Original Article

Ganglion cell complex and retinal nerve fiber layer thickness in gestational diabetes mellitus

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Abstract:

PURPOSE: The purpose of this study was to compare ganglion cell complex and peripapillary retinal nerve fiber layer (RNFL) thickness between pregnant females with gestational diabetes mellitus (GDM) and healthy pregnant females.

MATERIALS AND METHODS: This was a single-center, prospective, analytical cross-sectional study including pregnant females with a gestational age of 24 weeks or more in the GDM and control groups. The GDM group included 162 pregnant females with GDM, and the control group included 162 healthy pregnant females. Peripapillary RNFL (pRNFL), macular RNFL (mRNFL), GCL+ (ganglion cell layer [GCL] + inner plexiform layer [IPL]), and GCL++ (mRNFL + GCL + IPL) thickness were analyzed using spectral-domain optical coherence tomography (OCT), and comparisons were made between the groups.

RESULTS: Both the groups had similar mean age ($P = 0.219$), intraocular pressure ($P = 0.186$), central corneal thickness ($P = 0.689$), Schirmer test value ($P = 0.931$), and tear breakup time ($P = 0.651$). The mean pRNFL thickness of the GDM and control groups was 100.75 ± 8.36 μm and 106.77 ± 8.44 μm ($P < 0.0001$). pRNFL was significantly thinner in all four quadrants ($P < 0.05$) in the GDM compared to the control group. We observed that the mean mRNFL, GCL+, and GCL++ thickness were significantly reduced in GDM in comparison to the control group ($P < 0.05$).

CONCLUSION: Our study showed that OCT plays an indispensable role in determining initial retinal changes caused by GDM before the development of diabetic retinopathy.

Keywords:

Ganglion cell layer thickness, gestational diabetes mellitus, optical coherence tomography, retinal nerve fiber layer thickness

Introduction

Gestational diabetes mellitus (GDM) is a state where intolerance to glucose develops or is first appreciated during pregnancy, increasing the likelihood of type II diabetes mellitus (DM) later in life.[1,2] These patients are mostly symptomless before developing proliferative diabetic retinopathy or macular edema; thus, screening is crucial. Studies have shown that neurodegenerative changes (i.e., retinal thinning) occur before diabetic retinopathy (DR) in subjects with type II DM.[3-5] Still, there is a paucity of literature about neurodegenerative changes before developing DR in GDM.

Diabetic retinal neurodegeneration chiefly affects the inner layer of the retina, mainly the inner plexiform layer (IPL), ganglion cell layer (GCL), and retinal nerve fiber layer (RNFL).[3] Here, we aimed to compare peripapillary RNFL (pRNFL), macular RNFL (mRNFL), GCL+ (GCL + IPL), and GCL++ (mRNFL + GCL + IPL) thickness among pregnant females with GDM and

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healthy pregnant females using spectral-domain optical coherence tomography (SD-OCT). We also compared mean pRNFL, mRNFL, GCL+, and GCL++ thickness among pregnant females with GDM and healthy pregnant females with a history of GDM in a previous pregnancy, with no history of GDM in a previous pregnancy, with a family history of DM, and with no family history of DM.

Materials and Methods

An analytical cross-sectional study was conducted at All India Institute of Medical Sciences, Jodhpur, at the Department of Ophthalmology in collaboration with the Department of Obstetrics and Gynaecology from January 2020 to June 2021. We included 324 subjects (648 eyes), 162 (324 eyes) pregnant females diagnosed with GDM and 162 (324 eyes) healthy pregnant females. The study approval was obtained from the Institutional Ethics Committee of All India Institute of Medical Sciences, Jodhpur (Reference Number: AIIMS/IEC/2019-20/955), and is consistent with tenets of the Declaration of Helsinki.

In the study, the subjects were recruited depending on the following criteria:

Inclusion criteria
The pregnant females with the gestational age of 24 weeks or more, diagnosed with GDM were included in GDM group and healthy pregnant females with the gestational age of 24 weeks or more were included in control group.

The International Association of Diabetes and Pregnancy Study Groups diagnostic criteria were followed in the Department of Obstetrics and Gynaecology for GDM.[6] An oral glucose tolerance test (OGTT) was done at 24–28 weeks of gestation using 75 g of glucose in the fasting state, and a diagnosis of GDM was made depending on the following criteria:
1. Fasting blood glucose ≥92 mg/dL (≥5.2 mmol/l) or
2. Blood glucose ≥180 mg/dL (≥10 mmol/l) at 1 h or
3. Blood glucose ≥153 mg/dL (≥8.5 mmol/l) at 2 h.

Exclusion criteria
The exclusion criteria are as follows:

1. Females not giving consent for inclusion in the study
2. Pregnant females with gestational age < 24 weeks
3. Females with DM
4. Pregnant females with any coexisting systemic illness such as hypertension, autoimmune diseases, vascular disease, or renal diseases, any preexisting retinal diseases such as optic disc coloboma, optic disc pit maculopathy, glaucoma, central serous chorioretinopathy (CSCR), macular hole, and choroidal neovascular membrane (CNVM) that may affect the OCT parameters.

Demographic data included age, occupation, income, residence, previous history of GDM, family history of diabetes, education level, and parity. After obtaining written informed consent, a complete ocular examination inclusive of best-corrected visual acuity, intraocular pressure (IOP), central corneal thickness (CCT), Schirmer's test, tear film breakup time (TBUT), ocular surface staining score (OSSS), anterior and posterior segment evaluation, fundus imaging, and SD-OCT for evaluating pRNFL, mRNFL, GCL+, and GCL++ thickness was done. The thickness measurements were only taken at 24 weeks or more than 24 weeks of gestation. The level of glycated hemoglobin (HbA1c) was also recorded.

Optical coherence tomography measurement protocol
The retinal segments were measured using Topcon 3D OCT-1 Maestro SD-OCT device (Topcon, Inc., Tokyo, Japan), which captures 50,000 axial scans/second and produces a 20 μm lateral and 6 μm axial resolution. 3D optic disc protocol (scan length – 6 mm × 6 mm, scan resolution – 512 × 128 pixels) was used for evaluating pRNFL thickness. pRNFL was analyzed as (1) total pRNFL-average thickness in 360°; (2) superior pRNFL-average thickness in superior 90°; (3) inferior pRNFL-average thickness in inferior 90°; (4) nasal pRNFL-average thickness in nasal 90°; and (5) temporal pRNFL-average thickness in temporal 90° [Figure 1].

3D macula (V) protocol (scan length – 7 mm × 7 mm, scan resolution – 512 × 128 pixels) was used for evaluating mRNFL, GCL+, and GCL++ thickness. mRNFL, GCL+, and GCL++ thickness were analyzed as superior (average thickness in the upper half), inferior (average thickness in the lower half), and total (average thickness in the whole macular area) [Figure 2].

Data were entered in a Microsoft Excel sheet and analyzed using the Statistical Software Package for the Social Sciences (SPSS) version 23 (IBM SPSS Statistics, Armonk, NY, USA). All nominal variables like gender were described using frequency and percentages and analyzed using the Chi-square test or Fisher's exact test. All ordinal variables were described using median and (interquartile range) and analyzed using the Mann–Whitney U-test. All continuous variables were described using mean and standard deviation and analyzed using the independent sample t-test. $P < 0.05$ was considered statistically significant.

Results

Overall, 324 subjects (648 eyes) were included in the study; 162 (324 eyes) were pregnant females with GDM
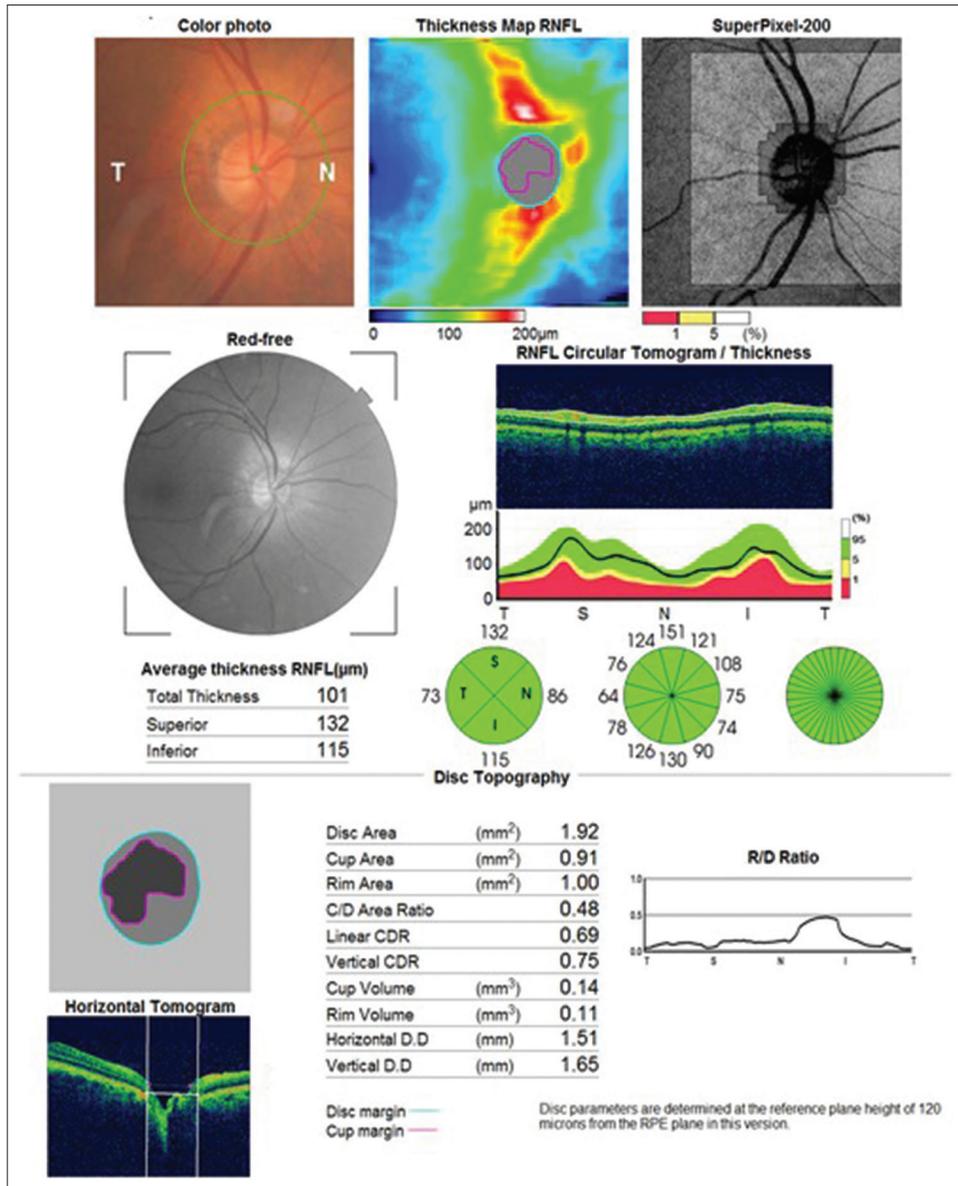
Figure 1: Peripapillary RNFL thickness measurements using spectral-domain optical coherence tomography, RNFL = Retinal nerve fiber layer

and 162 (324 eyes) were healthy pregnant females. Out of 162 pregnant females with GDM, 93.82% belonged to the urban area, and 7.40% were rural [Table 1].

The mean ages of the GDM and control groups were 28.72 ± 5.29 and 28 ± 5.27 years, respectively. Ages in both the groups ranged from 19 to 40 years and were normally distributed ($P = 0.219$). In the GDM and control groups, the mean IOP was 14.54 ± 2.06 mmHg and 14.32 ± 2.08 mmHg ($P = 0.186$), the mean CCT was 536.61 ± 12.77 μm and 536.04 ± 22.40 μm ($P = 0.689$), and the mean TBUT was 12.68 ± 1.50 s and 12.63 ± 1.45 s ($P = 0.651$), respectively. The mean Schirmer test values were 23.90 ± 2.71 mm and 23.92 ± 2.73 mm ($P = 0.931$) in the GDM and control groups, respectively.

The distribution of HbA1c levels in the study population is depicted in Table 2. The majority have HbA1c levels >7 (45.06%), and none have HbA1c levels <4.5 in the GDM group. On the other hand, none have an HbA1c level of >7 in the control group. No significant correlation was seen between HbA1c level and thickness.

Peripapillary retinal nerve fiber layer thickness
The mean pRNFL thickness was 100.75 ± 5.18 μm in the GDM group and 106.77 ± 5.76 μm in the control group; it was significantly reduced in the GDM group ($P < 0.0001$). pRNFL was significantly thinner in all four quadrants: superior ($P < 0.0001$), inferior ($P = 0.026$), nasal ($P < 0.0001$), and temporal ($P < 0.0001$) in the GDM group compared to the control group [Table 3]. Maximum thickness was seen in the inferior quadrant (136.30 ± 6.62 μm in
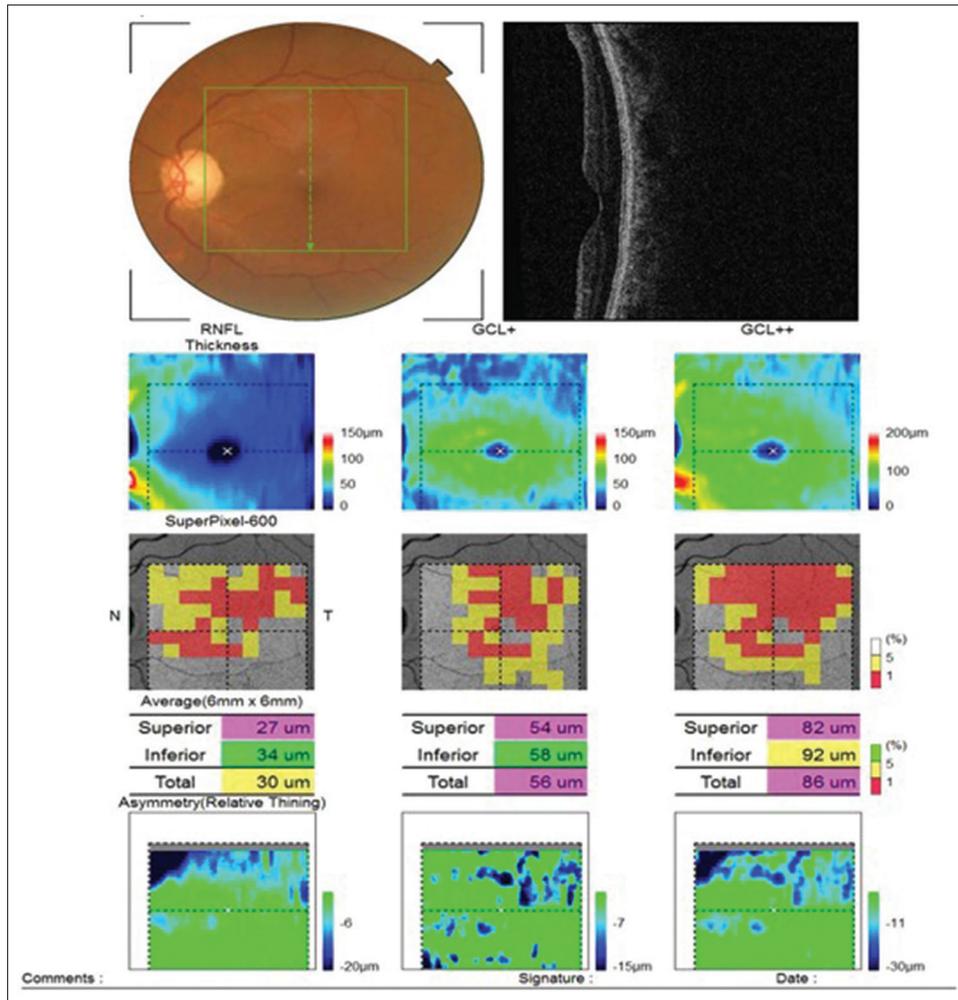
Figure 2: Macular RNFL, GCL+, and GCL++ thickness measurements using spectral-domain optical coherence tomography, RNFL = Retinal nerve fiber layer, GCL = Ganglion cell layer

Table 1: Sociodemographic details of the study population

Variables	Categories	GDM (*n*=162), *n* (%)	Healthy pregnant women (*n*=162), *n* (%)	*P*
Occupation	Homemaker	148 (91.35)	144 (88.88)	0.456
	Professional	14 (8.64)	18 (11.11)	
Income*	Median monthly income (IQR)	30,500 (23,000-37,000)	31,500 (20,000-46,500)	0.464#
Residence	Urban	150 (93.82)	148 (91.35)	0.682
	Rural	12 (7.40)	14 (8.64)	
Previous history of GDM	Yes	40 (24.69)	20 (12.34)	0.0042
	No	122 (75.30)	142 (87.65)	
Family history of diabetes	Yes	121 (74.69)	22 (13.58)	<0.0001
	No	41 (25.30)	140 (86.41)	
Education level	Illiterate	60 (37.03)	62 (38.27)	0.724
	School education	62 (38.27)	66 (40.74)	
	Above school education	40 (24.69)	34 (20.98)	
Parity	Primiparous	88 (54.32)	94 (58.02)	0.795
	Multiparous	72 (44.44)	66 (40.74)	
	Grand multiparous	2 (1.23)	2 (1.23)	

*Calculated only for participants with occupation, GDM group (*n*=14) and healthy pregnant group (*n*=18), #*P* value by Mann-Whitney *U*-test, *P* value for other variables calculated by Chi-square test. GDM=Gestational diabetes mellitus, IQR=Interquartile range

the GDM group and 138.93 ± 13.45 μm in the control group). Minimum thickness was seen in the temporal quadrant (65.81 ± 7.12 μm in the GDM group and 74.52 ± 6.03 μm in the control group).

Macular retinal nerve fiber layer thickness

The mean mRNFL thickness was 33.62 ± 2.74 μm and 35.80 ± 2.43 μm in the GDM and control groups, significantly lower ($P < 0.0001$) in the GDM group. In the GDM group, significant mRNFL thinning was observed in both superior (32.49 ± 3.05 μm in the GDM group and 35.23 ± 2.83 μm in the control group, $P < 0.0001$) and inferior quadrants (34.31 ± 3.09 μm in the GDM group and 35.89 ± 3.19 μm in the control group, $P < 0.0001$) [Table 4].

Ganglion cell layer+ and ganglion cell layer++ thickness

In the GDM and control groups, the mean GCL+ thickness was 68.30 ± 4.29 μm and 71.12 ± 3.52 μm ($P < 0.001$) and the mean GCL++ thickness was 102.33 ± 5.20 μm and 105.95 ± 4.94 μm ($P < 0.001$), respectively. The GDM group showed significantly lower mean GCL+ and GCL++ thickness ($P < 0.0001$). In the GDM and control groups, superior GCL+ thickness was 68.41 ± 4.53 μm and 71.64 ± 4.61 μm ($P < 0.001$); inferior GCL+ thickness was 67.74 ± 4.35 μm and 70.14 ± 3.94 μm ($P < 0.001$); superior GCL++ thickness was 101.87 ± 6.10 μm and 105.35 ± 5.91 μm ($P < 0.001$); and inferior GCL++ thickness was 102.43 ± 5.59 μm and 106.16 ± 5.97 μm ($P < 0.001$), respectively. Among the GDM and control groups, considerable thinning of GCL+ and GCL++ was seen in both the superior and inferior quadrants ($P < 0.0001$). Considerable GCL+ and GCL++ thinning ($P < 0.001$) was seen in both superior and inferior quadrants in the GDM group [Table 5].

The comparison of mean pRNFL, mRNFL, GCL+, and GCL++ thickness measurements in subgroups (pregnant females with a history of GDM in previous pregnancy, pregnant females with no history of GDM in previous pregnancy, pregnant females with a family history of DM, and pregnant females with no family history DM) between the GDM group and the control group is shown in Table 6. The mean pRNFL, mRNFL, GCL+, and GCL++ thickness was significantly lower in pregnant females with no history of GDM in a previous pregnancy, pregnant females with a family history of DM, and pregnant females with no family history of DM between the GDM group and the control group ($P < 0.05$). In pregnant females with a history of GDM in a previous pregnancy, between the GDM and control groups, lower values of mean pRNFL, mRNFL, GCL+, and GCL++ were observed, with mean pRNFL showing significantly lower values ($P = 0.05$).

In the control group, thinning of pRNFL ($P = 0.171$), mRNFL ($P = 0.352$), GCL+ ($P = 0.452$), and GCL++ ($P = 0.281$) was noted in pregnant females with a history of GDM in previous pregnancy in comparison to pregnant females with no history of

Table 2: Glycated hemoglobin levels of the study population

HbA1c levels (%)	GDM (*n*=162), *n* (%)	Healthy pregnant women (*n*=162), *n* (%)
<4.5	0	5 (3.08)
4.5-4.9	3 (1.85)	48 (29.62)
5.0-5.4	2 (1.23)	75 (46.29)
5.5-5.9	5 (3.08)	22 (13.58)
6.0-6.4	21 (12.96)	10 (6.17)
6.5-6.9	58 (35.80)	2 (1.23)
≥7	73 (45.06)	0

GDM=Gestational diabetes mellitus, HbA1c=Glycated hemoglobin

Table 3: Comparison of peripapillary retinal nerve fiber layer thickness measurements of the eyes between gestational diabetes mellitus group and control group

pRNFL thickness (μm)	Mean±SD		*P**
	GDM group (*n*=324)	Control group (*n*=324)	
Inferior	136.30±6.62	138.93±13.45	0.026
Superior	127.91±12.92	133.87±11.01	<0.0001
Nasal	72.44±7.83	79.22±5.61	<0.0001
Temporal	65.81±7.12	74.52±6.03	<0.0001
Mean	100.75±5.18	106.77±5.76	<0.0001

**P* value calculated by independent *t*-test. GDM=Gestational diabetes mellitus, RNFL=Retinal nerve fiber layer, pRNFL=Peripapillary RNFL, SD=Standard deviation

Table 4: Comparison of macular retinal nerve fiber layer thickness measurements of the eyes between gestational diabetes mellitus group and control group

mRNFL thickness (μm)	Mean±SD		*P**
	GDM group (*n*=324)	Control group (*n*=324)	
Superior	32.49±3.05	35.23±2.83	<0.0001
Inferior	34.31±3.09	35.89±3.19	<0.0001
Mean	33.62±2.74	35.80±2.43	<0.0001

**P* value calculated by independent *t*-test. GDM=Gestational diabetes mellitus, RNFL=Retinal nerve fiber layer, mRNFL=Macular RNFL, SD=Standard deviation

GDM in a previous pregnancy. In the GDM group, thinning of pRNFL ($P = 0.436$), mRNFL ($P = 0.141$), GCL+ ($P = 0.0.961$), and GCL++ ($P = 0.862$) was noted in pregnant females with no history of GDM in previous pregnancy in comparison to pregnant females with a history of GDM in a previous pregnancy.

Discussion

Pregnancy commonly exacerbates DR in pregestational diabetes.[7] The plausible cause for the worsening of DR during pregnancy comprises metabolic, hormonal, cardiovascular, and immunologic changes.[8] The retina is liable to be influenced by ischemia or substrate imbalance as one of the most metabolically active organs in the body.[9] Retinal thinning occurs before the development of microvascular changes in diabetes, and loss of

microvascular endothelial cells and retinal pericytes occurs at a very early stage of diabetes.[3-5,10]

In this study, we found significantly lower mean pRNFL, mRNFL, GCL+, and GCL++ thickness in GDM as compared to the control group. We observed thinner mean pRNFL, mRNFL, GCL+, and GCL++ in all the four subgroups; significantly thin mean pRNFL in all the four subgroups (pregnant females with a history of GDM in a previous pregnancy, pregnant females with no history of GDM in a previous pregnancy, pregnant females with a family history of DM, and pregnant females with no family history DM); and significantly thin mean mRNFL, GCL+, and GCL++ in the three subgroups (pregnant females with no history of GDM in previous pregnancy, pregnant females with a family history of DM, and pregnant females with no family history DM) in GDM as compared to the control group, suggesting that even the short-term elevation of blood sugar levels during gestational diabetes causes neurodegenerative changes before development of DR. However, we found no thinning and nonsignificant thinning of pRNFL, mRNFL, GCL+, and GCL++ in pregnant females with a history of GDM in previous pregnancy in comparison to pregnant females with no history of GDM in a previous pregnancy in the GDM and control groups, respectively, which may be because of small and unequal sample size of subgroups.

In line with our study, Sasikumar et al. found significantly lower average pRNFL thickness in pregnant women with GDM in comparison to healthy pregnant.[2] Acmaz et al. noted significant thinning of nasal pRNFL in pregnant women with GDM in comparison to healthy pregnant.[11] A significantly lower mean GCL, GCL+, and GCL++ thickness were reported in all quadrants in pregnant females with

Table 5: Comparison of ganglion cell + inner plexiform layer thickness and retinal nerve fiber layer + ganglion cell layer+inner plexiform layer thickness measurements of the eyes between gestational diabetes mellitus group and control group

Thickness measurements (μm)	Mean±SD		P*
	GDM group (n=324)	Control group (n=324)	
GCL+			
Superior	68.41±4.53	71.64±4.61	<0.0001
Inferior	67.74±4.35	70.14±3.94	<0.0001
Mean	68.30±4.29	71.12±3.52	<0.0001
GCL++			
Superior	101.87±6.10	105.35±5.91	<0.0001
Inferior	102.43±5.59	106.16±5.97	<0.0001
Mean	102.33±5.20	105.95±4.94	<0.0001

*P value calculated by independent t-test. RNFL=Retinal nerve fiber layer, GCL=Ganglion cell layer, GCL+=Ganglion cell+inner plexiform layer thickness, GCL++=RNFL+GCL+inner plexiform layer, GDM=Gestational diabetes mellitus, SD=Standard deviation

Table 6: Comparison of peripapillary retinal nerve fiber layer, macular retinal nerve fiber layer, ganglion cell + inner plexiform layer thickness, and retinal nerve fiber layer + ganglion cell layer+inner plexiform layer total thickness measurements of the eyes in subgroups between gestational diabetes mellitus group and control group

Thickness measurements (μm)	Mean±SD		P*
	GDM group	Control group	
pRNFL_Mean			
History of GDM in previous pregnancy	101.40±4.43	105.28±4.94	0.005
No history of GDM in previous pregnancy	100.54±5.41	106.98±5.85	<0.0001
Family history of DM	100.70±4.66	105.73±6.46	0.001
No family history of DM	100.90±6.55	106.93±5.65	<0.0001
mRNFL_Mean			
History of GDM in previous pregnancy +	34.24±2.17	35.23±2.98	0.198
No history of GDM in previous pregnancy	33.42±2.89	35.89±2.35	<0.0001
Family history of DM	33.80±2.50	36.11±2.75	0.001
No family history of DM	33.10±3.36	35.76±2.39	<0.0001
GCL+_Mean			
History of GDM in previous pregnancy +	68.34±4.30	70.48±4.13	0.069
No history of GDM in previous pregnancy	68.29±4.31	71.22±3.44	<0.0001
Family history of DM	68.07±4.07	71.39±3.23	0.0002
No family history of DM	68.99±4.86	71.09±3.58	0.013
GCL++_Mean			
History of GDM in previous pregnancy +	102.48±4.42	104.85±4.77	0.070
No history of GDM in previous pregnancy	102.29±5.45	106.11±4.97	<0.0001
Family history of DM	102.54±4.85	105.27±5.08	0.026
No family history of DM	101.73±6.17	106.06±4.94	0.0001

*P value calculated by independent t-test. RNFL=Retinal nerve fiber layer, GCL=Ganglion cell layer, pRNFL=Peripapillary RNFL, mRNFL=Macular RNFL, GCL+=Ganglion cell+inner plexiform layer thickness, GCL++=RNFL+GCL+inner plexiform layer, DM=Diabetes mellitus, GDM=Gestational DM, SD=Standard deviation

GDM and nonpregnant females with type II DM than in healthy nonpregnant females by Akpolat et al.[12] In contrast, no statistically significant differences in mean pRNFL thickness were reported in pregnant females with GDM in comparison to healthy pregnant females in all quadrants by Tengku-Fatishah et al. and Akpolat et al.,[12,13] except for inferior quadrant thinning which was nonsignificant.[12]

Significant thinning of GCL and RNFL has been reported in DM without DR compared to controls in other studies.[14-17] Among type II DM without DR and controls, RNFL thinning in all sectors was seen in one study,[18] predominantly decreased RNFL thickness in the inferior quadrant was reported in other studies,[19,20] and significantly thin nasal RNFL was found in others.[11,21] Contrary to this, no difference in GCL or RNFL thickness was reported among type I DM without DR and nondiabetics.[22]

The disparities in our results might be due to differences in population, sample size, and blood sugar levels. In the GDM group in our study, the majority have HbA1c levels > 7% and the mean HbA1c was 6.89%. In comparison, the mean HbA1c was 5.32% in the study by Akopolat et al. and[12] 5.6% in the study by Tengku-Fatishah et al.[13] Concurrently, HbA1c levels are not mentioned by Acmaz et al. and Sasikumar et al.[2,11]

Kida et al. revealed reduced optic nerve head perfusion during the 75-g OGTT in the glucose intolerant group, ascribed partially to elevated endothelin-1.[23] Pigment epithelium-derived growth factor (PEDF) possesses an anti-inflammatory, antioxidative, and anti-atherogenic property and is found to be raised in the hyperglycemic state.[24] Besides this, PEDF downregulates vascular endothelial growth factor (VEGF).[25] Hence, high blood sugar levels lead to raised endothelin-1 and PEDF levels, which suppress the VEGF and further decreases ocular perfusion, causing RNFL thinning in pregnant females with GDM.[23-25]

Diabetes induces apoptosis of retinal neural cells and activation of glial cells, which give rise to ganglion cell-IPL (GC-IPL) and RNFL thinning.[26-28] Retinal neural cells apoptosis increased after 1 month of induction of experimental diabetes. Significant GCL loss occurs within 7.5 months of experiment diabetes in an animal model.[29] Barber et al. reported that thickness is reduced by 22% in the IPL, 14% in the inner nuclear layer, and 10% in the GCL. Therefore, hyperglycemia during 9 months of gestation in GDM causes increased retinal neural apoptosis resulting in IPL GC-IPL and RNFL thinning.[29]

Our results indicate that in GDM, retinal neurodegeneration occurs before developing diabetic retinopathy; these neurodegenerative changes may or may not be permanent. An explanation regarding retinal neurodegeneration in GDM without DR could be that retinal neurodegeneration proceeds through the vascular process in the development of diabetic retinopathy and appears to be separate from vascular endothelial damage. RNFL and ganglion cell complex (GCC) thinning on OCT might be an early sign of retinal neurodegeneration. Evaluating RNFL and GCC thickness with OCT early in GDM will help prevent further neurodegenerative changes in the retina and the development of diabetic retinopathy by improving glycemic control.

Some of the limitations of our study included a cross-sectional design, the smaller and unequal sample size of the subgroups. Additionally, the majority of pregnant females with GDM were having HbA1c >7%, so there is a possibility that these females were already having undiagnosed DM. In light of these limitations, further longitudinal prospective studies were needed to explore retinal neurodegeneration in GDM.

Conclusions

Peripapillary and mRNFL, GCL+, and GCL++ thickness were decreased in pregnant females with GDM compared to healthy pregnant females, which might be the early retinal neurodegenerative alteration in gestational diabetes. Our study proposes that short-term elevation of blood sugar levels in GDM leads to retinal neurodegeneration; OCT should be done in gestational diabetes for early detection of retinal alteration before the occurrence of microvascular changes.

Conflicts of interest
The authors declare that there are no conflicts of interest of this paper.

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