0.05). The fovea thickness and MMT of the control group were significantly smaller than those of other three groups.

treated as soon as possible. Targeted treatment of DM patients can effectively reduce the incidence of DR.

Disclosure of conflict of interest

None.

Address correspondence to: Hongwen Jiang, Department of Ophthalmology, The First People's Hospital of Kashgar, No. 120, Yingbin Avenue, Kashgar, Xinjiang Uygur Autonomous Region, China. Tel: +86-0998-2964653; E-mail: hongwenjiang100@163.com

References

[1] Kanamori A, Nakamura M, Tabuchi K, Yamada Y and Negi A. Effects of ocular rotation on parapapillary retinal nerve fiber layer thickness analysis measured with spectral-domain optical coherence tomography. Jpn J Ophthalmol 2012; 56: 354-361.

[2] Oliveira TL, Andrade RE, Muccioli C, Sallum J and Belfort R Jr. Cystoid macular edema in gyrate atrophy of the choroid and retina: a fluorescein angiography and optical coherence tomography evaluation. Am J Ophthalmol 2005; 140: 147-149.

[3] Ziegler D, Winter K, Strom A, Zhivov A, Allgeier S, Papanas N, Ziegler I, Brüggemann J, Ringel B, Peschel S, Köhler B, Stachs O, Guthoff RF and Roden M. Spatial analysis improves the detection of early corneal nerve fiber loss in patients with recently diagnosed type 2 diabetes. PLoS One 2017; 12: e0173832.

[4] Nittala MG, Gella L, Raman R and Sharma T. Measuring retinal sensitivity with the microperimeter in patients with diabetes. Retina 2012; 32: 1302-1309.

[5] Elnahry AG, Hassan FK and Abdel-Kader AA. Bevacizumab for the treatment of intraretinal cystic spaces in a patient with gyrate atrophy of the choroid and retina. Ophthalmic Genet 2018; 39: 759-762.

[6] 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.

[7] Tavakoli M, Mitu-Pretorian M, Petropoulos IN, Fadavi H, Asghar O, Alam U, Ponirakis G, Jeziorska M, Marshall A, Efron N, Boulton AJ, Augustine T and Malik RA. Corneal confocal microscopy detects early nerve regeneration in diabetic neuropathy after simultaneous pancreas and kidney transplantation. Diabetes 2013; 62: 254-260.

[8] dell'Omo R, Cifariello F, De Turris S, Romano V, Di Renzo F, Di Taranto D, Coclite G, Agnifili L, Mastropasqua L and Costagliola C. Confocal microscopy of corneal nerve plexus as an early marker of eye involvement in patients with type 2 diabetes. Diabetes Res Clin Pract 2018; 142: 393-400.

[9] Ishibashi F, Kojima R, Taniguchi M, Kosaka A, Uetake H and Tavakoli M. The expanded bead size of corneal C-nerve fibers visualized by corneal confocal microscopy is associated with slow conduction velocity of the peripheral nerves in patients with type 2 diabetes mellitus. J Diabetes Res 2016; 2016: 3653459.

[10] Ishibashi F, Kojima R, Kawasaki A, Yamanaka E, Kosaka A and Uetake H. Correlation between sudomotor function, sweat gland duct size and corneal nerve fiber pathology in patients with type 2 diabetes mellitus. J Diabetes Investig 2014; 5: 588-596.

[11] Villarroel M, Ciudin A, Hernández C and Simó R. Neurodegeneration: an early event of diabetic retinopathy. World J Diabetes 2010; 1: 57-64.
[12] Nitta J, Tazawa Y, Murai KI, Egawa I, Nabeshima T, Endo T, Tanaka M and Machida S. Relationship between the s-wave amplitude of the multifocal electroretinogram and the retinal nerve fiber layer thickness in glaucomatous eyes. Jpn J Ophthalmol 2005; 49: 481-490.
[13] Srivastav K, Saxena S, Mahdi AA, Shukla RK, Meyer CH, Akduman L and Khanna VK. Increased serum level of homocysteine correlates with retinal nerve fiber layer thinning in diabetic retinopathy. Mol Vis 2016; 22: 1352-1360.
[14] Sahin SB, Sahin OZ, Ayaz T, Karadag Z, Türkyılmaz K, Aktas E and Bostan M. The relationship between retinal nerve fiber layer thickness and carotid intima media thickness in patients with type 2 diabetes mellitus. Diabetes Res Clin Pract 2014; 106: 583-589.
[15] El-Shazly AAE, Farweez YA, Hamdi MM and El-Sherbiny NE. Pattern visual evoked potential, pattern electroretinogram, and retinal nerve fiber layer thickness in patients with migraine during and after aura. Curr Eye Res 2017; 42: 1327-1332.
[16] Toffoli G, Vattovani O, Cecchini P, Pastori G, Rinaldi G and Ravalico G. Correlation between the retinal nerve fiber layer thickness and the pattern electroretinogram amplitude. Ophthalmologica 2002; 216: 159-163.
[17] Luo X, Patel NB, Harwerth RS and Frishman LJ. Loss of the low-frequency component of the global-flash multifocal electroretinogram in primate eyes with experimental glaucoma. Invest Ophthalmol Vis Sci 2011; 52: 3792-3804.
[18] Fukuda M, Nakanishi Y, Fuse M, Yokoi N, Hamada Y, Fukagawa M, Negi A and Nakamura M. Altered expression of aquaporins 1 and 4 coincides with neurodegenerative events in retinas of spontaneously diabetic Torii rats. Exp Eye Res 2010; 90: 17-25.
[19] Lee SB, Kwag JY, Lee HJ, Jo YJ and Kim JY. The longitudinal changes of retinal nerve fiber layer thickness after panretinal photocoagulation in diabetic retinopathy patients. Retina 2013; 33: 188-193.
[20] Wang Z, Liu XW, Li XY, Zhang WJ and Dai H. Detection of the changes of retinal nerve fiber layer thickness by GDx-VCC laser scanning polarimetry in primary open angle glaucoma patients. Zhonghua Yan Ke Za Zhi 2012; 48: 497-501.
[21] Firat PG, Doganay S, Demirel EE and Colak C. Comparison of ganglion cell and retinal nerve fiber layer thickness in primary open-angle glaucoma and normal tension glaucoma with spectral-domain OCT. Graefes Arch Clin Exp Ophthalmol 2013; 251: 831-838.
[22] Wang XM, Sun XH, Dai Y, Kong XM and Chen YH. The function-structure impairment pattern of optic nerves in primary open-angle glaucoma and normal-tension glaucoma. Zhonghua Yan Ke Za Zhi 2018; 54: 811-819.
[23] Alasbali T, Lofty NM, Al-Gehaban S, Al-Sharif A, Al-Kuraya H and Khandekar R. Macular ganglion cell-inner plexiform layer and retinal nerve fiber layer thickness in eyes with primary open-angle glaucoma compared with healthy saudi eyes: a cross-sectional study. Asia Pac J Ophthalmol (Phila) 2016; 5: 196-201.
[24] Bambo MP, Güerri N, Ferrandez B, Cameo B, Fuertes I, Polo V and Garcia-Martin E. Evaluation of the macular ganglion cell-inner plexiform layer and the circumpapillary retinal nerve fiber layer in early to severe stages of glaucoma: correlation with central visual function and visual field indexes. Ophthalmic Res 2017; 57: 216-223.
[25] Kwon JW, Choi JA, Kim JS and La TY. Ganglion cell-inner plexiform layer, peripapillary retinal nerve fiber layer, and macular thickness in eyes with myopic β-Zone parapapillary atrophy. J Ophthalmol 2016; 2016: 3746791.