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Association between retinal neuronal degeneration and visual function impairment in type 2 diabetic patients without diabetic retinopathy

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The changes in retinal thickness and visual function in type 2 diabetic patients without clinical evidence of diabetic retinopathy were evaluated. A total of 141 diabetic subjects without retinopathy and 158 healthy subjects were enrolled in this study. Superior macular ganglion cell complex thicknesses were significantly decreased in diabetic cases, and no significant peripapillary retinal nerve fiber layer thickness changes were observed. The contrast sensitivities at all space frequencies were significantly different between diabetic patients and controls. The mean P50 amplitude from pattern electroretinogram results was reduced significantly in the diabetic group. In the diabetic group, average superior ganglion cell complex thicknesses positively correlated with both contrast sensitivities at high spatial frequencies and P50 amplitudes. The results indicated that ganglion cell complex thickness and visual function changes could be observed in diabetic subjects before the onset of any significant diabetic retinopathy. Macular ganglion cell complex reduction occurred much earlier than peripapillary retinal nerve fiber layer thinning in diabetic patients without retinopathy.

diabetes mellitus, diabetic retinopathy, retinal nerve fiber layer, retinal ganglion cell, contrast sensitivity, electroretinogram

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Diabetic retinopathy (DR) is one of the major complications in patients with diabetes mellitus (DM) that can lead to blindness. DR has been considered primarily a retinal microvascular disorder caused by the direct effects of hyperglycemia and by the metabolic pathways it activates [1]. Previous studies have shown that vascular abnormalities and neuronal alterations, including neural apoptosis, loss of ganglion cells, glial reactivity, and reduction in thickness of the inner retinal layers, accompany the pathogenic changes at the earliest stages of DR [2–5]. Moreover, structural neuropathy can occur prior to the onset of visible diabetic vasculopathy, as shown in earlier experimental studies [5,6]. Structural alterations of retinal nerve tissue have also been reported in several clinical studies, as evidenced by thinning of the retinal nerve fiber layer (RNFL) in diabetic patients without diabetic retinopathy (NDR) compared with non-diabetic patients [7–9].

In addition to typical retinopathies, neurovisual impairments have been reported. Abnormalities in visual evoked potentials, contrast sensitivity, and dark adaption and electroretinogram (ERG) scans have been assessed in diabetic patients and indicated neuronal system involvement

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[2,10–14]. Morphological changes of retinal nerve tissue may explain the neurovisual functional deficits that are observed in diabetic patients, even before the overt retinopathy is seen. However, to the best of our knowledge, relationships between early retinal structure alterations and visual function impairments in a same population of NDR have not been reported. The purpose of our study was to evaluate the hypothesis that RNFL thickness and ganglion cell complex (GCC) thickness measured by spectral domain optical coherence tomography (SD OCT) and the visual functions tested with contrast sensitivity and pattern ERG (PERG) were associated in NDR patients.

1 Materials and methods

1.1 Study participants

This was a cross-sectional, case-control study. Patients were randomly recruited from the outpatient clinic of the Zhongshan Ophthalmic Center (Sun Yat-Sen University, Guangzhou). Inclusion criteria were type 2 DM patients without any signs of DR as evaluated by a retinal specialist (J Ma) through indirect fundoscopy and stereo color fundus photography, according to the International Clinical Diabetic Retinopathy Disease Severity Scale [15]. Exclusion criteria were clinically observed DR, myopia more than six diopters, visual acuity below 0.1, intraocular pressure (IOP) higher than 21 mmHg, history of glaucoma, uveitis, or retinal disease, or previous history of laser or intraocular surgery. Age- and sex-matched subjects, free of ocular disease, diabetes, hypertension, or other systemic diseases were recruited as controls from among those who accompanied patients visiting the outpatient clinic. The study was approved by the Zhongshan Ophthalmic Center institutional review board and conformed to the tenets of the Declaration of Helsinki, and all participants gave written informed consent.

Each subject underwent a complete ophthalmic examination, including determining best-corrected visual acuity (BCVA), refraction measurement, IOP measurement by noncontact tonometry, slit-lamp biomicroscopy, and dilated fundus examinations. All subjects were divided into two study groups, the NDR and control group, and NDR was defined as the absence of all features of DR [15].

1.2 SD OCT measurements

OCT was performed to obtain measurements of the peripapillary RNFL thickness using the RTVue-100 device (Optovue, Inc., Fremont, CA, USA). One eye of each subject was randomly chosen for measurement, and every eye was repeatedly measured three times. The peripapillary thickness was determined by optical nerve head mode, in which data along a 3.4-mm diameter circle around the optic disc were recalculated with a map created from *en face* imaging, using six circular and 12 linear data inputs. Average, superior, and inferior RNFL thicknesses were calculated. The GCC parameters were obtained by the macular map protocol, centered 1 mm temporal to the fovea. This protocol used one horizontal line with a 7-mm scan length (934 A-scans), followed by 15 vertical lines with a 7-mm scan length and 0.5-mm interval (800 A-scans). The GCC thickness was measured from the internal limiting membrane to the inner plexiform layer boundary; average, superior, and inferior GCC thicknesses were calculated.

1.3 Contrast sensitivity test

Contrast sensitivity was evaluated with the OPTC 6500 (Stereo Optical; Chicago, IL, USA). This test provided presentation of sine-wave gratings of different spatial frequencies (1.5, 3, 6, 12, and 18 cycles per degree (cpd)) with a contrast-level change step corresponding to 0.15 log contrast sensitivity. Following the manufacturer's protocol, the testing distance was 3 m for distance. The optimum additional spectacle corrections were used and an evaluation of the contrast sensitivity test was done monocularly in each subject. The contrast sensitivity measurements were performed under a constant luminance condition of 85.0 cd m^{-2}.

1.4 PERG

PERG was performed according to the International Society for Clinical Electrophysiology of Vision standard for clinical patterns [16]. In brief, gold foil corneal recording electrodes were positioned directly under the center of the pupil so that there was no movement of the electrode when the patient blinked. Reference and ground electrodes were placed in the outer canthus and on the forehead, respectively. A black-and-white reverse checkerboard pattern was used with an aspect ratio of width over height of the stimulus field not exceeding 4:3. The mean of the width and height of the stimulus field was 15 degrees, with a check size of 0.8 degrees. The contrast between black and white squares was close to 100%. The reversal rate was 2.2 Hz. A minimum of 100 artifact-free sweeps was collected and averaged. The P50 amplitude was calculated from the trough of N35 to the peak of P50. All data were recorded without pupil dilation.

1.5 Data analyses

Descriptive statistical data were described as the mean with standard deviation. All statistical analyses were performed using SPSS software version 17.0 (SPSS Co., Chicago, IL, USA). The distributions of characteristic data such as age, sex, and IOP in two groups were checked by using χ^2 tests or unpaired *t*-tests, as appropriate. For the statistical comparison of RNFL thickness and GCC thickness between two

groups, the ANOVA analysis was used. Correlation analyses were performed using Pearson's correlation coefficient for parametric data. *P* values less than 0.05 were considered as statistically significant.

2 Results

2.1 General characteristics

A total of 141 eyes from 141 NDR subjects and 158 eyes from 158 healthy subjects met our criteria and were included in this study. The characteristics of the two groups are presented in Table 1. No significant difference was found for age, sex, and IOP among groups.

2.2 Peripapillary RNFL and macular GCC thickness

After adjusting for age and gender, the average, superior and inferior peripapillary RNFL thicknesses were 102.0±12.1 μm, 128.5±15.3 μm, and 124.1±14.9 μm in controls, respectively, and 99.2±14.7 μm, 126.0±16.1 μm, and 120.0±15.3 μm in NDR subjects, respectively. The average, superior and inferior macular GCC thicknesses were 101.6±10.2 μm, 111.3±11.1 μm, and 110.2±10.2 μm in controls, respectively, and 99.3±9.5 μm, 103.2±13.2 μm, and 106.0±11.3 μm in NDR subjects, respectively. Differences in all RNFL parameters between NDR and control eyes were not statistically significant. The macular GCC thickness in the NDR eyes was significantly reduced by 6.8% in the superior region (ANOVA, $P<0.05$), whereas no significant difference was found in the inferior area (Figure 1).

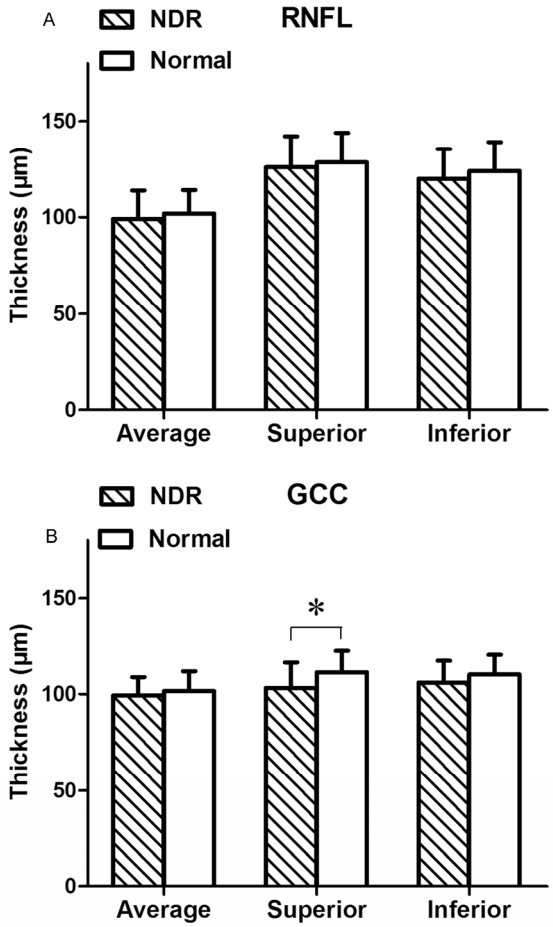

Figure 1 Peripapillary retinal nerve fiber layer (RNFL) thickness (A) and macular ganglion cell complex (GCC) thickness (B) measured by spectral-domain optic coherence tomography in diabetic patients without diabetic retinopathy (NDR) and in normal subjects. The asterisk indicates statistically different changes.

2.3 Visual function

Table 2 shows visual function parameters in the two groups, including BCVA, contrast sensitivity values, P50 implicit times, and amplitudes from PERG. According to Table 2, all data showed normal distributions upon Kolmogorov-Smirnov normality testing. There was no significant difference in BCVA among the control and NDR groups. Contrast sensitivity values were significantly decreased at every spatial frequency in the NDR versus control groups (ANOVA, all $P<0.05$). Results of PERG showed that the P50 amplitudes were significantly different between groups (ANOVA, $P<0.05$), whereas the P50 implicit time was not changed significantly.

Table 1 Clincal characteristics of normal and NDR subjects[a)]

Characteristics	Normal	NDR	*P* value
Case number	158	141	–
Male sex, *n* (%)	86 (54.4)	76 (53.9)	0.91
Age (year), mean±SD	63.62±10.57	68.10±9.33	0.38
IOP (mmHg), mean±SD	16.05±2.25	14.53±2.50	0.22
Diabetes duration (year)	–	9.75±2.11	–

a) NDR, no diabetic retinopathy; IOP, intraocular pressure. Age and IOP were analyzed by *t* test, male sex was analyzed by Chi-square test.

2.4 Correlations

In NDR eyes, significant positive correlations were found between superior macular GCC and contrast sensitivity at spatial frequencies of 6, 12, 18 cpd (r=0.51, 0.52, and 0.49, respectively; all $P<0.05$), and lower positive correlations were also found between inferior RNFL and contrast sensitivity at high spatial frequencies of 12 and 18 cpd (r=0.3 and 0.25, respectively; $P<0.05$). For the PERG data, there were positive correlations between P50 amplitudes and both inferior RNFL thickness and superior GCC thickness (r=0.65 and 0.41, respectively; both $P<0.05$). Interestingly, no significant correlation was found between P50 implicit times and any retinal structure parameter (Table 3).

Table 2 Comparison of visual function parameters in normal and NDR subjects[a)]

	BCVA (LogMAR)	Contrast sensitivity					PERG	
		1.5 cpd	3 cpd	6 cpd	12 cpd	18 cpd	Amplitude (μm)	Implicit time (ms)
NDR	0.10±0.19	37.78±11.06	49.02±10.81	61.21±15.09	30.22±4.73	10.19±1.26	0.91±0.16	63.29±8.15
Normal	0.08±0.11	49.01±10.77	64.11±13.08	79.33±16.21	45.5±8.70	17.55±2.62	1.42±0.20	61.11±8.39
P value*	0.82	**0.03**	**0.04**	**0.01**	**0.01**	**0.02**	**0.02**	0.15

a) NDR, no diabetic retinopathy; BCVA, best corrected visual acuity; cpd, cycles per degree; pERG, pattern electroretinogram. Data are reported as mean±SD. Bold font indicates significant difference between NDR and normal groups. *, ANOVA analysis.

Table 3 Correlations between retinal neural thicknesses and visual function parameters in NDR subjects[a)]

Parameters		Contrast sensitivity					PERG	
		1.5 cpd	3 cpd	6 cpd	12 cpd	18 cpd	Amplitude (μm)	Implicit time (ms)
Average RNFL	*r*	0.19	0.13	0.11	0.16	0.34	0.11	0.29
	P value	0.18	0.25	0.32	0.25	0.13	0.23	0.11
Superior RNFL	*r*	0.16	0.07	0.13	0.14	0.17	0.19	0.22
	P value	0.15	0.51	0.32	0.22	0.17	0.09	0.09
Inferior RNFL	*r*	0.12	0.19	0.22	0.3	0.25	0.65	0.19
	P value	0.33	0.28	0.09	**0.01**	**0.04**	**0.01**	0.09
Average GCC	*r*	0.13	0.14	0.19	0.22	0.17	0.16	0.07
	P value	0.32	0.22	0.09	0.09	0.17	0.15	0.51
Superior GCC	*r*	0.2	0.24	0.51	0.52	0.49	0.41	0.32
	P value	0.13	0.11	**0.01**	**0.01**	**0.01**	**0.04**	0.07
Inferior GCC	*r*	0.12	0.13	0.24	0.19	0.32	0.19	0.2
	P value	0.33	0.32	0.11	0.13	0.07	0.09	0.11

a) NDR, no diabetic retinopathy; BCVA, best corrected visual acuity; cpd, cycles per degree; pERG, pattern electroretinogram. Data are reported as mean±SD. Bold font indicates significant correlation.

3 Discussion

In this study we demonstrated that macular GCC thickness was significantly correlated with visual function parameters, such as contrast sensitivity and PERG amplitudes, in NDR patients compared with control subjects. To our knowledge, this is the first study exploring the structure-function relationships of the retina in diabetic patients before the onset of DR.

Previous work suggested that early neuronal degeneration in the retina could occur even though the retinal vascular lesions in diabetic patients were minimal. The inner retina, which is supplied by the retinal vessels, seems to be more vulnerable to metabolic stress induced by diabetes, compared with the outer retina, which is supplied by the choroidal circulatory system [17]. Therefore, in our study the peripapillary RNFL and macular GCC thicknesses were measured by SD OCT to detect early neuronal degeneration. It is well known that RNFL and GCC thicknesses decreased with age [18,19]. As shown in Table 1, there was no significant difference with respect to age between diabetic and normal subjects. Moreover, to exclude the possibility that retinal inner layer thickness was decreased with age, in this study we adjusted the ages within the study groups.

In the present study, we did not find significant differences in peripapillary RNFL thicknesses between the NDR and normal groups, although there was a trend of sectional RNFL reduction in NDR patients versus controls. This finding was consistent with other studies of preclinical DR [20–22]. One possible reason may be the high density of retinal nerve fibers in the peripapillary region [22]. However, significant thinning of the peripapillary RNFL thickness in preclinical DR has been reported in some previous studies [8,23,24]. This discrepancy between studies may be due to the difference in patient populations, devices for RNFL measurements, or study designs. It has been suggested that the peripapillary RNFL thickness profiles measured with OCT vary among individuals, and this variation was large relative to other factors, such as measurement error [25,26], optic disc size [27], or the retinal arterioles and venules extending from the optic disc [28].

In addition to peripapillary RNFL, we also evaluated macular GCC thickness to detect inner retinal damage. The macular region may be more susceptible to diabetic damage, because of its higher metabolic demands when compared with the peripapillary region [22]. The GCC thickness measured in the present study consisted of the macular RNFL, ganglion cell layer and inner plexiform layer. As reported by Kim et al. [29], the GCC thickness was a more direct measure of the integrity of retinal ganglion cells, and could be considered a better indicator of early retinal neuronal damage than peripapillary RNFL. Although the peripapillary RNFL thickness was not changed in the NDR group, in this study we observed a significant decrease of up

to 6.8% in superior macular GCC thickness in NDR patients compared with controls. Similar results have been reported previously [8,30,31]. Our finding of macular GCC loss could be explained by the loss of retinal ganglion cells and axons prior to the thinning of the RNFL [32,33]. In addition, the superior region of the macular is more susceptible to initial diabetic damage than the other regions. A previous diabetic animal model study reported that the superior area had twice the number of microaneurysms and cellular capillaries compared with the inferior area in the retina [34], suggesting a different retinopathy in the superior versus inferior regions. However, further studies are needed to determine the cause of the reduction in macular GCC thickness in diabetic patients without clinical DR.

The BCVA did not differ between NDR and normal groups in the present study. We hypothesize that the slight macular GCC loss in NDR patients may be insufficient to detect significant BCVA changes. Previous contrast sensitivity tests revealed abnormal functions before visual acuity tests, and correlated positively with the presence and the degree of diabetic retinopathy [35]. Several contrast sensitivity studies in diabetic patients showed a general decrease of sensitivity across low, medium, and high spatial frequencies, suggesting that both the parvocellular and magnocellular systems involved in contrast processing were affected by the disease [12,35–37]. Similar results were found in our study, where contrast sensitivities at each spatial frequency (from 1.5 to 18 cpd) were significantly decreased in NDR patients, compared with normal subjects. It has been suggested that the contrast abnormality occurring before the onset of the DR may be due to early retinal neural degeneration [37–39]. Interestingly, in our study we found that only contrast sensitivities at high spatial frequencies were positively correlated with macular GCC and peripapillary RNFL thickness. These correlations are expected because previous studies indicated that the selective losses at high spatial frequencies may be due to the dysfunction in the parvocellular pathway [35,37], and approximately 80% of ganglion cells are parvocellular cells [40].

The PERG is a mass potential that sums information primarily from the electrical potential of retinal ganglion cells [41,42]. It was suggested that the PERG response measured retinal ganglion cell activity; therefore, the direct loss of ganglion cell counts may affect the PERG response. In the present study, we also found a significant PERG amplitude reduction in NDR patients, which correlated with decreased superior macular GCC thickness. These results support the theory that the PERG relied on a centrally presented stimulus, in particular GCC thickness, and was strongly associated with macular parameters. However, the significant association between PERG amplitude and peripapillary inferior RNFL thickness in the NDR group also suggested that the PERG was measuring more than a central response [43]. For PERG implicit times, we did not observe any significant change or correlation with retinal inner layer thickness. A previous study suggested that a delay in ERG implicit times correlated with the chance of onset and development of DR [44]. Thus, there was a slight increase in implicit times in the NDR group, which was not significant, because in this study we only evaluated diabetic patients without DR.

There are several limitations of the present study. First, the sample size was small, although significant GCC changes were measured in NDR patients. Second, most of the diabetic patients we included in this study had controlled blood glucose levels, and some were receiving insulin therapy. It has been suggested that insulin can reverse retinal apoptosis and provide trophic support for retinal neurons [45]. The changes in GCC and RNFL thicknesses between NDR patients and control subjects may be larger because untreated diabetics were not included. Furthermore, the SD OCT could not provide a sectorial analysis of macular GCC; therefore we evaluated only the more limited data of GCC (average, superior, and inferior GCC thickness). If subdivided macular GCC data were available, the results could be more conclusive.

In summary, our results provided proof of concept that early neuronal degeneration existed in the inner retina in diabetic patients before the onset of clinical DR. SD OCT demonstrated that macular GCC thickness decreased much earlier than peripapillary RNFL thinning. In addition, correlations between GCC thicknesses and contrast sensitivities in NDR patients suggested that a loss of parvocellular cells may be involved in macular GCC damage. However, whether the macular GCC changes in diabetic eyes were a result of the effect of vascular diabetic retinopathy or whether they were primarily caused by direct neurological damage from chronic hyperglycemia requires further study.

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