Nonselective Loss of Contrast Sensitivity in Visual System Testing in Early Type I Diabetes

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OBJECTIVE — Psychophysical methods in patients with diabetes mellitus reveal deficits of central or foveal vision. Our aim was to evaluate the contrast-sensitivity thresholds in 24 insulin-dependent (type I) diabetic patients with a short disease duration and without retinopathy, taking into account metabolic control.

RESEARCH DESIGN AND METHODS — The control group consisted of age-matched nondiabetic subjects. None had visual or systemic symptoms. Contrast sensitivity measured at eight different spatial frequencies to sinusoidal bar patterns of 0.6–12.2 cycles/deg can detect functional defects in the spatially sensitive retinal ganglion cells or in higher visual pathways. We performed two different temporal types of contrast-sensitivity testing, dynamic (8 Hz) and static (0 Hz).

RESULTS — Significant losses with dynamic contrast-sensitivity test at all but the highest spatial frequencies (i.e., 12.2 cycles/deg) were shown, whereas there was significant attenuation of contrast sensitivity at five spatial frequencies (1.0, 1.4, 2.2, 7.1, and 9.6 cycles/deg) in the static mode. Grating losses (<2SD of control means) of contrast sensitivity were found in 33.3% (dynamic) and in 72.9% (static) of eyes of diabetic patients. HbA_{1c} values were positively correlated at variable spatial frequencies (1.0, 1.4, and 2.2 cycles/deg for dynamic test and 0.6, 1.0, 1.4, 2.2, 4.8, and 7.1 cycles/deg for static test).

CONCLUSIONS — Our results suggest an early, generally nonselective neuronal damage of visual pathways that occurs before the onset of clinically detectable retinopathy. The visual deficit may be related directly to the effects of diabetes; repetitive minor hypoglycemic insults may contribute more than a marked hyperglycemic condition to the mechanisms underlying physiological changes along the optic nerve.

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Contrast sensitivity is a measure of the amount of contrast required to detect or recognize a visual target. The usefulness of contrast sensitivity measurements as an indication of early-stage disorders of diabetic retinopathy, has been shown in many studies (1–8). To clinically understand the physiological basis of these defects, techniques based on stimuli that use grating patterns consisting of alternating vertical light-dark bars presented on a television monitor yield the most information about visual pathways. Gratings that can vary in spatial frequency (i.e., the number of light-dark cycles/degree of visual angle) are used to consider the quality of the optic system. Psychophysical (contrast sensitivity) and electrophysiological (visual-evoked potentials and pattern electroretinogram [P-ERG]) studies have benefited from the application of spatial-frequency methods (9). With contrast-sensitivity testing, the lowest detectable contrast across a range of spatial frequencies can be measured. In this way, a contrast-sensitivity function is derived for a subject.

The spatial response of the visual system can be discriminated as a series of multiple channels, each channel sensitive to a narrow band of spatial frequency (10,11). Channels may be the expression of single-neuron function. Activities of ganglion cell subpopulations of the visual pathway that respond well to gratings of different spatial frequency can be psychophysically isolated (12,13). The number of distinct neural channels in the primary visual pathway that respond to gratings justifies the use of spatial-frequency techniques in clinical psychophysics to assess visual function deficiencies.

In our previous studies (14,15), the early effect of insulin-dependent (type I) diabetes on the central retina was shown with P-ERG gratings, but no information about the overall function of the visual system in diabetic patients was given. In this study, our aim was to investigate possible spatial frequency–

dependent optic pathway losses in type I patients who had no signs of retinal microangiopathy with psychophysical static and dynamic contrast-sensitivity testing.

RESEARCH DESIGN AND METHODS

— The study included 24 patients (11 men, 13 women) with type I diabetes without retinopathy ranging in age from 13 to 32 yr (mean ± SD age 22.7 ± 5.1 yr), with an average disease duration of 3.9 ± 2.3 yr (range 0.8–15 yr). The current metabolic control status was estimated by HbA_{1c} concentrations (6.7 ± 1.2%) ranging from 4.6 to 10.1%. Thirty nondiabetic subjects (16 men, 14 women) with an age (23.2 ± 2.4 yr) and sex distribution comparable to that of the diabetic patients comprised the control group.

All participants received a rigorous and systematic clinical evaluation that consisted of a complete neuro-ophthalmological examination including the two contrast-sensitivity tests designed for this protocol. Visual acuity, direct and indirect ophthalmoscopy, and slit-lamp biomicroscopy were performed. Color fundus photographs and fluorescein angiography of both eyes were also used in each diabetic patient. None of these patients was found to have macular edema or systemic and/or other ocular diseases. The best-corrected visual acuity was 20/20 or better. Refractive errors, when present, were <±1.00 diopters and were fully corrected during contrast-sensitivity testing. Diabetic patients whose glycemia value before testing was consistently <5.6 mM were tested in the morning after eating breakfast to avoid hypoglycemia. Informed consent was obtained after the nature of the technique and the aim of our research were thoroughly explained.

Fluorescein angiography was performed with a Kowa (Japan) (Pro 1 50°) fundus camera after rapid injection of 5 ml of 10% fluorescein sodium into the antecubital vein. Angiograms were taken with ASA400 black-and-white film and graded according to a standard protocol (16).

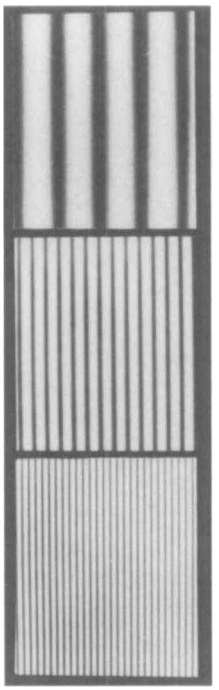

Figure 1—*Grating detection of variable spatial frequencies are demonstrated in contrast-visual testing. Sinusoidal modulation results in a graded transition between light and dark. The higher the spatial frequency, the finer the grating. Dynamic and static testing differ from their presentation of gratings to examine spatial contrast sensitivity. Dynamic test is performed by alternating gratings, whereas static test consists of stationary gratings.*

Dynamic and static tests were used to assess contrast sensitivity by methods of adjustment (17). In the testing monitor, the stimuli used for determining an observer's contrast sensitivity were simple gratings (Fig. 1). The dynamic contrast-sensitivity test, which uses counterphase grating, measures the visibility threshold of a stimulus whose contrast varies cyclically, alternating between light and dark. The static contrast-sensitivity test measures the threshold contrast at which gratings become visible. We performed contrast-sensitivity tests with gratings of eight spatial frequencies 0.6, 1.0, 1.4, 2.2, 4.8, 7.1, 9.6, and 12.2 cycles/deg. Gratings were generated electronically on a high-resolution television monitor (mean luminance 84 cd/m^2) and modulated at a temporal frequency (i.e., *n* of stimulus cycles per second) of 8 Hz (for dynamic testing) and 0 Hz (for static testing). The monitor was placed in the center of a large equiluminant white cardboard (70 × 70 cm) to isolate the stimulating field. Subjects with undilated pupils monocularly maintained visual fixation on the stimulating field from a 57-cm viewing distance for spatial frequencies ranging from 0.6 to 4.8 cycles/deg (stimulation field size 24 × 14°); 85 cm for 7.1 cycles/deg (16 × 9°); 114 cm for 9.6 cycles/deg (12 × 7°), and 145 cm for 12.2 cycles/deg (9 × 6°). Pupil sizes were measured, and no differences were observed between diabetic patients and control subjects. In contrast-sensitivity testing, the same vertical bars varying in contrast were displayed on the television monitor. The subject's ability to see the presented patterns depended on the contrast between light and dark bars, i.e., the contrast threshold. For a given spatial frequency, an initial grating that determined the suprathreshold was shown for a brief period. Then, this contrast was reduced to a subthreshold value. The contrast of the grating was then slowly increased with a logarithmic attenuator until the observer was able to detect the grating. At least five such estimates of contrast sensitivity were made. The variability of each test was usually <1 dB and did not differ between diabetic and control subjects. The sensitivity and specificity of contrast-sensitivity testing were 10.2 and 97.7% (for dynamic test) and 23.7 and 96.9% (for static test), respectively.

A fasting blood sample to measure HbA_{1c} values was drawn from each patient in the morning. HbA_{1c} was measured with an automated HbA_{1c} analyzer by a high-performance liquid chromatography method with 5.8% as the upper limit of the normal range.

Table 1—*Contrast sensitivity test results for each spatial frequency*

	Spatial frequency (cycles/deg)							
	0.6	1.0	1.4	2.2	4.8	7.1	9.6	12.2
Dynamic test								
Control subjects	50.7 ± 2.4	50.6 ± 2.5	49.0 ± 2.7	47.4 ± 3.4	38.2 ± 3.6	35.9 ± 3.9	34.1 ± 5.3	28.0 ± 3.9
Diabetic patients	47.8 ± 2.1	47.6 ± 2.4	46.4 ± 2.7	44.0 ± 3.1	35.3 ± 3.3	33.6 ± 4.5	29.6 ± 5.0	25.7 ± 5.0
t test	5.5	5.1	4	4.5	3.5	2.1	3.7	1.9
P	0.0001	0.0001	0.0001	0.0001	0.0008	0.04	0.0005	NS
Static test								
Control subjects	48.7 ± 2.4	50.4 ± 2.5	50.3 ± 2.5	50.6 ± 2.2	43.4 ± 2.0	41.9 ± 3.2	39.9 ± 4.2	32.7 ± 3.7
Diabetic patients	46.9 ± 3.4	47.5 ± 2.8	47.8 ± 2.7	46.9 ± 3.0	41.4 ± 4.2	38.5 ± 4.2	34.2 ± 4.3	30.1 ± 5.6
t test	1.9	3.7	3.2	4.5	1.9	3	4.6	1.7
P	NS	0.0005	0.002	0.0001	NS	0.004	0.0001	NS

Values are means ± SD (dB).

Statistical analysis

Results are means ± SD. Statistical significance was assessed with Student's unpaired *t* test and multiple regression analysis. Statistical analysis in diabetic and control subjects was based on the observed inter-eye correlation. Only the right-eye measurements in control subjects were considered, because their inter-eye correlation was always significant. On the contrary, because the inter-eye correlation in our diabetic population was not significant, diabetic left- and right-eye measurements according to Ray and O'Day (17) were considered.

RESULTS — No significant difference between diabetic and control subjects for sex and age was found.

Table 1 shows the mean contrast-sensitivity thresholds in control and diabetic subjects. The contrast-sensitivity means were significantly reduced in diabetic groups compared with those of control subjects at all spatial frequencies except 12.2 cycles/deg if they were presented in the dynamic mode. In the static mode, significant contrast-sensitivity losses were found at five spatial frequencies (1.0, 1.4, 2.2, 7.1, and 9.6 cycles/deg).

Figure 2 shows the individual contrast-sensitivity thresholds in diabetic patients with the dynamic test for each spatial frequency. The contrast–visual threshold curve shows a peak for a stimulus of 0.6 cycles/deg spatial frequency with a progressive decline from lower to higher spatial frequencies. Numerous contrast-sensitivity losses were detected by the static test at middle (2.2 and 4.8 cycles/deg) and higher (7.1–12.2 cycles/deg) spatial frequencies (Fig. 3).

To determine what proportion of control and diabetic subjects had abnormal contrast sensitivity for each test (dynamic and static), a subject was considered to be abnormal when the contrast threshold was 2SD below the normal means for at least one spatial frequency in one eye. In diabetic patients, dynamic testing showed a significant reduction in contrast threshold in 16 eyes (33.3%) and static testing showed losses in 35 eyes (72.9%) with respect to eyes in the control group, a greater contrast-sensitivity loss with the static than with the dynamic tests.

Multiple regression analysis was

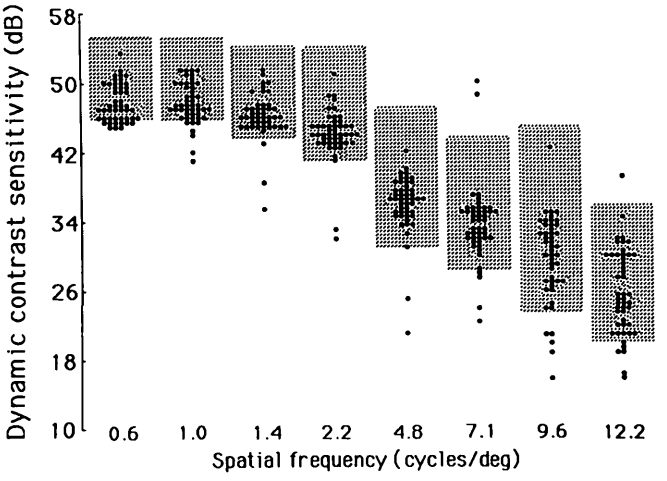

Figure 2—*Dynamic contrast-sensitivity thresholds in each eye of diabetic patients. Shaded areas, 2SD from the mean of control subjects at corresponding spatial frequencies. Contrast sensitivity function is generally affected at all spatial frequencies. Reduced sensitivity most frequently occurred at lower (0.6–1.4 cycles/deg) spatial frequencies.*

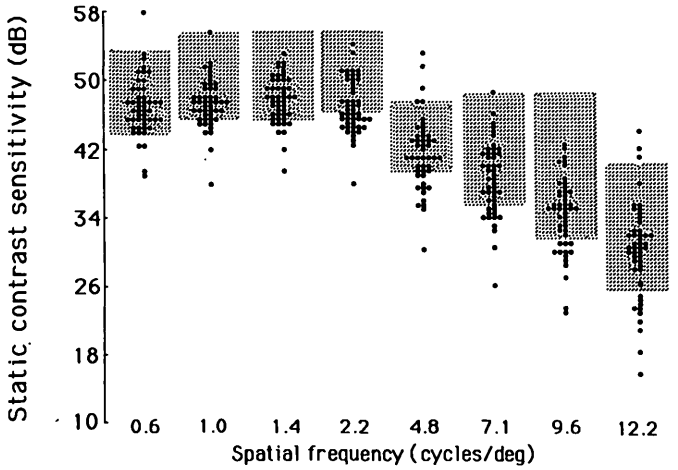

Figure 3—*Static contrast-sensitivity thresholds in each eye of diabetic patients. Shaded area, 2SD from the mean of control subjects at corresponding spatial frequencies. Note the normal mean maximum sensitivity occurred at 2.2 cycles/deg. Diabetic patients showed more functional eye changes at middle (2.2 and 4.8 cycles/deg) and higher (7.1–12.2 cycles/deg) spatial frequencies.*

performed with dynamic and static test responses as the dependent variables and duration of disease and HbA_{1c} values as the independent variables. We found a significant positive correlation between contrast-sensitivity thresholds with dynamic test and HbA_{1c} values at 1.0 ($r = 0.35$, $P = 0.02$), 1.4 ($r = 0.34$, $P = 0.03$), and 2.2 ($r = 0.35$, $P = 0.02$) cycles/deg spatial frequencies. The duration of disease was not correlated. Static contrast-sensitivity thresholds were positively correlated with HbA_{1c} concentrations at 0.6 ($r = 0.51$, $P = 0.01$), 1.0 ($r = 0.41$, $P = 0.03$), 1.4 ($r = 0.42$, $P = 0.02$), 2.2 ($r = 0.36$, $P = 0.02$), 4.8 ($r = 0.34$, $P = 0.02$), and 7.1 ($r = 0.39$, $P = 0.04$) cycles/deg spatial frequencies. A negative correlation between sensitivity losses and diabetes duration ($P = 0.03$) was found only at 7.1 cycles/degree.

CONCLUSIONS— Visual testing by psychophysical methods can significantly contribute to the evidence of neuropathological abnormalities in type I diabetes. Our results show that both dynamic and static contrast-sensitivity methods detected early changes of visual function in type 1 diabetes before the appearance of microvascular retinal damage. The static test appeared more sensitive than the dynamic test. Not all investigators (4,5,8) have found contrast-sensitivity losses before retinopathy in the diabetic retina. In fact, these previous studies have not demonstrated diagnostic reliability of detecting early optic nerve damage. Ghafour et al. (1) found dysfunctions only at certain spatial frequencies. Regan and Neima (3) tested their diabetic population with Snellen letter charts (i.e., a printed-chart test that uses white cardboard with black letters) because they considered these charts to be a better alternative for contrast-sensitivity testing than gratings. They observed more visual losses at low spatial frequencies but only in diabetic patients with retinopathy. The limitations of these studies may be partly due to the fact that the techniques used either had a too-small stimulation field size (18) or a less reliable method of testing. Comparison of contrast-sensitivity results have been difficult because different measurement procedures, calibration methods, and equipment can produce significant changes in results (19,20).

Previous studies (1–5,7,8) did not correlate contrast sensitivity thresholds with metabolic control (as estimated by HbA_{1c} concentrations). It is thought that hyperglycemia is the entity that is at least in part linked to the development of retinal complications (21). In this study, we found direct correlations between contrast-sensitivity measurements at certain spatial frequencies and HbA_{1c} values, especially for the static test. Based on our previous electrophysiological studies (14,15) and the results of this study, there is probably not an obvious association between the effect of chronic exposure to hyperglycemia and the functional impairment observed in the visual pathways. Other factors also may play an important role in damage to the visual pathway. The convergence of many cells onto relatively few ganglion cells demands an efficient code of information processing along the visual pathway to the visual cortex. Given that the long-term benefits of intensive insulin therapy with good metabolic control on neuropathic complications remain unproven, consideration must be given to its risks. In this study, patients with well-controlled diabetes had an increased rate of recurrent hypoglycemic episodes. Hypoglycemia is potentially dangerous because the tissues of the central nervous system are exclusively dependent on glucose as a metabolic fuel (22). Accumulating data (23,24) suggest that hypoglycemia results in impairment of cerebral function that is not immediately normalized after normalization of blood glucose levels. However, we cannot establish whether persistent damage to the optic nerve fibers may result after years of repetitive hypoglycemic episodes. In type I diabetes, visual pathways may be more vulnerable to the effect of a strict metabolic control than to the effect of poor glycemic control.

Based on the observation that morphological subpopulations of human retinal ganglion cells have been described (25), there is also psychophysical evidence for parallel visual pathways.

Psychophysical contrast sensitivity could be related, at least in part, to postsynaptic retinal neurons or neuronal networks (26). Because the visual system is organized to distinguish spatial elements depending on the neural subsystems that include both small- and large-sized retinal ganglion cells (27,28), small-sized ganglion cells are primarily responsible for the detection of rapidly modulated gratings, i.e., at high spatial frequencies, whereas large-sized ganglion cells subserve low spatial frequencies (12). A selective involvement of one class of ganglion cells in early diabetes could be expected to also produce specific psychophysical deficits, because in our previous study, preferential losses of large retinal ganglion cells in diabetic patients without retinopathy were electrophysiologically found with P-ERG (15). However, results of this study did not show selective losses at spatial or temporal frequencies. The nonselective nature of psychophysical losses implies that the physiological basis of this reduced sensitivity in early diabetes was also nonselective: Large axons may be affected as much as the small axons of retinal ganglion cells. This result was surprising because both contrast-sensitivity tests and P-ERG monitor central visual function. However, differences in the nature of these methods could account for the contrasting findings. The lack of evidence for selective contrast-sensitivity losses in early diabetes can be explained by the different sensitivity of psychophysical and electrophysiological tests. Contrast sensitivity detects a subclinical visual dysfunction, but fails to distinguish between abnormalities of different ganglion cell subsets. P-ERG is probably more sensitive than contrast sensitivity in detecting early neurosensorial disorders because P-ERG gives a more direct and objective index of inner retina function (29,30). Pathophysiologic changes may be initiated at the retinal level. Any dysfunction in the retina area may be, to some extent, compensated by higher visual pathways. In diabetes, further research is necessary to determine whether contrast sensitivity–based measurements provide different information from that of electrophysiology-based tests.

In conclusion, type I diabetic patients with disease of short duration who showed no retinopathy on fluorescein angiography showed nonselective spatial-frequency losses with contrast-sensitivity testing. The static contrast-sensitivity method seemed to be more sensitive to the diabetic condition than the dynamic contrast-sensitivity method, although we require additional evidence to verify their clinical usefulness in detecting a neurovisual disorder in early diabetes.

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