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ORIGINAL ARTICLE

Association of diabetic neuropathy with contrast sensitivity impairment and OCT parameters in type-2 diabetic patients without retinopathy

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Abstract

Purpose: To demonstrate the retinal neurodegeneration findings caused by diabetes and diabetic neuropathy in patients without retinopathy, anatomically with spectral domain optical coherence tomography (SD-OCT) and functionally with contrast sensitivity (CS).

Methods: The presence of diabetic neuropathy was objectively revealed together with neurologists by electromyography (EMG). SD-OCT and CS were evaluated in patients with peripheral neuropathy (diabetic peripheral neuropathy [DPN] + group), without neuropathy (DPN- group), and healthy controls. Average and sectoral retinal nerve fiber layer (RNFL) thickness, average, and 6 sectoral quadrants ganglion cell complex (GCC) were compared between groups. Furthermore, CS measurement values were calculated between groups.

Results: Although there were significant differences between the three groups in the average RNFL, in pairwise comparisons there were no statistical differences in the average RNFL between the DPN (–) and healthy control groups (p=0.679). Average GCC thickness also showed significant differences between the three groups (p<0.001). The post hoc test was performed to determine the group that made the difference, it was seen that the average ganglion cell values of the DPN+ group were lower than the other groups. Furthermore noteworthy, when the diabetic group with "no neuropathy" compared to the healthy control group, GCC values were significantly lower in the diabetic group. When the DPN group was compared with the healthy group, CS values were significantly lower in the diabetic group (p<0.001). Analysis of mesopic CS values and each of the average RNFL and GCC thickness indicated significant positive correlations (r=0.238, 0.326, respectively).

Conclusion: Our results suggest that there is evidence of early retinal neuronal damage, particularly on SD-OCT, before DPN occurs in patients with type 2 diabetes mellitus. Although visual acuity is unaffected in diabetic patients, decreased CS and GCC may be an early warning for DPN.

Keywords: Contrast sensitivity; diabetic peripheral neuropathy; electromyography; ganglion cell complex; retinal nerve fiber layer; retinal neurodegeneration.

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Diabetes mellitus (DM) is a disease whose prevalence is increasing, affecting a more significant percentage of the population over time and presenting with many complications. Diabetes causes microvascular complications such as nephropathy, retinopathy, and neuropathy, as well as macrovascular complications such as atherosclerosis, hypertension, cerebrovascular disease, ischemic heart disease, and diabetic foot may occur and cause morbidity. Early diagnosis of these complications is vital for reducing diabetes-related morbidity, mortality, and improving the quality of life.

When we look at the ocular findings of diabetic neuropathy, in some studies, its effect on the cornea has been shown by confocal biomicroscopy.[1,2] The changes in the retina caused by diabetic neuropathy are still a matter of debate. Although some studies suggest that diabetic retinal neurodegeneration occurs before the formation of visible diabetic retinopathy (DRP) in the retina, it has not been clarified whether diabetic retinal neurodegeneration occurs as a result of retinopathy or is a factor that causes retinopathy.[3,4] Previous studies have shown that there is a thinning of the ganglion cell layer in patients with mild non-proliferative DRP.[5,6] It has been proven that deteriorations in neuroretinal deficit indicators such as electroretinography anomalies decrease in contrast sensitivity (CS), decrease in dark adaptation, visual field changes, and color vision disorders begin without any visible vascular pathology in the fundus.[7] The existence of studies showing retinal neurodegeneration without such advanced DRP supports the view that retinopathy occurs as a result of neurodegeneration. Retinal neurodegeneration due to diabetic neuropathy can be termed "diabetic retinal neuropathy," as the retina contains a neuronal system and this neurodegeneration constitutes neuropathy.

In some recent studies, it has been shown that the retinal ganglion cell layer of patients diagnosed with diabetic neuropathy by diabetic neuropathy scoring is thinner as a result of examination with optical coherence tomography (OCT) compared to patients without neuropathy.[8,9] However, diabetic neuropathy scoring does not provide as accurate and objective results as electrophysiological tests in diagnosing diabetic neuropathy.[10] In this study, patients were divided into groups with and without neuropathy according to electromyography (EMG) results, an objective diagnostic method, and these patients were compared among themselves and with the healthy control group.

Our study's aim is to demonstrate the retinal neurodegeneration findings caused by diabetes and diabetic neuropathy in patients without retinopathy, anatomically with spectral domain optical coherence tomography (SD-OCT) and functionally with CS. In this study, unlike the existing literature, another aim was to diagnose diabetic neuropathy with an objective method, EMG, and thus obtain more accurate results of the effects of neuropathy.

Materials and Methods

This research was conducted following the principles of the Declaration of Helsinki and with the approval of our hospital's clinical research ethics committee (Decision number: 0343– June 24, 2021). The study was cross-sectional, and EMG examinations were performed in the neurology clinic on 78 diabetic patients (39 patients with neuropathy [diabetic peripheral neuropathy (DPN) (+)]) and 39 age-matched patients without neuropathy (DPN [–]) were included in the age-matched patients who were referred to the eye clinic for DRP screening. Thirty-nine healthy cases were included in the study as a control group.

Patient Selection

Patients with type 2 DM between the ages of 40 and 65, who were referred from the electrodiagnostic outpatient clinic, were included in the diabetic patient group. The aim of the age selection criteria was to exclude alterations due to aging in CS measurements and OCT findings. Patients who had diabetes for more than 10 years were excluded from the study. Patients with poor cooperation, any systemic problem that would cause neuropathy other than DM, patients with −6/+3 spherical, −1/+1 non-spherical refraction disorders, and any history of intraocular surgery were excluded. The eye examination of all patients was performed by the same physician, who did not know whether these patients had neuropathy. After visual acuity examination with distance refraction correction, patients whose best-corrected visual acuity level was 0.0 according to logMAR were included in the study. After CS examination, intraocular pressure measurement with a Goldmann applanation tonometer and anterior segment examination with slit light biomicroscopy were performed after topical anesthesia with 0.5% proparacaine HCL (Alcaine, Alcon-Couvreur, Switzerland). All eyes were dilated by instilling 2.5% phenylephrine hydrochloride (Mydfrin, Alcon, Switzerland) and 0.5% tropicamide (Tropamid, Bilim Pharmaceuticals, Türkiye) drops, and a detailed fundus examination was performed indirectly with the help of a +90 diopter lens. Patients with any pathology in the anterior segment or posterior segment examination were excluded from the study.

After pupil dilation of diabetic patients, fundus photographs were taken in nine quadrants with a 45° digital retina camera (ZEISS VISUCAM). As a result of the examination of the photographs, it was confirmed by two retina specialists that there was no microaneurysm, hard exudate, hemorrhage, cotton wool appearance, venous beading, intraretinal microvascular anomaly, or new vessel formation in the retina according to ETDRS and that there was no retinopathy. Only the right eye of each patient was included in the study.

The control group consists of age-matched volunteer patients between the ages of 40 and 65 who apply to the outpatient clinic. They do not have any systemic or ophthalmological diseases (other than refractive error) and have similar demographic characteristics to the diabetic group.

CS Testing

The CSV 1000 CS Test (Vector Vision) was used to measure CS. Since refraction affects CS, all patients received full refraction correction. All measurements were made under mesopic (3 cd/m^2) illumination. CS was measured for spatial frequencies of 3, 6, 12, and 18 cycles per degree (cpd) from a distance of 2½ two and a half meters. CS measurement values were expressed as logarithmic units (Log CS) for statistical calculation.

OCT

OCT examination was performed with SD-OCT (Cirrus HD-OCT 4000; Carl Zeiss Meditec Inc., Dublin, CA, USA) device. The built-in algorithms of the Cirrus HD-OCT software (version 8.0) are capable of calculating the average, minimum, and ganglion cell inner plexiform layer (GC-IPL) thickness of six sectoral quadrants. 1, 3, and 6 mm diameter circular areas centered on the macula are separated into nine ETDRS subfields. The map of retinal nerve fiber layer (RNFL) thickness was measured along a circle of 3.45 mm in diameter centered on the optic disc. The parameters of RNFL thickness were divided into average and quadrant as temporal, superior, nasal, and inferior.

EMG

In this study, nerve conduction studies were performed with the Medelec Synergy (Oxford Instruments Medical, Old Woking, UK) device. In our study, the nerve conduction study was reviewed in the peroneal motor nerve and the posterior tibial motor nerve by measuring velocity, terminal latency, F-wave latency, and the velocity in the sural sensory nerve. The diagnosis of DPN was established by electrophysiological criteria modified by Kwon et al. after the Diabetes Control and Complication Trial.[11,12] Subjects with diabetes in this study were subdivided into two groups "no neuropathy" and "definite neuropathy."

Statistical Analysis

Study data were analyzed using the Statistical Package for the Social Sciences program (SPSS package for Windows. ver 21, Illinois, USA). Frequency (%), mean value, standard deviation (±SD), and highest and lowest values were used for descriptive statistics. Before starting the analyses, the distributions of the variables were tested with the Kolmogorov–Smirnov test. Mann–Whitney U, Kruskal–Wallis, Chi-square, and Spearman correlation tests were applied to compare the results. Statistical significance was accepted as $p<0.05$.

Results

There were 39 cases in the control group with an average age of 51.02±3.57 years, 39 cases in the DPN (–) group with an average age of 51.30±3.28 years, and 39 cases in the DPN (+) group with an average age of 50.84±4.04 years. There was no statistical difference in age between the patient and control groups (p=0.926). There was no statistical difference in gender ratios. The body mass index (BMI) of the diabetic patients was calculated as weight divided by their height squared. The BMI of the DPN (–) group was 31.68±5.55 and the DPN (+) group was 30.01±3.47 (p=0.200). DM duration of the DPN (–) group was 6±3.37 years, whereas it was 7±3.15 in the DPN (+) group. The mean HbA1c of the DPN (–) group was 8.75±9.15, and for the DPN (+) group, it was 8.88±2.44.

When the CS results in the mesopic environment of all three groups were compared, a statistically significant difference was found (p<0.001) (Tables 1 and 2; Fig. 1). When the diabetic group with "no neuropathy" (DPN [–]) compared with the healthy group, CS values were significantly lower in the DPN (–) group (p<0.001) (Table 2).

There were significant differences between the three groups in the superior nasal, inferior quadrants RNFL thicknesses, and overall average ([p=0.014], [p=0.003], [p=0.003], and [p=0.009], respectively) (Table 2). In pairwise comparisons, there was no statistical difference in the overall average

Table 1. Contrast sensitivity values of the groups

	3 cpd	6 cpd	9 cpd	12 cpd	Average*
Control	1.91	2.13	1.82	1.38	1.82
DPN (–)	1.66	1.85	1.53	1.08	1.53
DPN (+)	1.41	1.5	1.12	0.71	1.19

DPN: Diabetic peripheral neuropathy; cpd: Cycles per degree. *There is a statistically significant difference between average values (P<0.001)

Table 2. The values of RNFL, GC-IPL, and CS of all three groups

	DPN(-)	DPN(+)	Control	P
Average RNFL	95.13±7.99	88.46±12.61	95.94±8.04	**0.009**
Superior RNFL	116.32±12.06	108.85±19.22	119.83±13.16	**0.014**
Nasal RNFL	74.0±9.88	66.36±13.46	72.69±10.95	**0.003**
Inferior RNFL	126.16±16.04	115.74±19.11	126.86±15.07	**0.015**
Temporal RNFL	63.29±6.73	61.51±13.61	65.44±8.6	0.094
Average GC-IPL	86±5.81	81.95±8.39	88.97±5.25	**<0.001**
Superotemporal GC-IPL	84.1±6.74	82.08±7.6	87.25±5.23	**0.019**
Superior GC-IPL	88.16±7.43	83.23±9.31	90.19±6.5	**0.004**
Superonasal GC-IPL	88.06±6.94	82.05±11.66	90.47±6.77	**0.003**
Inferonasal GC-IPL	85.71±6.22	80.87±10.29	89.61±6.09	**<0.001**
Inferior GC-IPL	82.52±14.67	81.21±9.53	88±7.22	**0.004**
Inferotemporal GC-IPL	85.13±6.07	82.59±7.94	88.29±5.99	**0.004**
CS	1.53±0.16	1.19±0.22	1.82±0.1	**<0.001**

DPN: Diabetic peripheral neuropathy; RNFL: Retinal nerve fiber layer; GC-IPL: Ganglion cell-inner plexiform layer; CS: Contrast sensitivity.

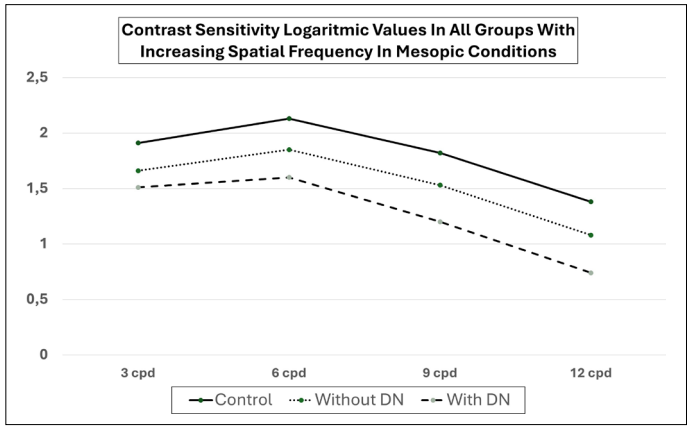

Fig. 1. Contrast sensitivity logarithmic values in all groups with increasing spatial frequency in mesopic conditions.

RNFL between the DPN (–) and healthy control group (p=0.679) (Table 3).

Average GC-IPL thickness also showed significant differences between the three groups (p<0.001) (Table 2). In the post hoc test performed to determine the group that made the difference, it was seen that the average ganglion cell values of the group with neuropathy (DPN [+]) were lower than the other groups. When the GC-IPL thickness was evaluated separately for each quadrant between the groups, the thickness values of all quadrants showed a statistically significant difference between the groups (Table 2). When the diabetic group with "no neuropathy" (DPN [–]) compared to the healthy control group, GC-IPL values were significantly lower in the DPN (–) group (Table 3).

Analysis of mesopic CS values with average RNFL and GC-IPL thickness indicated significant positive correlations (r=0.238 and 0.326, respectively) (Table 4).

Table 3. Comparison of DPN (–) and control groups

	DPN (–)	Control	P
RNFL	95.13±7.99	95.94±8.03	0.679
GC-IPL	86.00±5.80	88.97±5.24	**0.031**
CS	1.64±0.15	1.89±0.08	**<0.001**

DPN: Diabetic peripheral neuropathy, RNFL: Retinal nerve fiber layer, GC-IPL: Ganglion cell-inner plexiform layer, CS: Contrast sensitivity.

Table 4. Correlation between average OCT values and CS

	CS	
	rho	p
Average RNFL	0.238	**0.014**
Average GC-IPL	0.326	**0.001**

CS: Contrast sensitivity; rho: Spearman correlation coefficient; RNFL: Retinal nerve fiber layer; GC-IPL: Ganglion cell-inner plexiform layer.

Discussion

As it is known, the two main complications of DM are DPN and DRP. Although they do not seem to be very related to each other, considering that the retina is a neurosensorial structure, these two complications can be thought to be related. Although vascular impairment comes to mind when DRP is mentioned, it has been suggested that it is based on the neurovascular component disorder and that the neuro component may start before the vascular part.[13] It is believed that retinal neurodegeneration occurs first in DM patients, even before microvascular DRP findings.[14]

In our study, while RNFL was thinned only in the DPN (+) group, no statistical difference was observed between the DPN (–) and healthy group. What is remarkable here is that while RNFL was similar, a statistical difference was observed in the ganglion cell complex (GCC) between the DPN (–) and healthy group. These findings in our study indicate that apoptosis may have started, especially in ganglion cells, in DM patients without detected peripheral neuropathy. Supporting our study, Barber et al. demonstrated that ganglion cells decreased by 10% in diabetic rats after approximately 7 months. They also detected decreases in neuronal cells such as also as amacrine cells in the inner layer of the retina.[15] Thinning of retinal layers in patients with type 1 DM has also been previously demonstrated. [16, 17]

As can be observed according to the data presented, the damage has been shown in many types of neuron cells, but GCC and RNFL, which can be obtained by OCT, an easy, non-invasive, and reproducible method in humans, may provide us with a significant clue about diabetic retinal neurodegeneration. From this perspective, thinning may occur in the GCC before DPN develops. GCC thinning can be seen even before RNFL thinning, just like in glaucoma, and may play a role in the early diagnosis of both DPN and diabetic neuronal degeneration. In other words, we believe that diabetic retinal neuropathy could be an early precursor of DPN. DM patients with damage of GCC detected by non-invasive OCT may be warned earlier for DPN. In addition, the risk of DPN may be detected with a short examination, such as OCT, without even needing an EMG. Furthermore, Kim et al. observed more proliferative DRP in patients with DPN, so we think it is crucial that early detection of ganglion cell damage (diabetic retinal neuropathy) for patients in terms of may be saved from both proliferative DRP and DPN.[18] The relationship between this retinal thinning in diabetes and other neural damage remains to be investigated and may be the subject of future clinical studies.

Various rat and human studies have also put forward the idea that diabetic retinal neuropathy may begin before DRP.[3,14,15,19] What distinguishes our study from these studies is that it is determined whether there is peripheral neuropathy with EMG and there are absolutely no DRP findings in the DM group. For example, in some studies, cases with DRP were included.[3,19] Since GCC damage has already started in the presence of DRP, reliability will decrease. For this reason, our DM group consisted of patients without any sign of DRP.

Another noteworthy result of our study is a difference in mesopic CS values between all three groups. In addition, the difference in CS between the DPN (–) and control group was statistically significant. Many studies in the literature show CS effects even without retinopathy in DM patients. [20,21] Gualtieri et al.[21] declared that the decreased CS was due to diabetes-related retinal neural degeneration, even if visual acuity was unaffected and retinopathy did not begin. Although this change has often been attributed to neural cells such as ganglion cells and parvocellular (P cells) and magnocellular (M cells) cells derived from ganglion cells, it has yet to be clearly demonstrated.[21]

Furthermore, the presence of diabetic neuropathy was not taken into account in the studies, and it was generally discussed based on the presence or absence of DRP. In our study, the presence of DPN was taken into account. The fact that CS was found to be decreased even in DPN (–) patients compared to the control group shows that ganglion cells may be affected even in the absence of DPN and DRP, and retinal neuron cells may be affected even before DPN. It has been repeatedly suggested that retinal glial cells may be affected before DRP, but we think that our study shows that retinal nerve cells may begin to be affected not only before DRP but even before DPN begins.[14,21,22] The decreased significant CS found in the DPN (–) and DRP- groups indicate that diabetic neural cells may be affected in the early period in diabetic patients and may be effective in long-term vision damage.

Conclusion

Our results suggest that there is evidence of early retinal neuronal damage, particularly on SD-OCT, before DPN occurs in patients with type 2 DM. Although visual acuity remains unaffected in diabetic patients, decreased CS and GCC may serve as early warnings for DPN. Studying these findings in wider groups and with other visual functional tests may enlighten the importance of neurodegeneration in the retina better.

Limitations

We did not obtain cycloplegic refraction for the examination but patients excluded with high refractive errors, as explained in the methods section. The cross-sectional design of the study is also another limitation.

Ethics Committee Approval: This research was conducted following the principles of the Declaration of Helsinki and with the approval of our hospital's clinical research ethics committee (Decision number: 0343– June 24, 2021).

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