

# Neurodegeneration in Type 2 Diabetes: Evidence From Spectral-Domain Optical Coherence Tomography

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**PURPOSE.** The purpose of this study was to assess changes in the neural retina in eyes with different stages of diabetic retinopathy (DR) in comparison to age-matched healthy subjects.

**METHODS.** Retrospective analysis of spectral-domain optical coherence tomography (SD-OCT) scans of 76 naïve eyes of 62 subjects with diabetes was performed. Key exclusion criteria included presence of diabetic macular edema, any other retinal disease, history of any treatment for DR, or incorrect segmentation of the retinal layers on SD-OCT scans. Eyes from diabetic patients were divided into three groups, including no DR, nonproliferative DR (NPDR), and proliferative DR (PDR). A control group of 67 eyes of 66 age-matched healthy volunteers was included for comparison. Average, minimum, and sectoral thicknesses for the ganglion cell-inner plexiform layer (GCIPL) and retinal nerve fiber layer (RNFL) were collected from both groups and compared using an ANOVA test.

**RESULTS.** Among the 76 included eyes, 43 had NPDR, 13 had PDR, and 20 had no signs of DR. Average and minimum GCIPL showed significant thinning in diabetic subjects compared with controls in all stages of DR ( $P < 0.05$ ), especially involving the papillo-macula bundle. However, GCIPL thickness was similar between diabetic groups. There was no significant difference in average or sectoral RNFL thicknesses among groups; however, the minimum RNFL thickness was lower in diabetics compared with controls ( $P < 0.05$ ). No relationship between GCIPL and RNFL thicknesses and duration of diabetes was present.

**CONCLUSIONS.** Early thinning on the inner retina happens in type 2 diabetes, even before visible vascular signs of DR. This supports the presence of a neurodegenerative process in eyes of patients with diabetes and warrants neuroprotective intervention to prevent chronic neurodegeneration. The SD-OCT may represent an indispensable tool for identifying early signs of neurodegeneration in diabetic patients.

**Keywords:** idiopathic macular telangiectasia, MacTel, IJRT, retinal ganglion cells, ganglion cells analysis, GCIPL, RNFL

Diabetic retinopathy (DR) is a disease with increasing prevalence that affects a working-age population and represents a growing public health problem due to eventual loss of vision and blindness, especially in developed countries.<sup>1</sup> Early clinical signs of DR include microaneurysms, hard exudates, and retinal hemorrhages. The pathogenesis behind these changes is thought to be mostly vascular; therefore, at present, therapeutic approaches are directed toward vascular remodeling. However, before clinically visible retinal changes occur, functional changes due to neural degeneration have been reported in subjects with diabetes.<sup>2</sup>

Functional changes secondary to inner retinal dysfunction, such as abnormalities on electroretinogram,<sup>3,4</sup> psychophysiological changes in contrast sensitivity,<sup>5-7</sup> loss of dark adaptation, color vision disturbances, and abnormal micro-perimetry results, have been previously described even before the onset of vascular lesions.<sup>2,8-10</sup> Experimental and histopathology studies have confirmed that eyes with diabetes are prone to neural changes such as neural apoptosis, retinal ganglion cell (RGC) loss, reactive changes in macroglia, thinning of the inner

retina, glial reactivity, neurofilament abnormality, and slowing of optic nerve retrograde transport. Such changes are suggestive of chronic neurodegeneration.<sup>11-14</sup> At present, VEGF is the most common target for treating diabetic macular edema (DME) and several other retinovascular diseases; however, it is essential for neuroprotection because it reduces apoptosis of retinal ganglion cells.<sup>15</sup> Thus, anti-VEGF agents causing reduction in VEGF levels may potentially speed up neurodegeneration in diabetes.<sup>16</sup> Therefore, suspicion and detection of early signs of neurodegeneration could be beneficial in preventing vision loss and deciding appropriate therapeutic approach in the management of diabetic retinopathy.

In vivo evaluation of the retinal microstructures with spectral-domain optical coherence tomography (SD-OCT) technology allows visualization of individual retinal layers.<sup>17</sup> Recent SD-OCT research has focused on the analysis of RGCs integrity in multiple sight-threatening diseases such as glaucoma, optic neuropathies, and maculopathies.<sup>18-20</sup> Integrity of RGCs is crucial for preserving visual function, because these

cells collectively transmit visual information from the retina in the form of action potential to several regions of the brain. Ganglion cell layer and inner plexiform layer consist of nuclei and dendrites of RGCs, respectively; retinal nerve fiber layer (RNFL) contains axons of the RGCs. The ganglion cell analysis (GCA) algorithm on Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, CA, USA) can successfully detect and measure the thickness of the macular ganglion cell-inner plexiform layer (GCIPL) without including the RNFL.<sup>21</sup> The reproducibility of GCIPL thickness measurements using the Cirrus HD-OCT GCA algorithm has been reported to be highly satisfactory.<sup>21,22</sup>

Because neurodegeneration could be the earliest sign of diabetic eye disease, evaluating *in vivo* morphologic changes in RGCs could guide clinicians in the suspicion of early functional damage in diabetes. The present study was performed to assess changes in neural retina (including GCIPL and RNFL) in eyes with different stages of DR in comparison to age-matched healthy subjects.

## METHODS

### Study Population

We retrospectively reviewed charts and SD-OCT images from 62 treatment-naïve diabetic patients (124 eyes) with or without DR, examined between January 2013 and June 2014 at the LV Prasad Eye Institute, Hyderabad, India. Prior approval from the Institutional Review Board of the institute was taken for this study, which was conducted in accordance with the tenets of the Declaration of Helsinki.

To be included in the study, diabetic participants must have undergone a comprehensive ophthalmic examination, indirect ophthalmoscopy, fundus fluorescein angiography (FFA), and SD-OCT scans. Diabetic retinopathy, if present, was classified as nonproliferative and proliferative as per standard early treatment diabetic retinopathy study (ETDRS) definition.<sup>23</sup> No DR was defined as no microaneurysms in the central retina and no lesions in the periphery as assessed by dilated indirect ophthalmoscopy. Exclusion criteria included the presence of DME, history of any treatment for DR, presence of any other retinal disease, high myopia greater than  $-6$  D or hyperopia greater than  $+3$  D, and history of retinal surgery. We also excluded SD-OCT images with visible eye motion or blinking artifacts, with any apparent failure in the automatic segmentation of the retinal layers, or with poor image quality (defined as signal strength  $< 6$ ). A control group of 67 eyes of 66 age-matched healthy volunteers with no ocular or systemic disease and no high refractive error (more than  $-6$  D or  $+3$  D) was included for comparison.

### Optical Coherence Tomography Protocol and Analysis

Optical coherence tomography image acquisition and processing SD-OCT scans were obtained by using the Cirrus HD-OCT after pupillary dilation. The Macular Cube  $512 \times 128$  scan protocol was used for all subjects as standard imaging protocol for our institute. The protocol performs 512 horizontal B-scans comprising 200 A-scans per B-scan over 1024 samplings within a cube measuring  $6 \times 6 \times 2$  mm centered on the fovea. GCA algorithm was applied to the Macular Cube scans as previously described.<sup>18</sup> The GCA algorithm identifies the outer boundary of the RNFL and the outer boundary of the IPL and provides measurements of GCIPL thickness. The average, minimum (lowest GCIPL thickness over a single meridian crossing the annulus), and sectoral (superotemporal, superior, superonasal, inferonasal, inferior, inferotemporal) GCIPL thicknesses were

measured in an elliptical annulus around the fovea (dimensions: vertical inner and outer radius of 0.5 and 2.0 mm, horizontal inner and outer radius of 0.6 and 2.4 mm, respectively; Fig.). The GCA algorithm measures the mean GCIPL thickness for each sector, compares them with the internal normative database of the device, and generates a thickness map, a deviation map, and a color-coded significance map. Measurements were displayed in green for normal range ( $P = 5$ –95%), in yellow for borderline ( $1\% < P < 5\%$ ), and in red for outside the normal range ( $P < 1\%$ ). Similar parameters and measurements were available for the macular RNFL thickness as well; because the internal database lacks normative data for macular RNFL thicknesses, data from the control group were used for comparison. The GCIPL and RNFL thicknesses data were exported in XML format using the built-in software for analysis.

### Statistical Analysis

Descriptive statistics included mean and SD for continuous variables. As both eyes of 10 subjects were included for analysis, the correlation between the two eyes of the same subject was adjusted using generalized estimating equations (GEEs) during the calculation of parameters. Comparison of the GCIPL and RNFL thicknesses between subjects with diabetes and control groups was performed using an ANOVA test. The ANOVA was used to evaluate changes in GCIPL thickness in different stages of the disease ranging from no DR to PDR. Statistical analyses was corrected for various factors including age, sex, spherical equivalent, and signal strength, which affects the quantitative measurements on OCT. Statistical analyses were performed using commercial software (Stata data analysis and statistical software, version 12.1; StataCorp, College Station, TX, USA).  $P < 0.05$  was considered statistically significant.

## RESULTS

Seventy-six eyes from 62 subjects with diabetes met the inclusion criteria and were included in the study. Thirty-seven were men and 25 were women, with a mean age of 57.5 years (range, 35–75 years). All eyes were phakic, with no significant lens opacities. Mean duration of diabetes was  $10.06 \pm 7.1$  years. Mean best-corrected visual acuity was  $0.177 \pm 0.27$  logMAR (Snellen's equivalent, 20/30). Mean spherical equivalent was  $1.1 \pm 0.6$  D. Forty-nine patients had associated hypertension, which was under control. Ten patients had both eyes included in the study, whereas for 53 patients, only one eye could be included. The fellow eyes of these 53 patients were excluded due to poor quality images (18 eyes), signal strength less than 6 (17 eyes), presence of pigment epithelial detachment (1 eye), or poor segmentation quality (17 eyes).

The control group included 67 eyes of 66 age-matched healthy volunteers with a mean age of 43.09 years (range, 32–69 years). There was no significant difference in terms of age ( $P = 0.30$ ), age distribution ( $P = 0.12$ ), sex ( $P = 0.20$ ), or mean spherical equivalent ( $P = 0.27$ ) between study and control groups.

Of the 76 eyes in the study group, NPDR was present in 43 eyes and PDR in 13 eyes, whereas 20 eyes had no signs of DR on indirect ophthalmoscopy. Among the 43 eyes with NPDR, mild and moderate NPDR was present in 22 and 21 eyes, respectively. None of the eyes had features of clinically significant DME. For analysis purpose, mild and moderate NPDR eyes were combined into a single NPDR group. The three diabetic groups (i.e., No DR, NPDR, and PDR) were

**Ganglion Cell OU Analysis: Macular Cube 512x128** OD ● OS

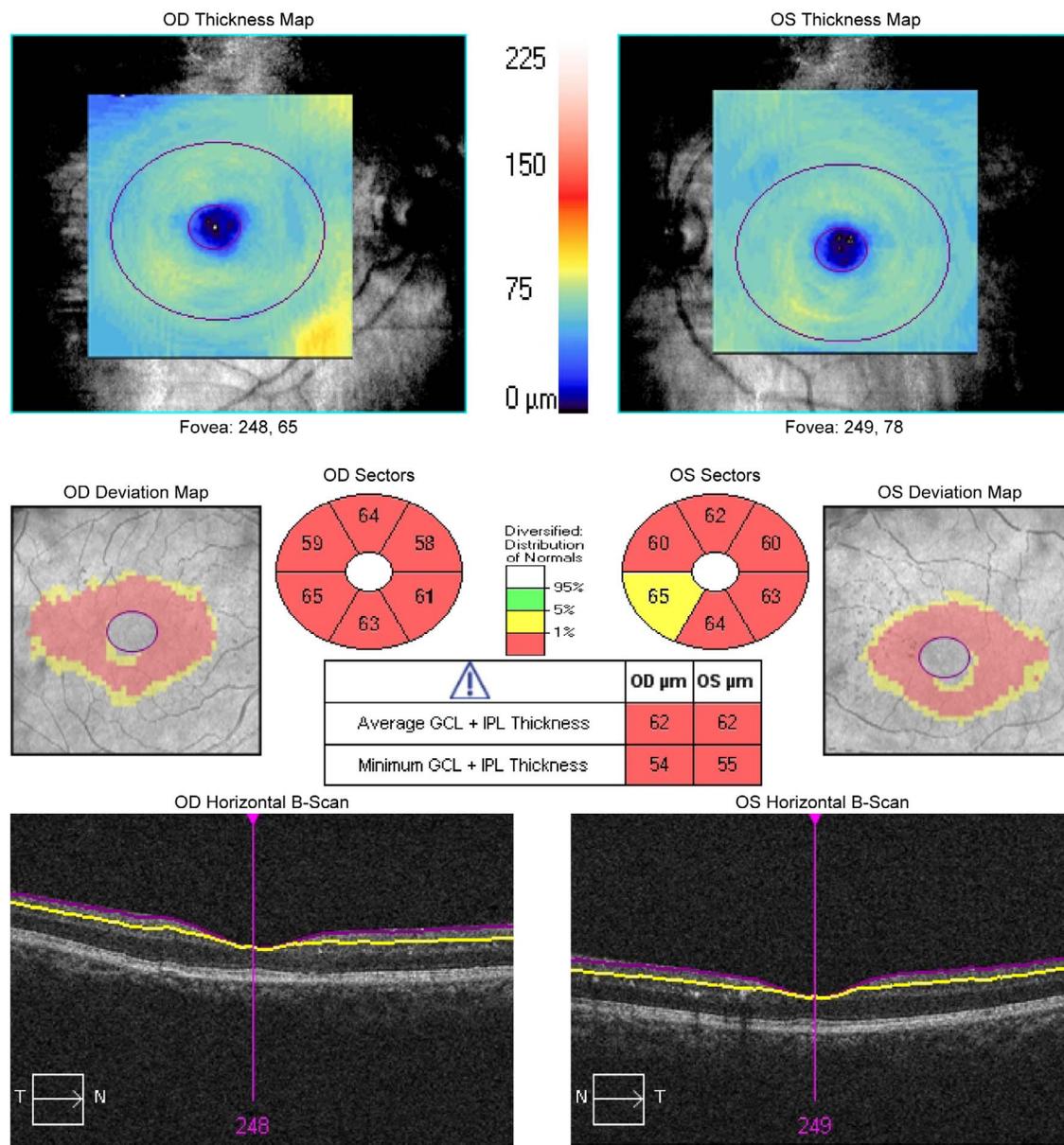


FIGURE. Ganglion cell analysis report of a 60-year-old man with features of mild NPDR shows severe inner retinal damage in both eyes, shown as thinning of the GCIPL.

matched in terms of age distribution, duration of diabetes, and presence or absence of hypertension (Table 1).

Mean average GCIPL thickness, minimum GCIPL thickness, and sectoral GCIPL thicknesses for the three groups of patients with diabetes and the control group are shown in Table 2. The average GCIPL and minimum GCIPL thicknesses were significantly lower in all diabetic groups compared with the control group ( $P < 0.05$ ). However, no significant differences in GCIPL thicknesses were present among eyes with no DR, NPDR, and PDR. Among the various sectors, significant thinning in diabetic subjects was present in the superior, nasal, and inferior sectors compared with age-matched healthy subjects.

Average and sectoral macular RNFL thicknesses were similar between diabetic groups and the control group. However, the minimum RNFL thickness was significantly lower in diabetic

patients compared with age-matched healthy subjects but not among the different grades of DR groups (Table 3).

No significant relationships between all GCIPL and RNFL thickness parameters and presence/absence of systemic hypertension or duration of diabetes were found.

**DISCUSSION**

Our study demonstrated that recent advancement in SD-OCT technologies are able to detect a significant thinning in RGC nuclei and dendrites (i.e., GCIPL) in eyes of diabetic patients without DME compared with age-matched healthy subjects, especially involving the papillo-macular bundle. A generalized GCIPL thinning was constantly found not only in eyes with NPDR or PDR, but even more interestingly in eyes of diabetic

TABLE 1. Clinical Characteristics of Diabetic Groups

	No DR	NPDR	PDR
Number of eyes (subjects)	20 (20)	43 (43)	13(12)
Mean age, y	59 ± 10.2	56 ± 9.1	56 ± 6
Male:female	12:8	30:13	11:1
Mean duration of diabetes mellitus, y	7 ± 7.4	9 ± 5.3	11 ± 9
Presence of hypertension, subjects	6	26	8
Best-corrected visual acuity	0.0 ± 0.22	0.0 ± 0.3	0.0 ± 0.1

patients with no signs of DR on indirect ophthalmoscopy. In addition, although RGC axons (i.e., RNFL) did not demonstrate a generalized thinning within the macula, diabetic eyes were found to have greater maximum thinning compared with controls. Finally, GCIPL and RNFL thinning was similar among patients with no DR, NPDR, or PDR. These findings suggest that early damage of the neural retina in diabetic patients occurs before and independently from diabetic vascular changes.

Previous animal and human studies have demonstrated that some RGCs die in diabetes, and some show structural alterations that are likely related to inflammation, excitotoxicity, and oxidative/nitrative stress.<sup>24</sup> Although the molecular mechanism by which RGCs die has not been clarified yet, apoptotic processes have been demonstrated histopathologically in RGCs in diabetes.<sup>11</sup> In particular, it was shown that apoptosis leads to RNFL thinning in rats with streptozotocin (STZ)-induced diabetes and in diabetic patients without or with only minimal DR by using scanning laser polarimetry or SD-OCT.<sup>25–27</sup> In addition, various signs of retinal neurodegeneration have been found postmortem in the retinas of diabetic donors without any microcirculatory abnormalities during ophthalmoscopic examinations performed the year before death.<sup>28,29</sup>

SD-OCT has been previously used to detect *in vivo* changes to the human retina in diabetes. Van Dijk et al.<sup>25–27</sup> reported thinning of inner retinal structures and RGCs in diabetic subjects with no DR or with minimal DR using automated segmentation of SD-OCT scans. Demir et al.<sup>30</sup> reported thinning of ganglion cells complex and RNFL in diabetic subjects with various stages of NPDR, but with no statistically significant difference compared with healthy controls. Lopes de Faria et al.<sup>31</sup> reported no significant difference in RNFL thickness in subjects with or without DR. In our study, we analyzed changes of the inner retina across multiple stages of DR, from no DR patients to PDR patients, and compared with healthy subjects. As previously reported on histopathology studies, we demonstrated using SD-OCT that RGC nuclei and

dendrites are diffusely affected in eyes of diabetic patients with no visible signs of diabetic vascular changes. Although GCIPL was found diffusely affected, similar to other studies, we did not find significant thinning of the RNFL. This could be due to a trailing step after RGC damage as reported by Van Dijk et al.<sup>25</sup> However, as a new finding, we demonstrated that diabetes does affect the minimum RNFL thickness in each stage of DR. Therefore, our results suggest that a broad damage of all RGC structures is present in diabetes. The damage primarily affects the RGCs nuclei and dendrites as shown by diffuse GCIPL thinning within the macula, and secondarily, the RGC axons as shown by the decreased minimum RNFL thickness. Indeed, as reported by Leung et al.,<sup>32</sup> after RGC damage, a progressive dendritic shrinkage happens first, followed by loss of the axon and the cell body. Results from our *in vivo* analysis of the macula using the GCA algorithm on SD-OCT support the findings of previous histology studies and strengthen the findings of previous SD-OCT studies on diabetic eyes.

Interestingly, we also found significant thinning of the nasal (papillomacular) GCIPL in subjects with diabetes, with no significant difference with severity of retinopathy. On the contrary, the temporal quadrants of diabetic eyes showed similar GCIPL thickness to control eyes. These findings could be due to the dense arrangement of RGCs in the nasal region, on their path toward the optic nerve. Similarly, significant RNFL thinning on the nasal compared with the temporal region has been reported previously.<sup>25</sup> Thinning of the papillomacular bundle has also been reported in neurologic and neuro-ophthalmologic disorders as a sign of neurodegeneration.<sup>33,34</sup> It is also widely recognized that neurodegeneration participates in early microvascular changes that occur in DR such as the breakdown of the blood-retinal barrier,<sup>35,36</sup> vasoregression,<sup>37</sup> and impairment of neurovascular coupling.<sup>38</sup> Various neuroprotective agents have been shown in animal models of DR to reduce RGC apoptosis.<sup>39</sup> Finally, two topical neuroprotective agents (brimonidine and somatostatin) are being evaluated in randomized clinical trials to prevent DR.<sup>40</sup>

In patients with type 2 diabetes mellitus, glucose metabolism can be disturbed years before the diagnosis is made. The duration of the disease process is, therefore, uncertain, and the assessment of a possible correlation between thinning of the inner retinal layers and duration of diabetes is, therefore, less precise. This could be the reason that we did not find any significant association with duration of diabetes.

There are a number of limitations in the present study. First, its retrospective nature and the small sample size for each individual group could have hampered potential associations. Second, the information about their diabetic status was collected as reported by the patient, and the HbA1c levels were not collected. Therefore, we could not evaluate the changes in SD-OCT parameters in relation to diabetic status.

TABLE 2. Macular GCIPL Thicknesses for the Three Groups of Patients With Diabetes and Control Group

Parameters	Age-Matched Healthy Subjects	No DR	NPDR	PDR
GC_AVERAGE	80.9 ± 7.4	75.55 ± 9.2 ( <b>P = 0.046</b> )	74.2 ± 9.1 ( <b>P = 0.001</b> )	75.83 ± 14.9 ( <b>P = 0.012</b> )
GC_MINIMUM	75.8 ± 9.8	64.45 ± 15.47 ( <b>P = 0.005</b> )	61.58 ± 16.7 ( <b>P = 0.000</b> )	62.75 ± 21.8 ( <b>P = 0.008</b> )
GC_TEMP_SUP	79.0 ± 7.3	75.75 ± 8.6 ( <b>P = 0.230</b> )	75.8 ± 10.52 ( <b>P = 0.212</b> )	76.08 ± 15.2 ( <b>P = 0.380</b> )
GC_SUP	81.2 ± 8.0	75.4 ± 12.1 ( <b>P = 0.085</b> )	74.4 ± 13.71 ( <b>P = 0.002</b> )	75.58 ± 15.1 ( <b>P = 0.017</b> )
GC_NAS_SUP	83.4 ± 8.5	75.5 ± 13.2 ( <b>P = 0.022</b> )	72.82 ± 16.2 ( <b>P = 0.000</b> )	79.8 ± 16.3 ( <b>P = 0.039</b> )
GC_NAS_INF	82.5 ± 8.32	76.4 ± 11.6 ( <b>P = 0.042</b> )	73.25 ± 14.6 ( <b>P = 0.000</b> )	78.3 ± 13.7 ( <b>P = 0.025</b> )
GC_INF	79.2 ± 8.2	73.9 ± 10.2 ( <b>P = 0.064</b> )	73.25 ± 8.6 ( <b>P = 0.005</b> )	72.1 ± 18.4 ( <b>P = 0.047</b> )
GC_TEMP_INF	80 ± 7.8	76.2 ± 10.6 ( <b>P = 0.207</b> )	75.45 ± 9.2 ( <b>P = 0.116</b> )	73.7 ± 21.1 ( <b>P = 0.092</b> )

All *P* values are in comparison to age-matched healthy subjects. GC\_AVERAGE, GCIPL average thickness; GC\_INF, GCIPL thickness in inferior sector; GC\_MINIMUM, GCIPL minimum thickness; GC\_NAS\_INF, GCIPL thickness in infero-nasal sector; GC\_NAS\_SUP, GCIPL thickness in supero-nasal sector; GC\_SUP, GCIPL thickness in superior sector; GC\_TEMP\_INF, GCIPL thickness in infero-temporal sector; GC\_TEMP\_SUP, GCIPL thickness in supero-temporal sector.

TABLE 3. Macular Retinal Nerve Fiber Layer Thicknesses Among the Three Groups of Patients With Diabetes and Control Group

Parameters	Normative	No DR	NPDR	PDR
RNFL_AVERAGE	30.51 ± 2.69	29.85 ± 8.89 ( <i>P</i> = 0.176)	29.09 ± 8.05 ( <i>P</i> = 0.206)	30.08 ± 6.77 ( <i>P</i> = 0.812)
RNFL_MINIMUM	13.16 ± 3.01	10.2 ± 4.04 ( <b><i>P</i> = 0.007</b> )	9.79 ± 4.79 ( <b><i>P</i> = 0.000</b> )	9.41 ± 5.53 ( <b><i>P</i> = 0.004</b> )
RNFL_TEMPSPUP	21.66 ± 2.59	20.6 ± 4.33 ( <i>P</i> = 0.585)	20.84 ± 5.28 ( <i>P</i> = 0.327)	22.08 ± 7.54 ( <i>P</i> = 0.759)
RNFL_SUP	32.53 ± 3.93	28.65 ± 7.96 ( <i>P</i> = 0.102)	29.02 ± 10.33 ( <i>P</i> = 0.180)	32.33 ± 9.78 ( <i>P</i> = 0.933)
RNFL_NASSUP	33.78 ± 4.17	39.35 ± 38.5 ( <i>P</i> = 0.150)	31.95 ± 10.72 ( <i>P</i> = 0.221)	34.33 ± 8.91 ( <i>P</i> = 0.821)
RNFL_NASINF	35.89 ± 4.37	33.55 ± 8.21 ( <i>P</i> = 0.208)	33.86 ± 10.6 ( <i>P</i> = 0.185)	33.33 ± 9.85 ( <i>P</i> = 0.300)
RNFL_INF	35.01 ± 4.09	32.9 ± 8.75 ( <i>P</i> = 0.267)	35 ± 11.4 ( <i>P</i> = 0.993)	34.5 ± 13.32 ( <i>P</i> = 0.848)
RNFL_TEMPINF	24.21 ± 2.36	23.4 ± 8.24 ( <i>P</i> = 0.487)	23.45 ± 6.88 ( <i>P</i> = 0.482)	24.41 ± 6.73 ( <i>P</i> = 0.906)

All *P* values are in comparison to age-matched healthy subjects. RNFL\_AVERAGE, RNFL average thickness; RNFL\_INF, RNFL minimum thickness in inferior sector; RNFL\_MINIMUM, RNFL minimum thickness; RNFL\_NASINF, RNFL minimum thickness in infero-nasal sector; RNFL\_NASSUP, RNFL minimum thickness in supero-nasal sector; RNFL\_SUP, RNFL minimum thickness in superior sector; RNFL\_TEMPINF, RNFL minimum thickness in infero-temporal sector; RNFL\_TEMPSPUP, RNFL minimum thickness in supero-temporal sector.

Third, one could argue that GCIPL thinning in DR eyes could be related to a possible segmentation issue of the GCA algorithm due to the presence of vascular changes such as microaneurysms or DME. However, eyes with DME and incorrect segmentation were excluded, and GCIPL thinning was present even in the absence of visible DR. Considering that we found strong and consistent results among our patients, we believe that it is unlikely that such results would be observed due to deficiencies in study procedures. Fourth, the HbA1c of the control group was unknown. Some healthy subjects may have had subclinical diabetes, which could have affected the inner layers of retina. Finally, our research focused only on subjects with type 2 diabetes; thus, our results cannot be applied on subjects with type 1 diabetes due to a difference in pathogenesis.

In conclusion, early thinning on the inner retina happens in type 2 diabetes, even before visible vascular signs of DR. This supports the presence of a neurodegenerative process in eyes with diabetes and warrants for neuroprotective intervention to prevent chronic neurodegeneration. Early identification of neurodegeneration using SD-OCT may become indispensable for developing neuroprotection strategies in diabetic patients. Longitudinal SD-OCT evaluation of diabetic eyes showing progression of the disease is needed to confirm our findings. Correlation between structural changes in neural retina and functional change may expand the understanding of the early neurodegenerative process in diabetes.

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