Abstract. The effect of continuous subcutaneous insulin infusion (CSII) and conventional injection therapy (CIT) on retinopathy was evaluated in a 1-year cross-over study (6 + 6 months) with 54 type 1 diabetic patients. The glycaemic control improved significantly but did not reach euglycaemic levels during CSII ($P < 0.01-0.001$), whereas no change was observed during CIT. At baseline, 50% of the patients had no retinopathy, 20% had only minimal changes, 26% had moderate background retinopathy, and 2 patients had proliferative changes. During CSII, the retinopathy grade impaired in 7 patients, whereas no deterioration occurred during CIT. Improvement of retinopathy grading was observed in 2 patients during CSII and in 5 during CIT, respectively. Individual retinal lesions also progressed more and improved less during CSII (12:3) as compared with CIT (10:9). The net impairment in both retinopathy grading and individual lesions was significant during CSII as compared with CIT ($P < 0.05$). There was no difference in the baseline characteristics (severity of retinopathy, age, sex, duration of diabetes, insulin dose, blood pressure, serum creatinine), in the fall of glycosylated haemoglobin or number of hypoglycaemic episodes between the patients with and without worsening of retinopathy during CSII. The present study suggests that even a moderate improvement in metabolic control induced by CSII may be associated with a risk of progression of retinopathy during the first months of therapy.

Glycaemic control and the duration of diabetes are perhaps the most important factors in the development of retinopathy (Hanssen et al. 1986; Weber et al. 1986). During the first years of continuous sc insulin infusion (CSII) therapy a few promising reports of improvement of diabetic retinopathy were published (Irsigler et al. 1979; White et al. 1981). Later it became evident that in association with a dramatic improvement of glycaemic control, retinopathic changes can progress during CSII treatment in patients with initially advanced retinopathy (Lawson et al. 1982; Van Ballegooie et al. 1984), whereas patients without retinopathy at the start of therapy may have a smaller risk (Beck-Nielsen et al. 1985). Studies comparing CSII to conventional injection therapy (CIT) (Canny et al. 1985; Dahl-Jörgensen et al. 1985; Lauritzen et al. 1983, 1985) have shown that CSII therapy may not be able to reverse or prevent the progression of overt diabetic retinopathy, inspite of restoring nearly normal blood glucose levels. Increased number of retinal infarcts during the first months of therapy have been reported in these studies. The prognosis of early retinopathy changes after two years treatment may, however, be more favourable with CSII as compared with CIT (Dahl-Jörgensen et al. 1986). None of the earlier studies have been performed in a cross-over manner allowing the comparison between CSII and CIT in the same patients. Furthermore, most of the previous studies have included only a small number of highly selected patients per centre with dramatic improvements.
in metabolic control. The influence of CSII therapy on retinopathy in large patient populations treated in everyday clinical practice and with a lesser change in glycaemic control is not known. Consequently, the present study was planned to evaluate the course of retinopathy in a large number of type I diabetics treated with CSII and CIT in a one year cross-over study.

Patients and Methods

Patients

Hundred and seventy patients attending the Diabetes Outpatient Clinic of Helsinki University Hospital were invited to the study and 65 of them participated. They were characterized as follows: 31 males, 34 females, age 31 ± 1 years (range 18–57), known history of diabetes for 12.3 ± 0.9 years (range 2–36), and relative body weight (RBW) 109 ± 2% (Metropolitan Life Insurance Company 1959). Fasting C-peptide levels were available in 57 patients: it was below the detection limit (53 pmol/l) in 27, and 83 ± 7 pmol/l in the remaining 30 patients (normal values 330–660 pmol/l in our laboratory). Glycosylated haemoglobin (HbA1) was 10.4 ± 0.2% (normal values in our laboratory 6.0–9.0% for males and 5.9–8.0% for females).

Before entering the study 13 (20%) of the patients had sensory neuropathy (absent vibration sense and/or missing ankle jerk), and 5 (8%) had mild proteinuria (<1 g/l). Baseline retinopathy is described in Results.

Of the 65 patients, who initially started the study, 54 completed the whole protocol. Eleven patients dropped out mainly owing to poor co-operation or the reluctance to switch from CSII to CIT.

Study protocol

The study was carried out as a 6-month cross-over study comparing CSII with CIT. Half of the patients were randomized to start the treatment using CSII (group A) and the other half remained on CIT (group B). After six months, the mode of treatment was changed from CSII to CIT in group A and from CIT to CSII in group B.

When CSII was started, the patients were admitted for 5 days to the Metabolic Ward of the Third Department of Medicine of Helsinki University Hospital for education of pump use and adjustment of insulin dose. CSII-therapy (Nordisk Infuser®, Nordisk Gentofté A/S, Gentofté, Denmark, or AS 6C® or AS 6MP®, Auto-Syringe, Inc, Hooksett, NH) was started during the second day. The previously injected insulin dose was reduced by 15–25%, and the remaining insulin dose for CSII was divided between the basal (50%) and four pre-meal boluses (15 + 15 + 15 + 5% before breakfast, lunch, dinner and evening snack, respectively).

After discharge the patients were seen at two visits at the outpatient clinic at 2-week intervals, and thereafter at 6-week intervals throughout the rest of the study. During CIT, insulin was injected as 2–3 daily doses and the patients were seen at the outpatient clinic at 6-week intervals.

The insulin dose during CSII and CIT was adjusted with the help of home blood glucose monitoring and glycosylated haemoglobin values taken at every outpatient visit. The blood glucose levels aimed at were fasting between 4 and 6 mmol/l and 2 h postprandial between 6 and 8 mmol/l. Values below 3 mmol/l were to be avoided. The goals were the same for both therapies.

Potential risks and benefits of the study were explained to all patients before their voluntary consent to participate was obtained. The protocol was approved by the Ethical Committee of the Helsinki University Hospital.

Measurements

Home blood glucose was monitored using 7 daily fingertip capillary samples taken by the patients on 2 days per week. The measurement was performed using either eye assessment of the strip alone, or with a reflectometer. HbA1 was determined at every outpatient visit by microcolumn chromatography (Isolab, Inc, Akron, OH) (Welch & Boucher 1978). Serum C-peptide was measured in the beginning of the study by Byk Mallinckrodt Kit (Byk Mallinckrodt, Dietzenbach, FRG) (Kuzuya et al. 1977).

Ophthalmological methods

Ophthalmologic survey of the patients was performed at baseline, after 6 months, and after 12 months. It comprised (a) clinical examination performed by a senior ophthalmologist (LM) including determination of the corrected visual acuity, biomicroscopy, and direct and indirect ophthalmoscopy, and (b) colour photography of the fundi.

Colour photography. Four standard 30–45° colour photographs were taken of both eyes. The photographic fields consisted of field 1: optic disc and macula centred at the fovea centralis; field 2: superior temporal; field 3: inferior temporal; and field 4: nasal to the optic disc.

The photographs were evaluated by another ophthalmologist (LL) without knowledge of the current mode of insulin treatment. The grade of retinopathy was assigned on the basis of the more severely affected eye at the baseline, after 6 months, and after 12 months. After assessing the photographs of each visit, a direct comparison of the photographs of the successive visits was performed. In three cases, where some of the photographic fields were missing or of poor quality, ophthalmoscopic findings were used to supplement the grading.
Classification of retinopathy. Retinopathy level was classified according to a simplified scheme of the Modified Airlie House Classification (Diabetic Retinopathy Study Research Group 1981). Each fundus colour photograph was assessed for microaneurysms, retinal haemorrhages, hard exudates, soft exudates (retinal infarcts), intraretinal microvascular abnormalities, retinal venous beading, neovascularisation, and preretinal haemorrhage. The classification was made according to the worse eye of each patient.

Retinopathy levels

Grade 1: no retinopathy.

Grade 2: microaneurysms only. 2a if less than 10 microaneurysms/eye, 2b if ≥ 10 microaneurysms/eye.

Grade 3: microaneurysms and one or more of the following: retinal haemorrhage, but the total of microaneurysms and haemorrhages less than those in the Standard Photograph 2A of the Airlie House Classification (Diabetic Retinopathy Study Research Group 1981); hard exudates less than those in the Standard Photograph 3; retinal infarcts questionably present; intraretinal microvascular abnormalities questionably present.

Grade 4: microaneurysms and one or more of the following: microaneurysms and haemorrhages equaling or exceeding those in the Standard Photograph 2A; hard exudates equaling or exceeding those in the Standard Photograph 3; retinal infarcts definitely present (4a if one soft exudate the only abnormality); intraretinal microvascular abnormalities definitely present.

Grade 5: at least three of the following: microaneurysms and haemorrhages more than in Grade 3; retinal infarcts present in at least two quadrants; venous beading present.

Grade 6: new vessels and/or fibrous proliferations on the disc or elsewhere with or without preretinal haemorrhages.

Statistical methods

Statistical comparisons were calculated using Student's t-test, t-test for period and carry-over effect (Pocock 1985) and McNemars χ² test. Values are given as mean ± SEM.

Results

Glycaemic control

No significant changes in mean home blood glucose levels were observed within group A or B, when the CSII and CIT period was compared. However, when the two subgroups were combined (A + B), the glycaemic control was better during CSII than CIT (8.6 ± 0.2 vs 9.0 ± 0.3 mmol/l, respectively, P < 0.05).

After the first six months of the study, a significant fall in HbA₁ level was observed in the group using CSII (A) (Table 1, P < 0.01), whereas HbA₁ remained unchanged in the CIT group (B) (Table 1). During the second six months, glycaemic control was slightly improved in the group using CSII (B) (Table 1, P < 0.05), and a minor increase in HbA₁ level was observed in patients on CIT therapy (A) (Table 1, NS). The effect of 6 months CSII therapy on HbA₁ (-0.7 ± 0.2%, P < 0.001) in the whole study group (A and B combined) exceeded that achieved with CIT (+0.1 ± 0.2%, NS, CSII vs CIT P < 0.02). No period effect of the cross-over design was observed.

Hypoglycaemic values (< 3.0 mmol/l) occurred equally often during CSII and CIT periods (2.2 and 2.3% of the samples). There were 16 cases of ketoacidosis during CSII and 2 cases during CIT (P < 0.01).

Table 1.

HbA₁ levels during 6 months of CSII and CIT in groups A and B.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>3–4 months</th>
<th>Cross-over</th>
<th>3–4 months</th>
<th>End</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A (N = 28)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSII</td>
<td>10.6 ± 0.4</td>
<td>9.9 ± 0.3b</td>
<td>9.7 ± 0.3c</td>
<td>10.0 ± 0.3</td>
<td>9.8 ± 0.4</td>
</tr>
<tr>
<td>CIT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group B (N = 26)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIT</td>
<td>10.1 ± 0.3</td>
<td>10.1 ± 0.3</td>
<td>9.9 ± 0.2</td>
<td>9.5 ± 0.3a,d</td>
<td>9.5 ± 0.3a</td>
</tr>
</tbody>
</table>

Values are mean ± SEM (%).
a,b,c indicate difference to baseline, a: P < 0.05, b: P < 0.01, c: P < 0.001,
d indicates difference to cross-over, d: P < 0.05.
There was no significant difference between groups A and B at any of the times of determination.

Values are mean ± SEM (%).
a,b,c indicate difference to baseline, a: P < 0.05, b: P < 0.01, c: P < 0.001,
d indicates difference to cross-over, d: P < 0.05.
There was no significant difference between groups A and B at any of the times of determination.
Baseline retinopathy levels in patients in groups A and B classified by worse eye.

<table>
<thead>
<tr>
<th>Retinopathy level</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group A</td>
</tr>
<tr>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>2 a</td>
<td>5</td>
</tr>
<tr>
<td>2 b</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>28</strong></td>
</tr>
</tbody>
</table>

**Retinopathy**

**Baseline retinopathy levels.** Baseline levels in group A and B are given in Table 2. Fifty percent of the patients had no retinopathy (grade 1), and 20% had only minimal changes (less than 10 microaneurysms/eye, grade 2a). Microaneurysms and retinal haemorrhages were initially found in 25 patients, whereas hard exudates occurred in 4 patients, and retinal infarcts in 8 patients, in 2 of them a single retinal infarct was the only abnormality. Definite intraretinal microvascular abnormalities were initially found in 6 patients. Proliferative retinopathy (grade 6) was present in two patients.

**The effect of treatment on retinopathy**

**Change in retinopathy level.** Of the 27 patients who had no retinopathy at the start of the study, 25 remained unchanged and 2 changed form grade 1 to 2 owing to the development of a few microaneurysms, both during CSII therapy (Fig. 1). Of the 27 patients with retinopathy at the beginning of the study, 20 remained within the same retinopathy level, 5 worsened and 2 improved during CSII therapy. During CIT, 22 remained unchanged, none progressed and 5 improved. Of the 5 who worsened during CSII therapy, progression was due to an increase in the number of microaneurysms, haemorrhages and microinfarcts. Improvement in the retinopathy level occurred in 7 patients (Fig. 1). It was due to the disappearance of soft exudates in 4 patients and decrease in the amount of intraretinal haemorrhages or lipid exudates in 3 patients.

During CSII, in 45 patients retinopathy level remained unchanged, in 7 deteriorated and in 2 improved (Fig. 1). During CIT, 49 were unchanged, none deteriorated and 5 improved. The net change in grading indicated significantly more progression of retinopathy during CSII when compared to CIT ($\chi^2 = 5.5, P < 0.05$).

*Fig. 1.*

Changes in the retinopathy grading in groups A and B during 6 months of CSII and CIT. The number of patients in each grading is indicated above the dots.
Table 3. Number of patients with changes in individual retinal lesions during CIT and CSII therapy.

<table>
<thead>
<tr>
<th>Retinal lesion</th>
<th>CIT</th>
<th>CSII</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Progressed</td>
<td>Improved</td>
</tr>
<tr>
<td>Ma/H</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>HE</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>SE</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>IRMA</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>9</td>
</tr>
</tbody>
</table>


Changes in individual retinal lesions. Table 3 demonstrates changes in individual lesions regardless of whether the change was great enough to alter the retinopathy grading. The individual lesions progressed more and improved less during CSII compared with CIT ($\chi^2 = 5.4, P < 0.05$).

Visual acuity. The visual acuity deteriorated owing to retinopathy in one patient who had a rapid progression of proliferative retinopathy during both study periods in spite of argon laser panphotocoagulation.

Progression vs no progression during CSII

When the group of patients with progression of retinopathy during CSII was compared with the group without progression, no differences was found in age, sex, duration of diabetes, blood pressure, insulin dose, baseline mean retinopathy grading, or the number of grade 1 eyes. The serum creatinine level was higher in patients with progression (83 ± 6 vs 72 ± 2 µmol/l, $P < 0.05$). However, when calculated separately for males and females, there was no significant difference. Neither did these groups differ from each other as to the glycaemic change or the amount of hypoglycaemic episodes during CSII.

Discussion

The present study demonstrates mild progression of retinopathy during a 6-month follow-up period in patients treated with continuous insulin infusion therapy. In contrast, retinopathy did not progress during conventional injection therapy.

Our study employed a cross-over design. The disadvantage of this design is that possible long-term effects of the treatment would not appear until after the cross-over. In the present study, however, there was no statistical carry-over or order effect on retinopathy or on HbA1c. If CSII had any post-therapy effect on retinopathy, that would be an improvement rather than impairment, since after cross-over from CSII to CIT retinopathy improved in 3 patients and in no case did it aggravate (Fig. 1). The advantage of the cross-over design is an opportunity to examine the same patients on both therapies. Thus, the progression of retinopathy has to be associated with the therapy or related factors rather than any particular HLA-type (Rand et al. 1985) or immunologic phenotype (Mijovic et al. 1986), which may also contribute to the development of microangiopathy. Our observations are consistent with previous reports demonstrating an impairment of retinopathy during the first months of intensified therapy (Van Ballegooie et al. 1984; Canny et al. 1985; Dahl-Jörgensen et al. 1985; Lauritzen et al. 1985) despite a lesser change in glycaemic control in our study.

The follow-up time in the present study was short, only six months for each treatment. Thus, changes observed during this period reflect initial alterations rather than long-term influences of the treatment. This time may not be long enough to see possible positive effects of the better long-term control reported to follow the initial aggravation of the retinopathy (Dahl-Jörgensen et al. 1986).

The reasons and mechanisms for the impairment of retinopathy during CSII have remained unresolved in previous reports. Speculations have been put forward about the involvement of a rapid and marked decline in mean blood glucose levels (Dahl-Jörgensen et al. 1985; Testa et al. 1985) or a frequent occurrence of hypoglycaemic episodes (Dahl-Jörgensen et al. 1985). These changes may reduce retinal blood flow leading to ischaemia (Frier & Hilsted 1985). A common feature of the progression of retinopathy has been the presence of retinal lesions prior to the continuous insulin infusion therapy (Tamborlane et al. 1982; Van Ballegooie et al. 1984; Canny et al. 1985; Dahl-Jörgensen et al. 1985; Lauritzen et al. 1985).
1985). If retinal lesions have been absent or minimal prior to CSII therapy, the progression has been lesser (Tamborlane et al. 1982; Beck-Nielsen et al. 1985). In the present study, there was no difference in the baseline retinopathy levels or other clinical characteristics between the patients with and without progression of retinopathy during CSII.

The ophthalmological methodology used may not have been sensitive enough to detect small differences at baseline or changes during the study. Fluorescein angiography would have been a more sensitive method than colour photographs (Kohner et al. 1985), but its use in a large group of patients as a follow-up method would have been questionable owing to its inconvenience.

Whereas the mechanisms remain unresolved, the data indicate that even a moderate improvement in metabolic control induced by CSII may be associated with a risk of progression of retinopathy during the first months of therapy. It is possible, however, that the impairment is transient as reported previously and that the effect of long-term CSII therapy on retinopathy would be more beneficial (Dahl-Jørgensen et al. 1986).

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References


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