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Assessment of Macular Peripapillary Nerve Fiber Layer and Choroidal Thickness Changes in Pregnant Women with Gestational Diabetes Mellitus, Healthy Pregnant Women, and Healthy Non-Pregnant Women

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Background: Gestational diabetes mellitus (GDM) is a risk factor for the development of type II diabetes and it causes maternal and child morbidity. Screening for diabetic retinopathy (DR) is important because patients who develop DR have no symptoms until macular edema and/or proliferative diabetic retinopathy (PDR) are already present. The aim of this study was to determine the early retinal findings of GDM.

Material/Methods: This study was conducted in a tertiary research center. We conducted a prospective cross-sectional study with 3 groups: Group 1 consisted of 36 pregnant women with GDM, Group 2 consisted of 24 healthy pregnant women, and Group 3 consisted of 38 healthy non-pregnant women of reproductive age. Spectralis optical coherence tomography (OCT) was used for the assessment. Macular, choroid, and retinal nerve fiber layer (RNFL) thicknesses were evaluated in patients with GDM and comparisons were made among pregnant women with GDM, healthy pregnant women, and healthy non-pregnant women for these parameters.

Results: The nasal part of the RNFL was significantly thinner in the GDM group than in the healthy pregnant group. None of the patients had retinopathy or macular edema at the time of examination.

Conclusions: Decreased nasal part of RNFL thickness may be the first retinal change in patients with GDM. Our study suggests that OCT should be performed for the patients with GDM for detection of early retinal changes associated with GDM.

MeSH Keywords: Diabetes, Gestational • Pregnant Women • Retina • Tomography, Optical Coherence

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Background

Gestational diabetes mellitus (GDM) is a risk factor for the development of type II diabetes and is responsible for both maternal and child morbidity. Placental secretion of diabetogenic hormones, including growth hormone, corticotropin-releasing hormone, placental lactogen, and progesterone, is mainly attributable to development of GDM. The prevalence of GDM reported in the literature ranges from 2% to 9% [1].

Screening for diabetic retinopathy (DR) is important because patients who develop DR have no symptoms until macular edema (ME) and/or proliferative diabetic retinopathy (PDR) are already present. Proliferative diabetic retinopathy and ME are major leading causes of blindness in the young population [2,3].

The American College of Obstetricians and Gynecologists (ACOG), the American Diabetes Association (ADA), and the Fifth International Workshop Conference on Gestational Diabetes [4–6] recommend long-term follow-up of women with GDM. However, reports in the literature present no consistent guidelines about when GDM screening should begin. Professional organizations recommend that diabetes screening for women with GDM should occur around the time of the first postpartum visit [7–9], whereas the ADA recommends screening at 6–12 weeks after delivery.

There is no data about early retinal findings of GDM. To the best of our knowledge, this is the first published study comparing macular and peripapillary nerve fiber layer (RNFL) and choroidal thickness changes among GDM patients, healthy pregnant women, and healthy non-pregnant women. Optical coherence tomography (OCT) is a non-invasive imaging technique that can measure retinal layers with a resolution of 3–10 microns [10].

The present study aimed to examine macular, peripapillary RNFL and choroidal thickness changes in patients with GDM and to compare them to healthy pregnant and non-pregnant subjects.

Material and Methods

This prospective, controlled trial was managed in Kayseri Education and Research Hospital of Medicine. Written informed consent form was obtained from each patient. This study conformed to the Declaration of Helsinki, and was approved by the Erciyes University Ethics Committee (no. 2013/064). The study is conducted with 3 groups: Group 1 consisted of 36 pregnant women with GDM, Group 2 consisted of 24 healthy pregnant women, and Group 3 consisted of 38 healthy non-pregnant women of reproductive age. All pregnant women in Group 1 and 2 were after 24th weeks of gestation and none had any medical or obstetrical problems except GDM.

Our diagnostic criteria for GDM was similar to that of the National Diabetes Data Group (NDDG), which include a 2-step approach, as still endorsed by the ACOG, which may be used at 24–28 weeks – a 1-h 50 gr OGTT, and if the first test result is positive (≥7.8 mmol/L), a 3-h 100 gr OGTT test is necessary for final diagnosis. Glucose concentration greater than or equal to cut-off values (105, 190, 165, and 145 mg/dL (5.8, 10.6, 9.2, and 8.0 mmol/L), respectively, at 2 or more time points indicates a positive test result.

The study was carried out with 3 groups. The first group consisted of 36 singleton-pregnant women after 24 weeks of gestation who were diagnosed with GDM according to NDGG Criteria, had no physical disease but diabetes, and did not receive any treatment (such as insulin) before the study. The second group consisted of 24 healthy singleton-pregnant women after 24 weeks of gestation. The third group consisted of 38 healthy non-pregnant women of reproductive age. The exclusion criteria for all groups were as follows: all types of hypertensive disease, renal disease, vascular disease, arteritis, and auto-immune disease, multiple pregnancies, and any using medication. We also excluded women who had ocular surgery, ocular trauma, glaucoma, cystoid macular edema, macular degeneration, optic atrophy, intraocular pressure higher than 21 mmHg, cataract, best corrected visual acuity worse than 20/30, high spherical (±3) or cylindrical (±2) diopters refractive errors, or uveitis.

Following detailed ophthalmologic examination, a Spectralis OCT (Heidelberg Engineering, Dossenheim, Germany) device was used for the evaluation without pupillary dilatation and under the same intensity of dim room lighting. The SD-OCT assessments involved in the study were performed by the same specialist (MA). Macular map analysis protocol was selected to display each of the 9 subfields as defined by the Early Treatment Diabetic Retinopathy Study (ETDRS) group [12]. The average of all points within the inner circle of 1-mm radius was defined as the central foveal subfield (CSF) thickness. The central point, which is an average of 6 radial scans at the foveola, was defined as the central point thickness (CPT) and was recorded for each of the subjects.

The peripapillary RNFL thickness parameters that were automatically calculated by the SD-OCT and divided into regions: temporal quadrant, temporal superior quadrant, nasal superior quadrant, nasal quadrant, nasal inferior quadrant, temporal inferior quadrant, and average thickness. Non-centered and low-quality scans were excluded from the study.

Diagnostic method of EDI OCT scans have been reported previously [11]. The choroid was screened by positioning the SD-OCT device close enough to the eye to obtain an inverted image. This image is averaged for 100 scans using the automatic

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Table 1. Evaluation of macular and choroidal thickness in non-pregnant healthy women, healthy pregnant and GDM.

Variables	Healthy women (*n*=76)	Healthy pregnant (*n*=48)	GDM (*n*=72)	*P*
CSF	265.09±21.67[a]	255.58±17.54[b]	252.53±18.7[b]	<0.001
SIM	343.76±13.05	342.86±11.45	338.14±16.16	0.059
TIM	335.37±13.02[a]	333.04±14.4[a,b]	328.54±17.55[b]	0.031
IIM	337.53±13.57	337.46±11.93	334.75±15.84	0.454
NIM	335.78±14.14	332.21±14.9	329.57±17.55	0.055
SOM	296.55±15.71	300.56±10.92	297.43±14.99	0.257
TOM	299.84±23.25	302.12±20.35	296.71±22.38	0.279
IOM	291.36±15.87	293.37±11.32	289.13±13.94	0.233
NOM	298.11±23.21	300.11±19.98	296.96±23.07	0.727
Foveal center	224.59±30.1[a]	213.84±16.82[b]	212.64±14.04[b]	0.009
Choroid	322.49±65.58[a]	393.77±61.83[b]	367.54±62.72[b]	<0.001

Values are expressed as mean ±SD. Different superscripts in a row indicate statistically significant difference. CSF – central subfield; IIM – inferior inner macula; IOM – inferior outer macula; NIM – nasal inner macula; NOM – nasal outer macula; SIM – superior inner macula; SOM – superior outer macula; TIM – temporal inner macula; TOM – temporal outer macula.

averaging and eye tracking features. Seven sections, each comprising 100 averaged scans, were obtained in a 5×30-degree rectangle encompassing the macula and optic nerve, and the horizontal section going directly through the center of the fovea was selected. The choroid was measured from the outer portion of the retinal pigment epithelium (RPE) to the inner surface of the sclera. Choroidal thickness was evaluated by the same author (MA) without knowledge of subject group.

Statistics analysis

The Kolmogorov-Smirnov test was used and histogram and q-q plots were examined to assess the data normality. The Levene test was used to assess the variance homogeneity. A 2-sided independent samples *t* test and 1-way analysis of variance (ANOVA) was applied to compare the differences between continuous variables. Welch test was applied when the homogeneity of variance assumption was violated. Tukey and Tamhane's T^2 tests were applied for multiple comparisons. Values are expressed as mean ± standard deviation. $p<0.05$ was considered as statistically significant.

Results

Mean age of the healthy non-pregnant group was 31.87±7.76, mean age of healthy pregnant group was 27.72±5.12 and mean age of GDM group was 32.51±4.88. GDM group was significantly older than healthy pregnant group.

The results of macular and choroidal thickness, macular volume, and peripapillary RNFL thickness analysis are shown in Tables 1–3, respectively. Macular central subfield and foveal center thickness were significantly thinner and choroidal thickness was significantly thicker in the healthy pregnant and GDM groups ($p<0.001$) (Table 1). However, there was no significant difference between the GDM group and the healthy pregnant group (Tables 1, 2). The nasal part of the RNFL was significantly thinner in the GDM group than the healthy pregnant group (Table 3). None of the patients had retinopathy at the time of examination.

Discussion

One of the most metabolically active organs in the body, the retina is particularly susceptible to substrate imbalance or ischemia [12]. Retinal pericytes and microvascular endothelial cells are lost at a very early stage of diabetes [13]. Proliferative diabetic retinopathy is a major complication of diabetes, which carries a high risk of visual loss [14]. Pregnancy is responsible for the worsening of PDR in women with pregestational type I or II DM [15]. Previous studies have shown that the prevalence of DR is 57–62% at the first examination in pregnancy with type I DM and is 17–28% in the type II DM. The Diabetes Control and Complications Trial (DCCT) and Research Group and the Diabetes in Early Pregnancy (DIEP) studies found the progression of retinopathy in pregnancy to range from 8% to 70% [16].

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Table 2. Average macular volume in healthy women, healthy pregnant and GDM.

Variables	Healthy women (*n*=76)	Healthy pregnant (*n*=48)	GDM (*n*=72)	*P*
CSF	0.21±0.02[a]	0.2±0.01[b]	0.2±0.01[b]	<0.001
SIM	0.54±0.02[a]	0.54±0.02[a,b]	0.53±0.03[b]	0.048
TIM	0.53±0.02[a]	0.52±0.02[a,b]	0.52±0.03[b]	0.031
IIM	0.53±0.02	0.53±0.02	0.53±0.03	0.454
NIM	0.53±0.02	0.52±0.03	0.52±0.03	0.055
SOM	1.58±0.08	1.59±0.06	1.58±0.08	0.257
TOM	1.6±0.11	1.6±0.1	1.57±0.12	0.379
IOM	1.55±0.09	1.55±0.06	1.53±0.07	0.167
NOM	1.59±0.12	1.59±0.11	1.57±0.12	0.727
Average	0.96±0.04	0.96±0.03	0.95±0.04	0.129
Total volume	8.64±0.33	8.65±0.28	8.52±0.45	0.099

Values are expressed as mean ±SD. Different superscripts in a row indicate statistically significant difference. CSF – central subfield; IIM – inferior inner macula; IOM – inferior outer macula; NIM – nasal inner macula; NOM – nasal outer macula; SIM – superior inner macula; SOM – superior outer macula; TIM – temporal inner macula; TOM – temporal outer macula.

Table 3. Average peripapillary RNFL thickness in healthy women, healthy pregnant and GDM.

Variables	Healthy women (*n*=76)	Healthy pregnant (*n*=48)	GDM (*n*=72)	*P*
Temporal	69.84±12.79	73.22±10.76	74.53±12.55	0.058
Ts	136.92±22.32	141.13±20.09	141.36±21.09	0.374
Ns	111.14±21.91	116.45±18.01	113.22±19.57	0.330
N	75.43±15.34[a,b]	80.89±18.14[a]	73.92±12.9[b]	0.034
Ni	114.68±24.93	116.56±22.46	113.17±19.72	0.702
Ti	143.72±25.83[a]	153.2±16.15[a,b]	150.75±20.15[b]	0.031
G	99.59±12.02[a]	104.45±10.06[b]	101.93±8.72[a,b]	0.032

Values are expressed as mean ±SD. Different superscripts in a row indicate statistically significant difference. T – temporal; Ts – temporal superior; Ns – nasal superior; N – nasal; Ni – nasal inferior; Ti – temporal inferior; G – global.

The literature is not clear on when GDM screening should begin. However, professional organizations recommend that diabetes screening for women with GDM should occur around the time of the first postpartum visit [7,8]. The ADA recommends screening at 6–12 weeks after delivery [9]. There is limited data on this issue and to the best of our knowledge this is the first study on GDM and the retina with OCT. The OCT technique can objectively and quantitatively assess macular and RNFL thickness [10,17].

The present study revealed that macular central subfield and foveal center thickness were significantly thinner and choroidal thickness was significantly thicker in the healthy pregnant and GDM groups than in the healthy non-pregnant group (p<0.001), but there were no significant difference between the GDM group and the healthy pregnant group. Cankaya et al. determined that the mean macular central subfield value was 192 µm in non-pregnant healthy women, but Grover et al. reported that the mean macular central subfield value was 270.2 µm in healthy subjects [18,19]. In our study macular

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thickness values in healthy non-pregnant subjects were similar to that reported by Grovers.

The novel finding of this study was that thickness of RNFL, especially the nasal part, significantly decreased in patients with GDM. Thus, the decreased nasal part of RNFL thickness may be the first change in patients with GDM. Timing of scanning for GDM is very important because screening allows detection of retinopathy in the early and non-proliferative stage. GDM patients have more severe insulin resistance compared to euglycemic pregnant women [20,21]. At this stage, improving glycemic control can reverse non-proliferative changes and prevent progression [22]. It was reported that choroidal thickness was reduced in diabetic eyes and that the nasal quadrant was the most affected area [23]. Nasal quadrant choroid layer supplies blood to this area; therefore, we are of the opinion that this situation may explain why the nasal part of RNFL was significantly reduced in patients with GDM. Kida et al. examined optic nerve head (ONH) blood circulation during 75-gr OGTT. They concluded that ONH circulation decreased in the abnormal glucose tolerance group, attributed partly to the increased endothelin-1 [24]. In a similar study, authors investigated the microcirculation and progression of macular edema [25]. It is pointed out that the reduction of perifoveal capillary blood flow velocity may occur before the increase of retinal thickness at the central fovea in the diabetic patients. In contrast to Sakata and Vujosevic, it is claimed that pregnancy has no long-term effect on future progression. The adverse effect of pregnancy on the retinal microvasculature is relatively transient, with risk of progression to PDR being high only within the first 8 weeks after delivery. Increased risk may persist into the first year postpartum, but eventually diminishes [14].

This situation has been investigated at the molecular level. Yamagishi found that advanced glycation end-product-induced endothelial cell damage is inhibited by pigment epithelium-derived growth factor (PEDF), which possesses antioxidative, anti-inflammatory, and antiatherogenic properties in both cell culture and animal models [26]. On the other hand, PEDF is accepted as a negative regulator of vascular endothelial growth factor (VEGF) [27]. A plausible explanation and interpretation of these studies [23–27] is that high glucose level may lead to increased PEDF and ET-1 levels. Then, as a result of increased PEDF and ET-1 levels, VEGF begins to decrease. This situation results in decreased choroid thickness, especially in the nasal quadrant. Deterioration of blood supply to nerves may lead to thinner RNFL in patients with GDM.

Conclusions

The decreased nasal part of RNFL thickness may be the first retinal change in patients with GDM. Our study suggests that OCT should be performed for patients with GDM for detection of early retinal changes associated with GDM. The main question now is whether nasal value of RNFL can show us DR occurrence. A large-scale study with more participants is needed.

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Conflicts of interests

None.

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