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André Alexandre Dosso
Emmanuelle Romaine Bonvin
Yves Morel
Alain Golay
Jean Philippe Assal
Peter Manuel Leuenberger

Risk factors associated with contrast sensitivity loss in diabetic patients

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A.A. Dosso (✉) · E.R. Bonvin
P.M. Leuenberger
University Eye Hospital, 22,
rue Alcide Jentzer, CH-1205 Geneva,
Switzerland
Fax +41-22-3828382

Y. Morel · A. Golay · J.P. Assal
Diabetes Treatment and Teaching Clinic,
Hôpital Cantonal, Bd de la Cluse,
CH-1205 Geneva, Switzerland

Abstract ● Background: Psychophysical tests in patients with diabetes mellitus reveal deficits of central vision before the development of overt retinopathy. We evaluated the contrast sensitivity thresholds in 30 patients with type II diabetes mellitus and without retinopathy, taking into account the crystalline lens density. Risk factors for contrast sensitivity deficits were investigated. ● Methods: Contrast sensitivity was compared in 30 aretinopathic diabetic patients and age-matched controls. Contrast thresholds were determined for stationary gratings at three spatial frequencies (6, 15, and 27 cycles/deg) and for mesopic (5 cd/m^2) and low photopic (85 cd/m^2) vision. Lens density was measured using a IntraOptics opacity lensmeter. ● Results: Significant contrast sensitivity losses at all three spatial frequencies were observed in low photopic and mesopic vision in diabetic patients. The optical density of the lens in the diabetic group did not differ from that in the controls. Contrast sensitivity deficits were positively correlated with patient's age, systolic blood pressure and nephropathy at all three spatial frequencies. No relationship between cardiovascular autonomic neuropathy and contrast sensitivity defects was observed. ● Conclusions: These data suggest that contrast sensitivity deficits in diabetic patients without retinopathy are not solely explained by a diabetes-induced increases in lens optical density. Abnormalities of the retina or its neural connections occurring before the onset of clinically detectable retinopathy may be involved. Risk factors for these deficits are advanced age, high systolic blood pressure, and nephropathy.

Introduction

Patients with diabetes mellitus frequently exhibit evidence of abnormal central vision before the development of either overt retinopathy or a reduction in visual acuity [1–7]. Spatial resolution defects, which can be detected with contrast sensitivity measurements, are found in some diabetic patients [3–7]. In the presence of overt diabetic retinopathy, contrast sensitivity deficits correlate with the severity of the retinopathy [3–5].

Although the pathophysiology underlying these visual abnormalities is unknown, they are considered to constitute evidence of a neurosensory anomaly that may precede, and may even contribute to, the development of both diabetic retinal vascular disease and diabetic optic neuropathy [8]. Therefore, an understanding of the nature of these abnormalities of central vision function, as well as their correlation with risk factors during the initial stages of retinopathy, could provide insight into the mechanisms involved in early visual loss in diabetic patients. This study examined contrast sensitivity deficits that occur in patients with diabetes mellitus who have no retinopathy. Furthermore, we determined risk factors for this defect and assessed the

contribution of the crystalline lens to contrast sensitivity loss.

Material and methods

Subjects

Thirty patients with type II diabetes mellitus of mean age 53.9 years (range 32–72 years) and with mean diabetes duration of 12.4 years (range 5–35 years) were investigated and compared with 30 age-matched controls. The current metabolic control status was estimated by hemoglobin A_{1c} concentrations (8.9%±1.4, mean±SD), ranging from 6.8 to 11.4% [9]. Eye examination in the diabetic patients comprised corrected Snellen acuity, tonometry, slit-lamp examination of the lens and anterior chamber, fundus biomicroscopy, and five-field fundus photographs, all of which were normal in every patient. None of the controls were receiving medication, none had a history of diabetes or eye disease, and none was known to have abnormal contrast sensitivity. Diabetic patients and controls did not have previous experience of the gradual contrast sensitivity test. Informed consent was obtained after the nature of the technique and the aim of our research were thoroughly explained.

Contrast sensitivity

Visual acuity measurements for each eye were obtained from all subjects and patients on the day of contrast sensitivity testing. Optical correction was worn when necessary. All patients had Snellen acuity of 20/20 or better. Subjects with undilated pupils monocularly maintained visual fixation on the stimulating field from a viewing distance of 3 m.

Contrast thresholds were obtained with a gradual contrast sensitivity test. This test use traditional optotypes and the letters are set out in 10 columns. Each column is numbered from C1 to C10 to take into account visual acuity marking habits (1/10 to 10/10). As a result, for each line, the best performance is marked C10, and the worst C1. Contrast thresholds were determined for stationary gratings at three spatial frequencies (6, 15, and 27 cycles/degree, and for mesopic (5 cd/m^2) and low photopic (85 cd/m^2) vision and expressed as a percentage on the basis of the following formula: (background brightness–optotype brightness)×100/background brightness.

Optical density of the crystalline lens

Optical density of the lens was evaluated using the IntraOptics opacity lensmeter, which functions like a slit lamp. The principle is the projection of a 1.5 mm diameter light source (LED at 700 nm) into the eye. Some of the projected light is scattered by the lens and varies with the degree of lens opacification. A portion of the back-scattered light is sampled by a detector mounted at an angle. The intensity of the sampled light is processed and displayed as a numeric value from 0 to 99, where 0 is a perfectly clear lens. When the density values approach 25–30, the patients typically request cataract surgery [10]. A built-in microcomputer controls automatic calibration, storage of measurements, rejection of false measurements (eyelid blinks), and data analysis. Two hundred and fifty readings are taken at the push of a button in 0.5 s and electronically stored as a single (averaged) measurement. Five measurements of each eye were taken in succession [10].

Cardiovascular autonomic nervous system testing

The patient's electrocardiogram was electronically monitored with chest leads to identify each R wave and to measure R-R intervals to within 1 ms. Four measurements of autonomic nervous system function, as previously described by Ewing et al. [11], were used:

1. R-R variation during deep breathing (R-R variation). One index was calculated: the E-I ratio, which is a ratio of the heart rate during expiration (E) to that during inspiration (I).
2. R-R variation in response to a change in position from supine to standing (brake index). Again, one index was considered: the 30:15 ratio, which is a ratio of the R-R interval at the 30th beat after standing to the R-R interval at the 15th beat after standing.
3. Change in blood pressure in response to a change in position from supine to standing. The blood pressure is measured using a standard sphygmomanometer while the subject is in a lying position, and again after standing up. The difference in systolic blood pressure is taken as the measure of postural blood pressure change.
4. Blood pressure response to sustained handgrip. Handgrip is maintained at 30% of the maximum voluntary contraction using a handgrip dynamometer up to a maximum of 5 min, and the blood pressure measured each minute. The difference between the diastolic blood pressure just before release of handgrip and that before starting is taken as the measure of response.

As proposed by others [11, 12], an index of cardiovascular autonomic neuropathy (CAN) was designed to provide an overall measure of impairment. R-R variation of less than 10 ms and a 30:15 index below 1.00 were considered abnormal. A fall in systolic blood pressure of more than 20 mmHg was used as the cut-off point to diagnose orthostatic hypotension [13]. A rise in blood pressure of less than 10 mmHg during sustained handgrip was considered abnormal.

Peripheral nervous system testing

Perception of vibration was registered on both big toes using a graduated tuning fork [14]. The tuning fork was graduated from 0 to 8 and values below 4 were considered abnormal.

Temperature perception was assessed using a Thermocross device [15]. This is a mains-powered hand-held instrument consisting of a cruciform arrangement of four cylindrical probes (25±0.1°C, 42±0.1°C, 50±0.1°C, and between 25±0.1°C and 35±0.1°C).

Laboratory tests

Microalbuminuria was determined using immunoassay technique [16]. Albumin concentration was calculated from one 24-h urine sample. The upper limit of normal for microalbuminuria was set at 20 mg/l.

Systolic and diastolic blood pressure were measured while the patient was sitting after 10 min rest. We recorded creatinine clearance, total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, atheromatous index (total cholesterol/HDL cholesterol), and body mass index [weight/(height)^2].

Statistical analysis

All data are expressed as mean±SD. Comparison of contrast sensitivity scores in diabetic patients and age-matched controls was made using an unpaired two-tailed Student's *t*-test. Multiple regression analysis was used to evaluate risk factors for the deficits in contrast sensitivity. $P<0.05$ was accepted as statistically significant.

Table 1 Descriptive characteristics of subjects with diabetes (n=30) *BP* Blood pressure, *HDL* high-density lipoproteins

Parameter	Mean±SD	Normal values
Insulin-treated (%)	43.3	
Systolic BP (mmHg)	138±21	
Diastolic BP (mmHg)	83±11	
Microalbuminuria (mg/L)	176±352	<30
créatinine clearance (ml/min)	92.7±25.0	80–100
cholesterol (mmol/L)	6.3±1.0	<6.0
HDL (mmol/L)	1.0±0.3	>1.2
triglycerides (mmol/L)	3.3±2.6	<2.3
Atheromatous index	6.43±2.4	<5.0
Body mass index	28.6±5.0	<25

Table 2 Results of the cardiovascular autonomic and peripheral nervous system testing of diabetic subjects (n=30)

Parameter	Mean±SD	Normal values
R-R variation	21.1±9.0	>15
Brake index (30: 15 ratio)	1.11±0.1	>1.04
Fall in systolic BP (mmHg)	1.9±5.6	<10
Handgrip (mmHg)	21.7±7.3	>16
Vibratory perception (X/8)	0.7±0.1	>0.5
Temperature perception (°C)	2.6±1.6	<3

Results

Some characteristics of the diabetic patients are shown in Table 1. Contrast sensitivity thresholds in the diabetic group and the age-matched controls are shown in Figs. 1 and 2. The contrast sensitivity means were significantly lower in diabetic patients than in control subjects at 6, 15, and 27 cycles/deg spatial frequencies (P=0.0001, P=0.0002, and P=0.0006, respectively) in low photopic vision (Fig. 1). In mesopic vision (Fig. 2), contrast sensitivity losses were less significant than in low photopic vision (P=0.01, P=0.03, and P=0.005, respectively).

A subject was considered to have abnormal contrast sensitivity when the contrast threshold was 2 SD below the means of the control group for at least one spatial frequency. Contrast sensitivity testing showed such losses in 18 diabetic patients (60%).

At the time of the study, the diabetic group and the age-matched controls had the same mean lens optical density as measured using the opacity lensmeter (14.9±3.1 versus 13.7±3.3).

The results of the cardiovascular autonomic and peripheral nervous system testing are shown in Table 2. Cardiovascular autonomic neuropathy and peripheral neuropathy were only observed in one diabetic patient (3%).

Microalbuminuria was found in 18 patients (60%) and nephropathy in 11 patients (36.6%).

Risk factors for the contrast sensitivity deficits for all three spatial frequencies, analyzed by logistic regression,

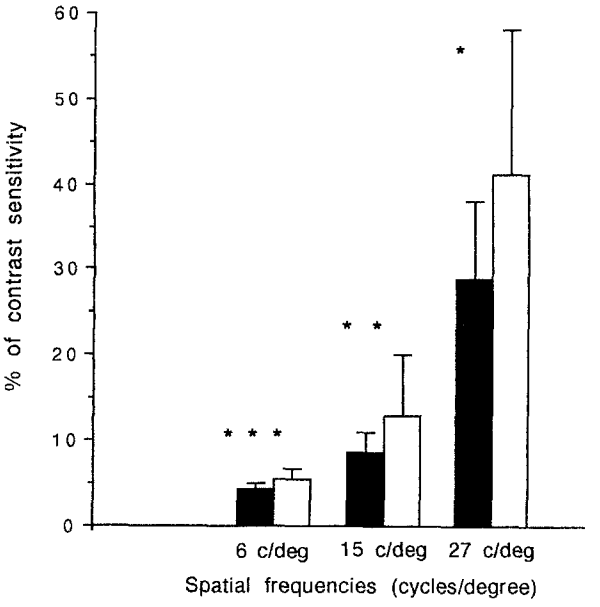

Fig. 1 Contrast sensitivity thresholds in diabetic patients and controls at photopic vision, expressed as percentages on the basis of the following formula: (background brightness–optotype brightness×100/background brightness. Values are means±SD. * P=0.0006, ** P=0.0002, *** P=0.0001; ■ Controls, □ Diabetics

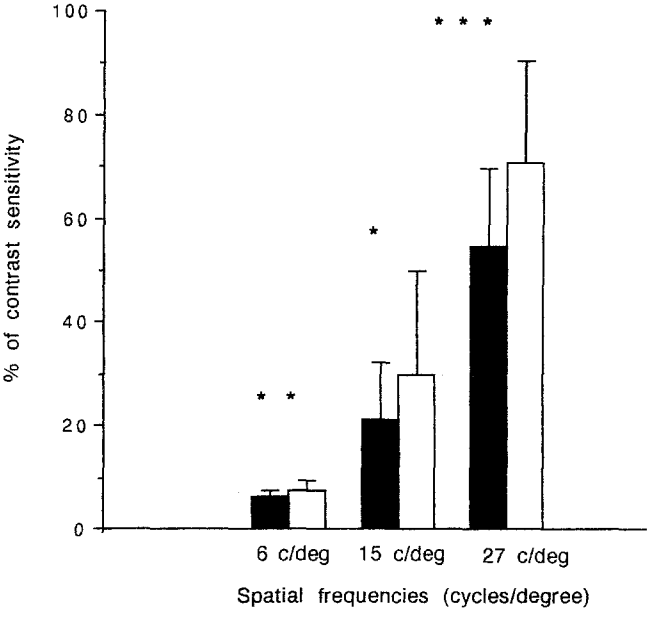

Fig. 2 Contrast sensitivity thresholds in diabetic patients and controls at mesopic vision, expressed as percentages on the basis of the following formula: (background brightness–optotype brightness×100/background brightness. Values are means±SD. * P=0.03, ** P=0.01, *** P=0.0005

were: age (P=0.02, P=0.004, and P=0.0004 for 6, 15, and 27 cycles/deg, respectively), systolic blood pressure (P=0.04, P=0.04, P=0.02), and nephropathy (P=0.04, P=0.04, P=0.02).

No correlation between sensitivity losses and duration of diabetes, hemoglobin A_{1c} or cardiovascular autonomic neuropathy was found.

Discussion

Retinal vascular disease is considered the most significant factor in the etiology of visual loss in patients with diabetes mellitus, even though it is now well established that many diabetic patients exhibit some signs of visual dysfunction prior to the development of clinically apparent retinopathy. Abnormal color vision [1, 2, 6, 17, 18], contrast sensitivity [3–7], electroretinograms [19], and visual evoked potentials [20] have been observed in these patients.

It is assumed that these changes represent functional disturbances in the retina or post-retinal neuronal pathways; yet the possibility exists that changes in lens optical density may explain all or part of the contrast sensitivity deficits. Moreover, risk factors for contrast sensitivity deficits in aretinopathic diabetic patients remains poorly defined.

The results of our study show that contrast sensitivity testing may detect early changes of visual function in diabetic patients prior to the appearance of microvascular retinal damage. Not all investigators [4] have found contrast sensitivity losses before diabetic retinopathy, and previous studies have not demonstrated diagnostic reliability of detecting early visual dysfunction. Comparison of contrast sensitivity results are difficult because different measurement procedures, calibration methods, and equipment can produce significantly differing results [21].

The optical density of the crystalline lens increases with increasing age and with decreasing wavelength of light. The increased absorption of short wavelength light sometimes causes the lens to appear yellow. Analysis of combined data from psychophysical and physical measurements of lens absorption has shown that in the general population lens optical density increases at a constant rate with age until approximately 60 years of age and at a greater rate thereafter [22]. However, persons with diabetes are at a greater risk of developing cataracts than nondiabetic persons [23]. Indeed, fluorophotometry [24], Scheimflug photography [25], and psychophysical measurements [26] have all demonstrated an increased rate of lens yellowing in diabetic persons. Increasing lens opacity is associated with a progressive decrease of contrast sensitivity. Studies on the effect of cataract type and severity on contrast sensitivity have shown that contrast sensitivity losses are significantly associated with cataract severity. Moreover, all types of opacity are associated with a progressive decrease of contrast sensitivity, but the association is greatest for nuclear lens opacity [27, 28]. In our study, mean lens opacity in diabetic patients, as determined using the IntraOptics opacity lensmeter, an accurate instrument for measuring nuclear lens changes [10, 29], did not differ from that in controls. These data suggest that contrast sensitivity losses cannot be explained solely on the basis of diabetes-induced increases in lens optical density. Recently, the effect of diabetes-associated increases in lens optical density on color discrimination in insulin-dependent diabetes was studied [30]. The results of the investigation were very similar to ours. Indeed, the authors suggested that color discrimination loss in aretinopathic insulin-dependent diabetic patients was not solely due to increases in lens opacity but might involve abnormalities of the retina, neuronal damage, or both.

Contrast sensitivity losses could be related, at least in part, to postsynaptic retinal neuron or neuronal network damages [31]. However, it is still unclear whether these early neurosensory deficits are caused by functional retinal vascular abnormalities (e.g., hemodynamic or permeability defects) that precede structural vascular lesions, or whether they result from metabolic abnormalities in the retina (e.g., neurotransmitters, glial cells, or nerve fiber sensitivity to hyperglycemia) that precede, and possibly contribute to, the vascular retinopathy. Probably both mechanisms are involved.

In our study, we found a positive correlation between contrast sensitivity deficits at the three spatial frequencies tested and advanced age, systolic blood pressure, and nephropathy. These findings are very similar to the observations described by Chihara et al. [32], who investigated the incidence of and risk factors for retinal nerve fiber layer defect in patients with type II diabetes mellitus. They concluded that the retinal nerve fiber defect is common in patients with early diabetic retinopathy and suggested that risk factors for this defect were systemic hypertension and advanced age. As suggested in their report, the existence of a positive relationship between advanced age and systemic hypertension and contrast sensitivity deficits may suggest a correlation between this defect and the vascular accident. Older patients who have both diabetes mellitus and systemic hypertension enhanced by nephropathy are at higher risk for an asymptomatic vascular accident in the eye and along the optic pathways.

The level of glycosylated hemoglobin at the time of examination was not correlated with the high incidence of contrast sensitivity found by Di Leo et al. [7]. This discrepancy can be explained by fluctuation in the glycosylated hemoglobin level. Moreover, this blood test does not reflect the severity of the metabolic disease or the long-term metabolic control. The discrepancy may also be explained by differences in the samples of patients.

As a matter of fact, all diabetic patients included in the study were inpatients in a diabetes treatment and teaching clinic. As admissions to this clinic were planned at least 3–6 months in advance, patients were probably careful to obtain good metabolic control, especially in the last few weeks before admission.

Duration of diabetes is the parameter most strongly correlated with the risk of diabetic retinopathy. However, no correlation between duration of diabetes and contrast sensitivity was found in our study. This could be explained by the exclusion of patients with a known history of diabetes of less than 5 years and by the difficulty in evaluating the exact duration of diabetes in type II diabetic patients, as the precise time of onset of the disease is impossible to determine.

In conclusion, the present findings suggest that contrast sensitivity deficits in diabetic patients without retinopathy are not only explained by diabetes-induced increases in lens optical density. They must also involve abnormalities of the retina or its neural connections or both. Risk factors for contrast sensitivity deficits are advanced age, high systolic blood pressure, and nephropathy.

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