

# The potential role of subclinical ischaemia in the visual dysfunction of patients with type 2 Diabetes Mellitus without diabetic retinopathy

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## Research article

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# Abstract

**Background** To evaluate visual function in patients with early type 2 Diabetes Mellitus (DM2) without diabetic retinopathy and good metabolic control, and to analyze the role of chronic systemic ischaemia in neuretina of these patients. **Methods** Sixty eyes of 60 patients with DM2 and without any signs of diabetic retinopathy, and 60 eyes of 60 healthy controls underwent visual acuity (VA), contrast sensitivity vision (CSV; using the Pelli Robson chart and CSV 1000E test), color vision (using the Farnsworth and L'Anthony desaturated D15 color tests) and visual field (Easyfield perimeter) evaluation to measure visual dysfunction. A comparison between patients with different disease duration time and presence/absence of systemic vascular complications was performed. **Results** The group of patients showed worse VA at 2.50% ( $p=0.002$ ) and 1.25% contrast ( $p=0.007$ ), worse CSV at high spatial frequencies (12 cpd,  $P=0.007$ ; 18 cpd,  $p=0.011$ ), and worse color vision (Farnsworth test,  $p=0.006$ ; Lanthony test,  $p<0.001$ ), compared to healthy controls. Visual field parameters were similar in both groups. Patients with longer disease duration had lower results in the ETDRS test, and those patients with chronic systemic vascular complications presented worse CSV at 18 cpd ( $p=0.024$ ) and color indexes in Lanthony color test ( $p=0.014$ ). **Conclusions** Patients with non-severe, early, type 2 DM without diabetic retinopathy and good metabolic control present visual dysfunction compatible with retinal neurodegeneration. Subclinical ischaemia might be a contributory factor to further neuronal damage in this pathology.

## Background

Despite retinal complications in diabetes mellitus (DM) patients were typically considered part of a vascular process, recent studies suggested that ocular degeneration in DM might be caused by 2 different processes: vasculopathy and neuropathy [1]. For some authors, neuropathic changes in the retina of these patients might precede microvascular alterations [2]. The theory of retinal neurodegeneration in early phases of the disease is supported by the alterations observed in functional tests, i.e. electroretinogram [3], contrast sensitivity [4,5], chromatic vision [6-8] and visual field results [9], in patients without diabetic retinopathy or just minimum changes. However, the possible role of subclinical microvascular alterations in retinal function parameters in diabetic patients is still not fully understood, and whether it precedes neurodegeneration in these patients is still unknown.

In this study, we evaluated patients with type 2 DM and good metabolic control, who had no clinical signs of diabetic retinopathy. A complete assessment of visual function parameters was performed and the possible role of chronic systemic ischaemia (as a possible indicator of subclinical retinal hypoperfusion) on visual results was analyzed.

## Methods

Sixty patients with type 2 DM and 60 age-and sex-matched healthy controls were recruited for this case-control study. All procedures adhered to the tenets of the Declaration of Helsinki, and the local ethics committee (CEICA, ethics committee for scientific research in Aragon) approved the experimental

protocol. All subjects provided informed written consent to participate in the study. The study was performed at Miguel Servet University Hospital, Zaragoza, Spain.

The diagnosis of type 2 DM was established by an experienced endocrinologist based on the American Diabetes Association criteria [10] and only subjects without diabetic retinopathy (at least 12 months prior recruitment) were eligible for the study.

The endocrine evaluation was carried out by a trained specialist from the Endocrine and Nutrition department of Miguel Servet University Hospital and provided demographic and disease related parameters. Age at the time of diagnosis, disease duration, prescribed treatments (for DM2 and other comorbidities), presence of micro- and macrovascular complications (such as cardiovascular disease, cerebrovascular disease, diabetic neuropathy or diabetic nephropathy) and presence of conditions associated with chronic complications in DM (such as arterial hypertension, hypercholesterolemia and obesity) were recorded. Endocrine variables such as glycosylated hemoglobin (HbA1C; most recent measured levels), microalbumin/creatinine ratio and total, HDL (high density lipoprotein) and LDL (low density lipoprotein) cholesterol levels were obtained through blood analysis during routine check-ups and recorded for the study. Arterial blood pressure and body mass index (BMI) were also registered. Subjects with arterial blood pressure levels of  $>140/90$  mmHg or under current hypotensive treatment were classified as "hypertensive"; subjects with a calculated BMI of  $\geq 25$  were classified as "overweight/obese". Smoking habit in patients and controls was also registered.

Inclusion criteria were: confirmed type 2 DM diagnosis of at least 6 months, best-corrected visual acuity (BCVA) of  $+0.4$  Log MAR in each eye to allow performance of the protocol, and intraocular pressure less than 21 mmHg. Exclusion criteria were: the presence or past history of diabetic retinopathy, confirmed by indirect funduscopy or retinography images, presence of significant refractive errors ( $\geq 5$  diopters of spherical equivalent refraction or 3 diopters of astigmatism), axial length  $>26$  mm or  $< 22$  mm, intraocular pressure  $\geq 21$  mmHg; media opacifications, concomitant ocular diseases, including history of glaucoma or retinal pathology, and systemic conditions that could affect the visual system, including neurodegenerative disorders such as Parkinson's disease, multiple sclerosis or dementia. Healthy controls had no history nor evidence of ocular or neurologic disease of any nature; their BCVA was  $\leq +0.2$  Log MAR. Only one eye per subject was randomly selected and included.

All subjects underwent a complete neuro-ophthalmic evaluation that included an in-depth funduscopy examination. Visual function was evaluated following a systematic protocol described previously by our team [11], using the ETDRS chart (for BCVA analysis), the CVS-1000E and Pelli-Robson tests (for contrast sensitivity vision – CSV- assessment), the Farnsworth desaturated D15 and L'Anthony desaturated D15 tests (for color vision analysis) and the automated perimeter Easyfield (Oculus Optikgeräte GmbH, Wetzlar, Germany).

Visual acuity (VA) was assessed at three different contrast levels: 100% (high contrast VA, using ETDRS chart), 2.50%, and 1.25% (low contrast VA, using Low-Contrast Sloan Letter Charts -Precision Vision,

LaSalle, IL-). All measurements were obtained under controlled lighting conditions and monocular vision with best correction, BCVA at all contrast levels was recorded in Log Mar.

Contrast sensitivity was evaluated to obtain more complete information about visual function than results provided by visual acuity tests. CSV was assessed using the Pelli-Robson chart and the CVS-1000E test. The Pelli-Robson chart evaluates CSV at a frequency of 1 cycle per degree (cpd). The test comprises horizontal lines of capital letters organized into triplets, with two triplets per line. Contrast decreases from one triplet to the next. All patients were evaluated under controlled photopic conditions (85 cd/m<sup>2</sup>) at a distance of 1 meter from the chart. The score corresponding to the last triplet of letters seen by the patient was recorded.

The CVS-1000E instrument is used worldwide for standardized CSV and glare testing. The chart comprises four rows with 17 circular patches each. The patches present a grating that decreases in contrast moving from left to right across the row. All patients were evaluated at a distance of 2.5 meters from the chart under monocular vision at 4 different spatial frequencies (3, 6, 12, and 18 cpd). Each contrast value for each spatial frequency was transformed into a logarithmic scale according to standardized values.

Color vision was assessed using the Color Vision Recorder (CVR) program. CVR software analyzes chromatic discrimination by classification of hues. The program includes the classic test of Farnsworth 100-hue (FM-100), Farnsworth - Munsell D15, and L'Anthony D15. Only the last two were used in our study and both tests were performed under monocular vision. The different output parameters such as the Color Confusion Index (CCI, representing the ratio between the radius or distance between caps), the Confusion angle (Conf Ang, which is the axis of color deficiency), and the Scatter Index (S-index, the parallelism of confusion vectors to the personal confusion angle) were recorded.[12,13]

Automated perimetry was evaluated with the Easyfield perimeter (Oculus Optikgeräte GmbH, Wetzlar, Germany). This visual field analyzer is equipped with LED stimuli of a maximum of 10,000 apostles (asb), presented on a background of 31.5 asb. The QuickSpark protocol (with a brief short and fast luminous flash), which performs a rapid (less than three minutes) but very accurate measurement of the thresholds in the central field of vision was used in all subjects. Refraction for adequate proximal vision was calculated for each subject; the test was performed in monocular vision. The parameters recorded were mean sensitivity (arithmetic mean of the sensitivities of all the points studied), mean defect (arithmetic mean of the differences in sensitivities of each point with respect to the normal value for a healthy person of the same age), deviation on the pattern, and reliability factor (percentage of failed answers). As a criterion of reliability, in case of results with more than 50% of losses in detected stimuli, the test was repeated a second time. In 3 of the subjects, a reliable test was not obtained despite a second attempt, so the result of this test was discarded and was not included in the statistical analysis.

All data analyses were performed using SPSS software version 20.0 (SPSS Inc., Chicago, IL). Due to the parametric distribution of the data, differences between evaluations of diabetic patients and healthy subjects were compared using Student's t-test. The linear correlation between endocrine (age at the time

of diagnosis, duration of the disease, HbA1C, total, HDL and LDL cholesterol levels, systolic and diastolic arterial blood pressure and BMI) and functional parameters was determined using Pearson's correlation coefficient. A binary logistic regression using Forward Wald method was performed to evaluate the predictor ability of all visual function test parameters to distinguish between DM eyes and control subjects.

Additionally, a sub-classification of subjects was performed, dividing DM2 patients into 2 different groups depending on the presence/absence of some particular characteristics: disease duration  $\geq$  or  $<$  to 10 years, presence/absence of micro-macrovascular complications and presence/absence of HbA1C levels  $>7$  mmol/ml. Values of  $p$  less than 0.05 were considered to indicate statistical significance. To avoid a high false positive rate, the Bonferroni correction for multiple tests was calculated and the corrected  $p$ -values were added to the previously calculated data (see all tables).

## Results

Sixty eyes of 60 patients with a mean age of  $61.60 \pm 9.40$  years and 60 eyes of 60 healthy individuals with a mean age of  $60.15 \pm 7.05$  were included in the study. There were 22 females (37%) and 38 (63%) males in the patients group, and 36 females (60%) and 24 (40%) males in the control group. Mean axial length was  $23.58 \pm 1.74$  mm in the patients group, and  $23.47 \pm 1.25$  mm in the control group. Patients and controls did not show significant differences in the five-confounding factors considered: age ( $p=0.341$ ), gender ( $p=0.220$ ), intraocular pressure ( $p=0.132$ ), smoking habit ( $p=0.439$ ) and axial length ( $p=0.722$ ). Disease duration in the group of patients was 12.62 years ( $SD=7.29$ ). All demographic and endocrinology variables are displayed in Table 1.

Diabetic patients presented lower BCVA at 2.50% ( $0.37 \pm 0.14$  in patients vs  $0.28 \pm 0.14$  in controls,  $p=0.002$ ) and 1.25% ( $0.48 \pm 0.15$  vs  $0.40 \pm 0.16$ ,  $p=0.007$ ) contrast levels compared to healthy controls. BCVA at 100% did not show significant differences between both groups. The group of patients also presented worse CSV at 12 and 18 cpd ( $1.41 \pm 0.30$  vs  $1.56 \pm 0.24$ ,  $p=0.007$ ;  $0.98 \pm 0.28$  vs  $1.12 \pm 0.28$ ,  $p=0.011$ , respectively). No differences were observed in the Pelli Robson test (see Table 2).

Color vision was also affected in patients with DM compared to controls. DM patients presented a significant alteration in the CCI ( $1.13 \pm 0.25$  vs  $1.04 \pm 0.09$ ,  $p=0.006$ ) and the Conf ang ( $50.69 \pm 4.83$  vs  $62.61 \pm 0.37$ ,  $p=0.011$ ) in the Farnsworth-Munsell test, and the CCI ( $1.58 \pm 0.46$  vs  $1.28 \pm 0.25$ ,  $p<0.001$ ) and the S-index ( $1.87 \pm 0.60$  vs  $1.66 \pm 0.43$ ,  $p=0.026$ ) with the Lanthony test (see Table 2).

No differences, however, were observed between patients and controls in any of the parameters of the visual field (see Table 2).

No significant associations were observed between visual function parameters and metabolic parameters such as arterial hypertension, blood cholesterol levels, metabolic control, disease duration, vascular complications or obesity.

Logistical regression found that 2 parameters have predictive ability to detect eyes from DM patients: Lanthony's CCI ( $p=0.050$ ) and the Deviation of the pattern of the Spark visual field ( $p=0.029$ ).

### *Subgroup analysis*

Diabetic patients were divided into 2 different groups depending on the presence or absence of a selected variable (disease duration of 10 years or more, presence/absence of vascular complications and  $HbA1C < 7$ ), and then compared. Age was considered a confounding factor for each group and compared: no differences were observed between groups ( $p=0.070$ ,  $p=0.060$  and  $p=0.054$ , respectively).

Patients with disease duration of at least 10 years ( $n=38$ ) presented worse BCVA results at all contrast levels compared to those with disease duration inferior to 10 years ( $n=22$ ). CSV was also worse in this group of patients at 3 ( $1.57 \pm 0.26$  vs  $1.70 \pm 0.12$ ,  $p=0.049$ ) and 12 cpd ( $1.32 \pm 0.30$  vs  $1.56 \pm 0.24$ ,  $p=0.005$ ). Color vision and visual field parameters did not show significant differences between different times of disease evolution (see Table 3).

Patients with the presence of chronic vascular complications of diabetes ( $n=21$ ) showed worse CSV at 18 cpd ( $0.86 \pm 0.29$  vs  $1.05 \pm 0.29$ ,  $p=0.024$ ) compared to those without chronic vascular complications ( $n=39$ ). Color vision was altered in these patients in the Lanthony test (CCI,  $1.79 \pm 0.43$  vs  $1.48 \pm 0.44$ ,  $p=0.014$ ; Conf ang,  $43.17 \pm 22.12$  vs  $62.30 \pm 20.81$ ,  $p=0.023$ ).

Visual function variables in patients with poor metabolic control ( $HbA1C > 7$ ;  $n=28$ ) did not show significant differences compared with those with good metabolic control ( $HbA1C < 7$ ;  $n=32$ ).

## **Discussion**

In this study, we evaluated visual function changes in patients with early and non-severe type 2 DM without any sign of diabetic retinopathy. Our patients presented worse BCVA at low contrast levels and worse CSV at high spatial frequencies. There are different driving paths for different frequencies in the processing of visual information and it is not known which paths are affected the most in DM [14]. Thus, the evaluation of CSV in different spatial frequencies is of great importance in these patients. It appears that, in the presence of clinical diabetic retinopathy, a decrease in contrast sensitivity is present [5,14], which may be independent of the visual acuity affectation [5,15]. However, there is no agreement on whether this CSV affectation begins before the diabetic retinopathy. In our study, patients with type 2 DM without diabetic retinopathy presented altered CSV only for high spatial frequencies (12 and 18 cpd). These results support previous findings, where loss of contrast sensitivity in type 2 diabetics who do not have diabetic retinopathy was hardly observed [5,14,16]. However, other researchers have found changes affecting CSV in all frequencies in patients with DM2 and no retinopathy [15,17]. It has been suggested that the selective loss of contrast sensitivity for the higher frequencies is a signal of parvocellular dysfunction [18]; this would account for 80% of the retinal ganglion cells (which are parvocellular) [19].

Color vision alterations were observed in our patients, using 2 different color tests. Color vision changes in patients with DM had previously been reported in different studies. However, most of these studies focus on type 1 DM or both types [20-22]. Research on type 2 DM has shown color vision defects in patients without diabetic retinopathy, but these studies preferably use chromatic tests with 100 shades [8,14], such as Farnsworth-Munsell 100, and the results would not be comparable to our study. However, experts have indicated that desaturated colour tests, as the ones used in our study, are more sensitive to detect early optic neuropathy [23].

Visual field defects were reported in type 1 DM patients in disease stages preceding diabetic retinopathy changes [9,24]. We could not find significant differences in visual field parameters between healthy controls and type 2 DM patients. Similar results were observed in the study by Nitta et al [25]. It has been suggested, however, that there may be a diffuse affectation of the visual field in patients with DM 2, even without diabetic retinopathy, and that this affectation increases significantly with the appearance and severity of the vascular retinal changes [26]. Similar to the previously mentioned research on color vision, previous visual field studies used different perimetry devices and patient samples are heterogeneous, mixing in some cases patients with and without diabetic retinopathy, and both types of DM. It is possible that in our study there were no differences in the visual field evaluation between the groups due to the small size of the sample, or because of the different design of the studies.

Diabetic retinopathy and retinal complications in patients with DM were typically considered part of a vascular process. However, recent research suggested that retinal degeneration in DM might be caused not only by vasculopathy, but also (and importantly) by neuropathy [1]. It was suggested that neuropathic changes might precede microvascular alterations in these patients [2]; however, the possible correlation between neuropathy and vasculopathy in this process is still unknown. Funduscopy alterations such as microaneurysms and hemorrhages which are present at early stages in diabetic retinopathy might be preceded by other vascular alterations that are not observable in a routine exam. Thus, preclinical diabetic retinopathy might be caused by changes in the caliber of retinal vessels or in the regulation of retinal blood flow [27-29]. However, changes affecting retinal neurons have also been observed, such as increased apoptosis of the retinal ganglion cells and activation of the microglia [30-32] without signs of vascular changes. The theory of retinal neurodegeneration in early phases of the disease is supported by observed alterations in electrophysiological tests such as electroretinogram [3,33], contrast sensitivity [4,5], chromatic vision [6-8] and visual field results [9,24,34], in patients without diabetic retinopathy or just minimum changes.

Our results would also support retinal neurodegeneration, since alterations in CSV and color vision were observed without any signs of vascular changes. However, even if our patients had good metabolic control and no visible retinal alterations, subclinical (unobserved) microvascular changes might still be present in our sample. In a subgroup analysis, the possible role of chronic systemic vascular alterations was evaluated. Patients in our study presenting these chronic vascular complications had worse BCVA, CSV and color vision results (in Lanthony test, which detects mild color vision changes that the Farnsworth test might not detect) than their peers without systemic vascular alterations. Diabetic

neuropathy is associated with the same risk factors in other macrovascular and microvascular complications, such as dyslipidemia, poor metabolic control and microalbuminuria. Animal models and biopsies demonstrated that in diabetic neuropathy there is an alteration in the microvascularization of the nerves, leading to endoneural hypoxia [35,36]. Therefore, given that they share pathogenic mechanisms, it is possible that the presence of extraocular complications of diabetes, generated by vascular alterations, appear simultaneously with a certain subclinical dysfunction of retinal perfusion. This incipient vascular alteration could lead to a hypoxia of the retinal nerve structures, manifesting as a deterioration in contrast sensitivity, chromatic vision, BCVA and perimetry. Past studies [14,17] reported worse CSV in patients with more than 10 years of disease evolution (supported by our own results) and also in patients with worse metabolic control [17]. However, we could not find similar studies analyzing the presence of systemic vascular complications in patients with type 2 DM and chromatic vision alterations. Our results would add more evidence to the possible role of hypoxia affecting the retinal nerve structures before visible vascular changes.

One limitation of our study is the (relatively) small sample size. Although notable differences were observed between the patient and the control groups, we failed to find differences in visual field parameters and in patients with worse metabolic control. Also, in our study metabolic parameters related to diabetes were not associated with functional results in our patients. As previously mentioned, we believe that due to different sample sizes and devices used, results might differ from past published studies. Moreover, most of our patients presented good metabolic control (mean HbA1C was 7.3%) and therefore the comparison between groups with/without HbA1C>7% might have not revealed true differences in functional parameters due to the small difference in HbA1C levels.

## Conclusions

Our study demonstrates the presence of visual function alterations in type 2 DM patients with good metabolic control and without any signs of vascular retinal changes, adding more evidence to the theory of neurodegeneration preceding vasculopathy in these patients. However, our results also suggest that possible incipient vascular alterations (related to systemic vascular changes) could appear simultaneously with a certain subclinical dysfunction of retinal perfusion or lead to a hypoxia of the retinal nerve structures causing the observed functional changes. Further histopathological studies would be needed to corroborate our findings.

## Abbreviations

DM: Diabetes Mellitus

HbA1C: glycosylated hemoglobin

BMI: body mass index

BCVA: best-corrected visual acuity

ETDRS: Early treatment diabetic retinopathy study

CSV: Contrast sensitivity vision

CCI: color confusion index

Conf ang: Confusion angle

S-index: Scatter index

## **Declarations**

### **Ethics approval and consent to participate**

All procedures adhered to the tenets of the Declaration of Helsinki, and the local ethics committee (CEICA, ethics committee for scientific research in Aragon) approved the experimental protocol. All subjects provided informed consent to participate in the study

### **Consent for publication**

Not applicable

### **Availability of data and material**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

### **Competing interests**

The authors declare that they have no competing interests

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### **Authors' contributions**

MS performed the study design, analysis and interpretation of data and drafting the manuscript; MC performed the acquisition and interpretation of data; IM performed the acquisition of data, contributed to data analysis and interpretation; LGA contributed to the study conception and design, interpretation of data and provided critical analysis of the manuscript; EV performed the acquisition of data, contributed to data analysis and interpretation; JML contributed to the study conception and design, interpretation of data and provided critical analysis of the manuscript; MJR contributed to the study conception and

design, interpretation of data and provided critical analysis of the manuscript; EGM contributed to the study conception and design, analysis and interpretation of data and provided critical analysis of the manuscript.

All authors listed gave their final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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## Tables

<b>Demographic parameters</b>	<b>Mean±SD</b>
Disease duration (years)	12.62±7.29
Age at diagnosis (years)	50,50±10.57
Glycated hemoglobin (%)	7.33±0.89
Mycroalbuminuria/creatinin index	18.23±21.20
	<b>Number of patients (%)</b>
Presence of hypertension	49 (81.87%)
Presence of dyslipemia	57 (95%)
Presence of vascular complications	
Ischaemic cardiopathy	8 (13.30%)
Cerebrovascular disease	2 (3.30%)
Peripheral vasculopathy	0 (0%)
Diabetic neuropathy	5 (8.33%)
Diabetic nephropathy	8 (13.30%)
Treatment	
No insuline (only oral antidiabetic agents)	43 (71.60%)
Insuline	17 (28.40%)

**Table 1** Demographic and epidemiologic data of the patients with type 2 diabetes mellitus included in the study.

Abbreviations: SD, standard deviation

	DM2		Controls		p
	Mean	SD	Mean	SD	
<b>Best corrected visual acuity</b>					
ETDRS 100%	0.01	0.09	-0.04	0.20	0.111
ETDRS 2.5%	0.37	0.14	0.28	0.14	<b>0.002</b>
ETDRS 1.25%	0.48	0.15	0.40	0.16	<b>0.007</b>
<b>Contrast sensitivity</b>					
CSV-1000 3 cpd	1.62	0.23	1.66	0.19	0.386
CSV-1000 6 cpd	1.83	0.23	1.89	0.20	0.176
CSV-1000 12 cpd	1.41	0.30	1.56	0.24	<b>0.007</b>
CSV-1000 18 cpd	0.98	0.28	1.12	0.28	<b>0.011</b>
Pelli-Robson	1.78	0.20	1.81	0.15	0.473
<b>Spark perimetry</b>					
Mean sensitivity	27.72	3.70	28.71	3.69	0.194
Mean defect	0.79	3.45	1.13	3.42	0.633
Deviation on the pattern	2.23	1.67	2.38	2.40	0.715
Reliability factor	0.93	0.09	0.97	0.24	0.215
<b>Farnsworth-Munsell 15D</b>					
CCI	1.13	0.25	1.04	0.09	<b>0.006</b>
S-index	1.69	0.47	1.57	0.29	0.106
Conf ang	50.69	4.83	62.61	3.77	<b>0.011</b>
<b>Lanthony D15</b>					
CCI	1.58	0.46	1.28	0.25	<b>&lt;0.001*</b>
S-index	1.87	0.60	1.66	0.43	<b>0.026</b>
Conf ang	55.81	30.80	57.51	33.32	0.775

**Table 2** Visual function parameters in patients with type 2 diabetes mellitus and healthy controls. Bold letters indicate statistical significance ( $p < 0.05$ ). Asterisk marks significance using Bonferroni correction ( $p < 0.002$ ). Abbreviations: DM2, type 2 diabetes mellitus; SD, standard deviation; ETDRS, Early treatment diabetic retinopathy study; CSV, contrast sensitivity; CCI, color confusion index; S-index, scatter index; Conf ang, confusion angle.

	DM duration < 10 years		DM duration ≥ 10 years		p
	Mean	SD	Mean	SD	
<b>Best corrected visual acuity</b>					
ETDRS 100%	-0.03	0.06	0.03	0.10	<b>0.013</b>
ETDRS 2.5%	0.30	0.10	0.40	0.15	<b>0.008</b>
ETDRS 1.25%	0.42	0.11	0.52	0.16	<b>0.015</b>
<b>Contrast sensitivity</b>					
CSV-1000 3 cpd	1.70	0.12	1.57	0.26	<b>0.049</b>
CSV-1000 6 cpd	1.89	0.19	1.79	0.25	0.166
CSV-1000 12 cpd	1.56	0.24	1.32	0.30	<b>0.005</b>
CSV-1000 18 cpd	1.07	0.28	0.92	0.27	0.060
Pelli-Robson	1.85	0.14	1.75	0.21	0.052
<b>Perimetry (Easyfield-Spark-)</b>					
Mean sensitivity	28.47	2.46	27.24	4.26	0.236
Mean defect	1.34	1.71	0.44	4.18	0.897
Deviation on the pattern	2.04	1.38	2.35	1.84	0.304
Reliability factor	0.92	0.10	0.93	0.07	0.088
<b>Farnsworth-Munsell 15D</b>					
CCI	1.14	0.32	1.12	0.19	0.625
S-index	1.65	0.49	1.70	0.45	0.056
Conf ang	46.37	38.51	56.06	32.92	0.698
<b>Lanthony D15</b>					
CCI	1.61	0.47	1.56	0.44	0.056
S-index	1.78	0.63	1.92	0.58	0.142
Conf ang	38.39	33.42	45.43	14.14	0.275

**Table 3:** Visual function parameters in patients with type 2 diabetes mellitus with less and more than 10 years of disease duration. Bold letters indicate statistical significance ( $p < 0.05$ ). Bonferroni significance applies for  $p < 0.002$ . Abbreviations: DM, diabetes mellitus; SD, standard deviation; ETDRS, Early treatment diabetic retinopathy study; CSV, contrast sensitivity; CCI, color confusion index; S-index, scatter index; Conf ang, confusion angle, Farnsworth-Munsell 15D and Lanthony D15, desaturated tests with 15 colors