# Short Communications

# The Effect of Strict Short-Term Metabolic Control on Retinal Nervous System Abnormalities in Newly Diagnosed Type 1 (Insulin-Dependent) Diabetic Patients

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**Summary.** The oscillatory potential of the electroretinogram and the initial 2-min phase of dark-adaptation were studied in seven newly diagnosed Type 1 (insulin-dependent) diabetic patients before and during initial insulin treatment. Strict metabolic control was achieved in all seven patients using multiple subcutaneous injections of insulin. Seven to 11 days of strict metabolic control improved the added amplitude value of the oscillatory potential from $236 \pm 8$ to $268 \pm 8 \, \mu V$ (mean $\pm$ SEM; $p < 0.01$) and the dark-adaptation from $90 \pm 5$ to $67 \pm 5 \, s$ ($p < 0.01$). Our study has demonstrated reversible neurophysiological abnormalities in the diabetic retina which are related to metabolic control.

**Key words:** Type 1 diabetes, metabolic control, dark adaptation, electroretinography.

Patients at high risk of developing severe diabetic retinopathy can be detected by both electroretinography and nyctometry [1, 2]. Recently, a close relationship has been demonstrated between these two methods [3]. Abnormalities in nyctometry and in the oscillatory potential, a fast component of the electroretinogram, can be demonstrated even in the absence of ophthalmoscopically visible diabetic fundus changes [3–5]. The possible influence of metabolic control on retinal neurophysiological function has not been elucidated previously. However, reversible functional abnormalities in the somatic and autonomic nervous system correlated with metabolic control are well established in diabetes [6].

The aim of this study was to elucidate the influence of strict short-term metabolic regulation on the retinal nervous system in newly diagnosed Type 1 diabetic patients.

## Patients and Methods

### Patients

Seven newly diagnosed Type 1 (insulin-dependent) diabetic patients (three men and four women) participated in the study after informed consent. They were between 20 and 43 years of age, the median age being 34 years. None of the patients received insulin before admission to the Steno Memorial Hospital. Investigations were started within 2 days of admission. None of the patients suffered from intercurrent illness and none received drugs. All had a history of classical diabetic symptoms for several weeks, including weight loss (2–8 kg). All had ketonuria on admission (Table 1) but none had ketoacidosis. The body weight was between 83 and 106% of ideal body weight [7]. The individual mean blood glucose before insulin treatment was

14.7–19.2 mmol/l (median: 16.9 mmol/l) and the urinary glucose excretion was 80–191 g/24 h (median: 130 g/24 h).

## Methods

Ophthalmological examinations including refraction and optimally corrected visual acuity, slit lamp examination, colour photographs of the fundus and fluorescein angiography did not reveal any eye abnormalities.

The macular recovery time was examined by nyctometry, a standardized method by which the course of the initial 2 min of the dark adaptation is recorded graphically by means of the registration nyctometer (Registrier-Nyktometer, VEB Carl Zeiss, Jena, GDR). The nyctometry was performed after about a 15-min stay in a dimly lit examination room. The recording was performed monocularly with the pupil unmedicated, the opposite eye being tightly covered with an eye pad in order to avoid interocular light adaptation.

The electroretinography was performed monocularly with the pupils maximally dilated. Using the Karpe contact lens the oscillatory potential was elicited by repeated strong flashes to the fully dark adapted eye and recorded by means of a dual-beam cathode ray oscilloscope (DISA, Copenhagen, Denmark). A more detailed description of the equipment and test procedures has been published elsewhere [1, 3]. The amplitudes of oscillatory wavelets were added together (added oscillatory potential). Nyctometry and electroretinography were carried out within 2 h on the same day.

Blood glucose was measured by a glucose oxidase method [8]. Standard bicarbonate and potassium were measured by standard techniques.

## Procedures

Nyctometry and electroretinography were carried out before and 7–11 days after the start of the initial insulin treatment. During this period, the patients took a diet containing approximately 40% of the energy as fat, 40% carbohydrates and 20% protein, but the total caloric intake was unrestricted. Potassium chloride (60 mmol/24 h) was
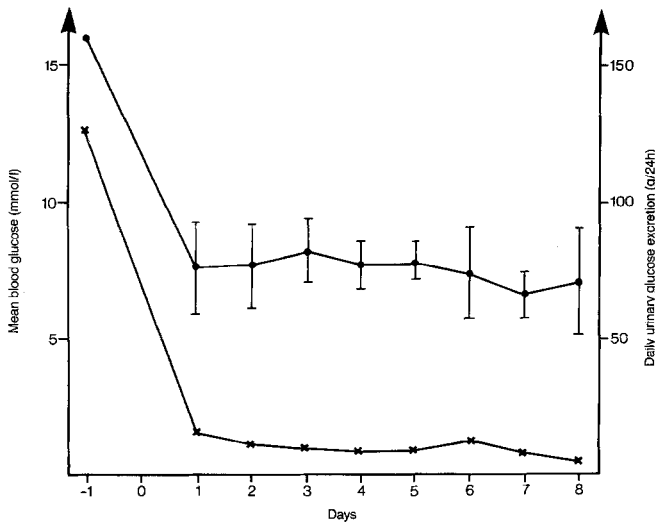
**Fig. 1.** Blood glucose levels (●————●, mean ± SD) and mean 24-h urinary glucose excretion (×————×) before and during initial insulin therapy in seven newly diagnosed Type 1 diabetic patients. Insulin treatment was started in the afternoon on day 0, immediately following the neurophysiological measurements

given by mouth during the first 3 days of insulin treatment. All patients received multiple subcutaneous injections of short-acting insulin 6–10 times/24 h during the first 3 days. The treatment was guided by blood glucose measurements taken 11 times/24 h. From day 4, insulin treatment was changed to a mixture of short-acting and intermediate acting insulin (three to six injections a day). The insulin dose during the study ranged from 22–60 U/24 h.

*Statistics*

The Wilcoxon rank sum test for paired observations was used for the statistical analysis.

**Results**

Twenty-four hour mean blood glucose values and mean urinary glucose excretion before and during the first 8 days of insulin treatment are shown in Figure 1. Mean blood glucose levels decreased from 16 mmol/l to a level between 7–8 mmol/l and urinary glucose excretion diminished from 165 to approximately 10 g/24 h. All

patients showed a significant improvement in the macular recovery time measured by nyctometry (90 ± 5 s before treatment versus 67 ± 5 s during treatment, mean ± SEM, $p < 0.01$; Table 1). Enhancement of the added amplitudes of the oscillatory potentials measured with electroretinography were demonstrated in all patients during strict metabolic control (236 ± 8 before treatment versus 268 ± 8 µV during treatment, $p < 0.01$). No correlation was found between blood glucose or serum potassium values and the neurophysiological variables.

**Discussion**

The major observation in our study is the demonstration of reversible neurophysiological abnormalities in the retina of newly diagnosed Type 1 diabetic patients. The reduction in the oscillatory potential and in the macular recovery time found before insulin treatment, was rendered completely normal after 1–2 weeks of strict metabolic control. It should be stressed that ophthalmological examination including fluorescein angiography did not reveal any eye abnormalities in the patients studied.

Micro-electrode investigations in animal retinae [9] and clinical observations in man indicate that the oscillatory potential originates in the middle retinal layers, particularly the inner nuclear layer [10, 11]. At present, it is not known which cell type acts as the generator of the oscillations. Recent pharmacological experiments suggest that the oscillatory potential depends upon neuronal activity in retinal inhibitory feed-back circuits which are initiated in the amacrine cell layer [12, 13]. Observations indicate that changes in the metabolism of the Müller cell, the retinal neuroglia cell, are responsible for reduction of the oscillatory potential [14, 15]. Histochemical examination of the retina in different pathological conditions has revealed that the Müller cells show the earliest pathological changes [16]. The Müller cells exert a crucial metabolic function in the retina serving as the main nutritional and excretional transport system between the capillaries of the choriocapillaris layer and the visual cells.

**Table 1.** Electroretinography and nyctometry (macular recovery time) in seven newly diagnosed Type 1 diabetic patients before and after 7–11 days of initial insulin treatment

| Subject No. | Macular recovery time (s) | | | | Oscillatory potentials (µVolts) | | | |
|---|---|---|---|---|---|---|---|---|
| | Before treatment | | After 7–11 days of treatment | | Before treatment | | After 7–11 days of treatment | |
| | Right eye | Left eye | Right eye | Left eye | Right eye | Left eye | Right eye | Left eye |
| 1 | 103 | 108 | 98 | 96 | 210 | 210 | 255 | 255 |
| 2 | 110 | 112 | 55 | 52 | 210 | 215 | 275 | 280 |
| 3 | 97 | 72 | 77 | 51 | 200 | 205 | 230 | 230 |
| 4 | 67 | 90 | 55 | 65 | 260 | 260 | 280 | 280 |
| 5 | 105 | 102 | 75 | 76 | 250 | 250 | 275 | 275 |
| 6 | 85 | 89 | 75 | 70 | 230 | 240 | 255 | 260 |
| 7 | 50 | 71 | 35 | 70 | 275 | 275 | 295 | 290 |
| Mean ± SEM | 88 ± 5 | 92 ± 5 | 66 ± 5 | 67 ± 5 | 234 ± 8 | 237 ± 8 | 267 ± 8 | 268 ± 8 |
| | | 90 ± 5 | | 67 ± 5 | | 236 ± 8 | | 268 ± 8 |

The pathophysiological mechanisms involved in the present abnormalities in the retina are not known. Our study revealed no significant correlation between plasma potassium, plasma glucose and the retinal neurophysiological changes, although the numbers studied were small. Simonsen [1] showed that the oscillatory potential of the electroretinogram in Type 1 diabetic patients remains unchanged during intravenous glucose infusion, resulting in a substantial plasma glucose increase. The effect of hyperosmolarity on the electroretinogram has been elucidated by changing the osmotic pressure in both the incubating medium on rabbit retinae in vitro and in vascular perfusion studies of the cat retina [17, 18]. Infusion of hypertonic saline was found to induce reversible reductions in both the oscillatory potential and another component of the electroretinogram (the c-wave). The central nervous system responds to peripheral hyperosmolarity and dehydration, as present in poorly controlled diabetes, by accumulation of osmotic active substances [19, 20]. There is no information available regarding the histological and biochemical counterparts of the neurophysiological abnormalities in the retina of early diabetes. It is of interest that intracellular oedema of the Müller cell and the amacrine cells has been demonstrated in diabetic retinopathy, probably due to the accumulation of glycogen [21].

Our findings are analogous with the recently demonstrated reversible changes in the central autonomic nervous system which have been related to the diabetic metabolic state [6]. Furthermore, it is well established that reversible functional abnormalities occur in the somatic nervous system in early diabetes in relation to metabolic control [22, 23]. Axonal shrinkage and endoneurial oedema have been demonstrated in the somatic nerves in animals with poorly controlled early diabetes. These changes are preventable by strict metabolic control [24, 25].

There is no information currently available on the relationship of these reversible retinal abnormalities with the development of diabetic retinopathy.

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