

# Early Functional Retinal Alterations in Mild NPDR: A Multimodal Assessment Including Color Contrast Sensitivity, Dark Adaptation, and Full-Field ERG

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## ABSTRACT

**Objective:** To evaluate color contrast sensitivity, dark adaptation (DA), and full-field electroretinography (ffERG) parameters in patients with mild nonproliferative diabetic retinopathy (NPDR) and to compare these findings with those of healthy individuals to identify early functional changes related to retinal neurodegeneration.

**Methods:** This cross-sectional study included patients with mild NPDR and healthy controls. Color contrast sensitivity along the protan and tritan axes was assessed using the ChromaTest. DA maximum sensitivity and ffERG parameters, including photopic negative response, were recorded using a Ganzfeld system in accordance with ISCEV standards. All participants had best-corrected visual acuity of 0.0 logMAR and no clinically significant cataract or other ocular pathology.

**Results:** Both protan and tritan color contrast thresholds were significantly higher in the NPDR group compared with controls ( $p < 0.001$ ). The maximum sensitivity threshold for DA was significantly reduced in patients with NPDR ( $p = 0.032$ ). In ffERG measurements, rod response b-wave implicit time was significantly longer ( $p = 0.005$ ), whereas maximal response b-wave implicit time was shorter ( $p < 0.001$ ) and maximal response a-wave amplitude was higher ( $p = 0.002$ ) in the NPDR group compared with controls. No significant differences were observed in other ffERG parameters.

**Conclusion:** Patients with mild NPDR exhibit impaired color contrast sensitivity and DA despite relatively preserved ffERG responses. These findings suggest that functional alterations related to retinal neurodegeneration may precede overt vascular changes in diabetic retinopathy. Psychophysical measures such as color contrast sensitivity and DA may represent accessible tools for detecting early functional retinal involvement in diabetes.

**Keywords:** Color vision, Dark adaptation, Diabetic retinopathy, Electroretinography

## INTRODUCTION

Advanced diabetic retinopathy (DR) causes vision-threatening retinopathy and is one of the leading causes of blindness in diabetics [1]. It has been suggested that vision loss in DR is not only due to microvascular changes, but also due to neurodegeneration. Retinal neurodegeneration is characterized by apoptosis of photoreceptors and multiple neuronal cell types in the inner retinal layers. These changes in the retina are thought to precede microvascular

changes [2]. Therefore, methods capable of detecting early neurodegenerative alterations are of particular importance in the study of DR.

Psychophysical and electrophysiological methods have become increasingly widespread in clinical practice due to their sensitivity in detecting functional and structural abnormalities in the preclinical stage of DR. In the early stage of the disease, visual functional disorders detected

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with these tests are explained by retinal neurodegenerative changes. Dark adaptation (DA) primarily reflects rod photoreceptor and retinal pigment epithelium function, while color vision is mediated by cone photoreceptors. DA and color contrast sensitivity are parts of visual function and studies have shown that they are affected by diabetes [3,4]. Full-field electroretinography (ffERG) provides information about retinal activity from photoreceptors to the inner retinal layers. Previous studies have also demonstrated that ffERG, which provides an objective measure of retinal function loss, is affected even in early DR [5,6].

Despite growing evidence of neurodegenerative changes in DR, there is still a need for studies that directly compare multiple functional parameters in the early stages of the disease. In this study, we aimed to evaluate color contrast sensitivity, DA, and ffERG in patients with non-proliferative diabetic retinopathy (NPDR) and to compare the results with those of healthy individuals. By assessing these complementary methods together, we sought to better determine their effectiveness in detecting early retinal neurodegeneration before the development of advanced retinopathic changes that threaten vision.

## **MATERIALS AND METHODS**

One eye from each of the 31 patients with NPDR and 21 healthy volunteers was included in this study. All patients were diagnosed with mild NPDR according to the Early Treatment Diabetic Retinopathy Study (ETDRS) classification [7], in which mild NPDR is defined as the presence of microaneurysms only. The inclusion criteria were absence of diabetic macular edema, no eye disease other than refractive defect, absence of anisocoria or pupil anomaly, absence of media opacities, including cataract, vitreous opacities, or corneal opacities, and a best-corrected visual acuity of 0.0 logMAR measured with the Snellen chart. Exclusion criteria were the presence of another systemic disease other than diabetes, continuous medication use, congenital color blindness, smoking and/or alcohol use, use of prosthetic devices or devices that generate electromagnetic fields, and observation of artifacts in the measurement records. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Necmettin Erbakan University Meram Faculty of Medicine (Approval No: 2017/1144). Written informed consent was obtained from all participants after

they were given detailed information about the course and possible results of the study.

All participants underwent detailed eye examination including objective refraction and intraocular pressure measurement, the BCVA measurement with Snellen chart, anterior segment measurement with biomicroscope, dilated fundus examination with 78 D lens, and macular analysis with spectral domain optical coherence tomography (Heidelberg Engineering, Heidelberg, Germany). Color contrast sensitivity was evaluated with ChromaTest, while DA maximum sensitivity and ffERG measurements were done using Ganzfeld sphere (MonPackONE®; Metrovision, France).

### **Color Contrast Sensitivity Assessment**

The ChromaTest is a computer program that analyzes the sensitivity threshold of the age-corrected protan and tritan axes [8]. In this program, letters are displayed on a constantly illuminated background with different colors set at the same brightness. All participants were positioned at the same distance from the test screen, thus the image that tests 6.5 degrees in the center of the retina is formed. The test is automated and the operator had no effect on the contrast of the letters shown. Participant responses were recorded by the operator as correct or incorrect in the program. If the answer was correct, on the next display, the difference in color contrast between the letter and the background was steadily reduced. If the answer was incorrect, the color contrast difference would automatically increase at a constant rate. Incorrect responses prolong the test but did not affect the final threshold value. Using this method, the program reliably determined the color contrast threshold (CCT) value (%) that represented the plateau.

### **Dark Adaptation Assessment**

The DA test evaluated the recovery of light sensitivity after exposure to bright light. Brightness adaptation was achieved with green light at 300 candela/meter<sup>2</sup> and 525 nanometer(nm) wavelength for 5 minutes. Subsequently, the participant was asked to press the button in their hand when the green light stimulus, 10 degrees in size with a duration of 50 milliseconds at a wavelength of 525 nm, was detected in complete darkness. The intensity of the stimulus decreased with the correct answer and increased with

the incorrect answer. The maximum sensitivity threshold value was recorded in decibels (dB).

**Full-Field Electroretinography**

The fERG and photopic negative response (PNR) were evaluated using the Ganzfeld sphere based on ISCEV standards [9]. Before the test, sufficient mydriasis (at least 8 mm) was achieved with 0.5% tropicamide and 2.5% phenylephrine. During the recordings, HK-Loop electrodes were placed in the inferior conjunctival sac following topical anesthesia with 0.5% proparacaine. Reference electrodes were positioned approximately 2 centimeters lateral to the outer canthus, and the ground electrode was placed on the forehead. Rod and maximal responses were recorded after at least 20 minutes of DA. Then, after at least 10 minutes of light adaptation, cone response, photopic 30 Hz flicker and PNR were recorded and all data were evaluated.

The measurements with the ChromaTest were performed by HBT, and all measurements with the Ganzfeld sphere were made by the same technician. The data pertaining to the right eyes of all patients were evaluated.

**Statistical Analyses**

The statistical analyses in this study were performed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). The chi-square (X2) test was used for the comparison of categorical characteristics between the NPDR and control groups. Normality of continuous study variables was assessed using the Shapiro–Wilk test, and non-parametric tests were applied accordingly.

Mann-Whitney U (Z) test was used to compare the mean values between the two groups. The significance level was set at  $p < 0.05$  for all analyses.

**RESULTS**

Of the 31 participants with NPDR, 14 (45.2%) were female and 17 (54.8%) were male, while 9 (42.9%) out of the 21 participants in the control group were female and 12 (57.1%) were male ( $p = 0.870$ ). The mean age of the participants in the NPDR and control groups was  $55.45 \pm 9.01$  years (range, 39-73 years) and  $54.86 \pm 5.61$  years (range, 41-65 years), respectively ( $p = 0.837$ ). BCVA was 0.0 logMAR in all participants in both groups. All patients had mild NPDR.

The protan CCT and tritan CCT were higher in the NPDR group than in the control group ( $p < 0.001$ ) (Table 1). The DA maximum sensitivity threshold value was lower in the NPDR group compared to the control group ( $p = 0.032$ ) (Table 2). In the fERG examination, rod response b-wave implicit time was longer in the NPDR group than in the control group ( $p = 0.005$ ). However, in the control group, the maximal-response a-wave amplitude was lower ( $p = 0.002$ ), and b-wave implicit time was longer ( $p < 0.001$ ) compared to the NPDR group. There were no significant differences between the groups in the amplitude of b-wave rod response, implicit time of a-wave maximal response, amplitude of b-wave maximal response, implicit time and amplitude of a- and b-waves of the cone response, amplitude of photopic flicker, and PNR ( $p > 0.05$ ) (Table 3).

<b>Table 1. Comparison of protan and tritan CCT values between the diabetes and control groups</b>			
	Diabetes Group (n=31)	Control Group (n=21)	
	Mean±SD (min, med, max)	Mean±SD (min, med, max)	p
Protan CCT (%)	4.06±3.69 (2.00, 3.00, 22.00)	1.70±0.46 (1.00, 1.70, 2.50)	<0.001
Tritan CCT (%)	15.82±8.64 (6.70, 15.40, 41.20)	5.83±2.76 (3.20, 5.10, 15.20)	<0.001

CCT: color contrast threshold, SD: standard deviation, Min: minimum, Med: median, Max: maximum

	Diabetes group (n=31)	Control group (n=21)	
	Mean±SD (min, med, max)	Mean±SD (min, med, max)	p
DA Maximum Sensitivity (dB)	65.97±4.52 (55.00, 66.00, 76.00)	68.71±5.59 (56.00, 69.00, 80.00)	= 0.032

DA: dark adaptometry, SD: standard deviation, Min: minimum, Med: median, Max: maximum, dB: decibel

	Diabetes group (n=31)	Control group (n=21)	
	Mean±SD (min, med, max)	Mean±SD (min, med, max)	p
Implicit time of b-wave rod response (ms)	86.98±10.03 (61.60, 86.40, 104.00)	79.30±7.53 (66.10, 79.30, 97.10)	= 0.005
Amplitude of b-wave rod response (μV)	106.44±42.21 (17.00, 108.00, 184.00)	127.30±32.76 (63.40, 120.00, 209.00)	= 0.075
Implicit time of a-wave maximal response (ms)	20.65±3.06 (15.60, 21.80, 25.30)	21.34±2.53 (14.70, 21.80, 25.30)	= 0.300
Amplitude of a-wave maximal response (μV)	104.75±35.44 (29.70, 100.00, 172.00)	77.71±20.98 (35.40, 76.60, 114.00)	= 0.002
Implicit time of b-wave maximal response (ms)	41.87±5.31 (33.30, 40.40, 58.10)	46.16±3.43 (38.60, 45.70, 52.80)	< 0.001
Amplitude of b-wave maximal response (μV)	191.71±49.49 (102.00, 191.00, 287.00)	169.95±33.77 (114.00, 167.00, 248.00)	= 0.090
Implicit time of a-wave con response (ms)	16.36±2.00 (11.10, 16.40, 22.60)	15.88±1.47 (13.70, 15.50, 19.90)	= 0.154
Amplitude of a-wave con response (μV)	12.13±4.58 (3.20, 10.90, 25.00)	13.33±6.48 (4.10, 11.80, 28.20)	= 0.911
Implicit time of b-wave con response (ms)	33.97±1.84 (31.40, 33.20, 39.40)	33.28±1.68 (31.40, 33.20, 38.50)	= 0.097
Amplitude of b-wave con response (μV)	49.95±18.33 (16.30, 52.70, 91.50)	50.40±12.07 (34.20, 47.00, 83.30)	= 0.874
Amplitude of photopic flicker (μV)	40.72±15.55 (4.90, 42.60, 79.40)	35.34±16.38 (11.30, 35.00, 85.40)	= 0.143
Photopic negative response (μV)	20.82±7.89 (0.10, 20.00, 35.70)	25.33±9.56 (10.40, 24.00, 44.40)	= 0.105

ffERG: full-field electroretinography, ms: millisecond, μV: microvolt, SD: Standard Deviation, Min: Minimum, Med: Median, Max: Maximum

## DISCUSSION

This study is the first, to our knowledge, to simultaneously evaluate color vision, DA, and fERG parameters in patients with mild NPDR. In our study, tritan and protan CCT were markedly higher in the NPDR group compared with the control group, while the maximum sensitivity threshold for DA was reduced. In contrast, despite the evident impairment observed in functional tests, only limited alterations were detected in fERG parameters. These findings suggest that retinal neurodegeneration may precede overt vascular changes in DR and that color vision and DA tests may serve as useful tools in demonstrating early functional impairment.

Psychophysical and electrophysiological examinations are sensitive tools for detecting early functional changes in the diabetic visual system. Many studies have identified an association between loss of color vision and diabetes, with or without DR, and used this visual function as a biomarker to show the status of diabetic disease [4,10-13]. Consistent with this, deterioration in tritan color vision is known to be dominant in DR [4,12]. Tritan color vision is primarily mediated by the blue-sensitive S-cone cells, and impairment along this axis generally reflects reduced sensitivity in these short-wavelength receptors. Yamamoto et al. reported that in diabetes, S-cone photoreceptor cells that perceive short wavelength light are affected before other cone cells [14]. Cho et al. also showed selective loss of S-cone histologically in postmortem retina with DR [15]. Similarly, our results demonstrated greater impairment along the tritan axis compared with the protan axis.

Previous ChromaTest studies have demonstrated color vision impairment in DR. In a ChromaTest-based study comparing patients with NPDR and diabetic individuals without retinopathy, tritan CCT was significantly increased in the NPDR group. In contrast, no significant difference was observed in protan CCT. In the same study, patients with previously untreated macular edema had significantly higher protan and tritan CCT than the other two groups [16]. Al Saeidi et al. evaluated 83 eyes from 42 patients with untreated NPDR using the ChromaTest, including eyes with macular edema. They demonstrated greater deterioration along the tritan axis than the protan axis, and this tritan-axis impairment was correlated with the severity of

macular edema, as assessed by increased macular thickness on OCT [17].

The underlying mechanisms responsible for color vision impairment in diabetes and diabetic retinopathy remain incompletely understood. However, accumulating evidence suggests that alterations in retinal oxygenation are associated with color vision deficits. Previous studies have indicated that changes in retinal oxygen availability may influence color contrast sensitivity [18,19]. Collectively, these findings support the notion that metabolic and oxygenation-related disturbances play a meaningful role in the color vision deficits observed in diabetes and DR. Because these disturbances are not limited to cone photoreceptors, rod function may also be affected, potentially explaining the impairment in DA observed in DR.

DA which reflects rod activity and the interaction between photoreceptors and the retinal pigment epithelium, was impaired in our study, as maximum light sensitivity was reduced in the NPDR group compared with healthy controls. Previous studies evaluating DA in diabetes have used various rod- and cone-based parameters to assess functional impairment. Bavinger et al. classified the DR cases according to their DR status and compared their DA with healthy controls. They reported that cone sensitivity during DA did not differ significantly between patients with NPDR and healthy controls. In contrast, rod recovery showed marked deterioration, particularly in patients with moderate NPDR. Moreover, they reported that cone sensitivity deteriorated later than rod function [20]. Hsiao et al. evaluated rod intercept time in diabetic patients and examined its relationship with retinal vascular perfusion density. They showed that rod intercept time was prolonged in diabetic patients, including those without clinically apparent DR, compared with healthy controls. Importantly, a significant negative correlation was reported between retinal vascular perfusion density and rod intercept time [3]. Taken together, the impairments in both color vision and DA detected by these functional tests reflect dysfunction of cone and rod photoreceptors, suggesting that diabetes exerts diffuse effects across the retina. In this context, fERG provides an appropriate tool for evaluating global retinal function.

Electroretinography is a non-invasive technique used to assess global retinal function and represents an important clinical tool in the evaluation of acquired retinal diseases

[21]. In diabetic patients, fERG abnormalities have been shown to correlate with disease severity, and early alterations—particularly in oscillatory potential amplitudes—have been suggested to be useful for predicting disease progression [22].

Chen et al. showed that PNR amplitude was significantly reduced in mild NPDR cases compared with healthy controls and further decreased with DR progression [23]. In contrast, in our study, no significant difference was observed in PNR parameters between patients with mild NPDR and healthy controls. In their study, no significant difference was observed in other fERG parameters between patients with mild NPDR and healthy controls. They reported that retinal neuropathy is an early and important component of DR, and PNR changes, which are thought to arise from retinal ganglion cells, are more sensitive than other electroretinography parameters for detecting cellular deterioration [23]. McAnany et al. compared standard 31.25 Hz and 62.5 Hz flicker responses in diabetic patients without retinopathy and those with mild NPDR to healthy individuals. While no significant difference was detected in standard 31.25 Hz flicker ERG responses, a significant decrease in amplitude was reported at 62.5 Hz in both diabetic groups compared with healthy controls. They suggested that flicker responses, which predominantly reflect bipolar cell activity, may be useful for demonstrating early retinal neural dysfunction when assessed using 62.5 Hz flicker ERG [24]. In our study, we assessed flicker responses at 30 Hz and did not observe any significant differences between the two groups.

In our study, rod response b-wave implicit time was prolonged in the NPDR group compared with controls. However, rod response a-wave amplitude was lower and b-wave implicit time was longer in the control group than in the NPDR group, representing an unexpected finding. No significant differences were observed in other fERG parameters. Some inconsistent and unexpected findings in fERG parameters may be attributable to the limited sample size of our study.

In diabetes, the impairment seen in functional tests, independent of the presence of vasculopathy, encourages investigation of the neurodegenerative processes in the retina. Neuronal damage and apoptosis in the inner and outer retinal layers have been demonstrated in animal experiments

and clinical studies. In diabetic animals, apoptotic retinal cells were seen in the vascular network isolated with trypsin using terminal dUTP nick end labeling (TUNEL)[25]. Barber et al. suggested that cell death is not only limited to vascular tissue, but also involves neurons and glial cells [26]. Degeneration of the photoreceptor layer and morphological changes in photoreceptor cells have also been demonstrated in experimental diabetes animal models [27,28]. In addition to animal experiments, the presence of neurodegeneration—an early stage of DR—has been confirmed by various clinical imaging studies evaluating the retinal layers. Significant reductions in retinal layer thickness have been found even in cases with little or no vascular retinopathy [29-31].

The presence of retinal neurodegeneration demonstrated at early stages of diabetes through morphological examinations and clinical imaging methods provides a contemporary perspective on the diagnosis and management of DR. Emerging neuroprotective therapeutic approaches for DR appear promising. Early detection of neurodegeneration using psychophysical and electrophysiological methods is feasible. Demonstrating early visual system deterioration may be important for guiding future neuroprotective interventions.

In our study, impairments in color contrast sensitivity and DA were observed despite relatively preserved fERG responses. These findings contribute to the growing body of evidence supporting early functional retinal involvement in diabetes. There is a need for the broader implementation of affordable, accessible, and practical functional testing methods to assess the visual system. Early detection and intervention are important from both public health and healthcare economic perspectives and are likely to become increasingly relevant in the future.

The relatively small sample size and the inclusion of only patients with type 2 diabetes represent limitations of our study and may have contributed to some of the inconsistent findings observed in fERG parameters. Further studies involving larger patient cohorts are needed to better characterize functional alterations in early-stage DR.

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None

## Conflicts of Interest

The authors declare that there is no conflict of interest to disclose.

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