WHAT MAY BE GAINED FROM STANDARD PHOTOCOAGULATION DURING EARLY WORSENING OF DIABETIC RETINOPATHY? AN OBSERVATIONAL STUDY IN TYPE-1 DIABETIC PATIENTS AFTER TIGHTENING OF GLYCAEMIC CONTROL

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SUMMARY - Objective: To assess the outcome of laser photocoagulation treatment for rapidly progressing diabetic retinopathy, so-called early worsening, subsequent to a rapid improvement of glycemic control.

For the purpose of this study, early worsening was defined as any incidence or progression of retinopathy that followed a reduction in HbA1c by ≥2% within 6 months.

Material and methods: Retrospective observational study in type-1 diabetic patients in a university diabetes center.

Patients: 23 patients with early worsening were identified during a 16-year period, with a mean age of 25 years, duration of diabetes of 12 years, and glycated hemoglobin HbA1c of 12.4%; retinopathy was absent or mild nonproliferative at baseline.

Focal, and/or panretinal laser coagulation was performed according to standard ETDRS criteria. Retinal pathology and visual acuity was followed-up for 12-120 months.

Results: Improving metabolic control induced mild non-proliferative retinopathy without macular edema in 4 patients, which regressed without treatment. In 18 patients, symptomatic diabetic maculopathy developed with macular edema, resolving by focal coagulation in 3 patients. Of the remaining 16 patients, 14 developed proliferative retinopathy (7 of whom despite focal, grid or scatter coagulation pretreatment), and were treated by full panretinal coagulation. In 7 of the 14 patients with proliferative retinopathy, vitreous hemorrhages occurred requiring pars plana vitrectomy. Proteinuria, polyneuropathy, and impaired vision prior to laser treatment were indicative of poor prognosis. Visual acuity > 0.3 in at least one eye was preserved in 22 of the 23 patients.

Conclusions: In patients with type-1 diabetes mellitus and early worsening of diabetic retinopathy, the benefit of standard laser photocoagulation was limited, and particularly in the presence of symptomatic macular edema.

Key-words: proliferative retinopathy, diabetes mellitus, complications, metabolic control, glycaemic control, JGF-1.

RÉSUMÉ - Quel bénéfice attendre de la photoocoagulation standard dans la détérioration précoce de la rétinopathie diabétique ? Une étude d’observation chez des diabétiques de type 1 soumis à une optimisation de leur contrôle glycémique.

Buts : Evaluer le résultat de la photocoagulation laser devant une rétinopathie d’aggravation rapide, encore appelée détérioration précoce, consécutive à l’amélioration rapide du contrôle glycémique. Pour cette étude, la détérioration précoce a été définie par toute incidence ou progression de la rétinopathie suivant une diminution de l’HbA1c de ≥2 % dans un délai de 6 mois.

Méthodes : Étude d’observation rétrospective chez des diabétiques de type 1 dans un centre diabétologique universitaire.

Patients : 23 patients avec détérioration précoce ont été identifiés pendant une période de 16 ans, âge moyen 25 ans, durée du diabète 12 ans, et HbA1c 12,4 %; la rétinopathie était absente ou modérée non proliférante au départ.

La photoocoagulation fœcale et/ou panrétinienne a été réalisée selon les critères standards de l’ETDRS. La rétine et l’acuité visuelle ont été suivies pendant 12-120 mois.

Résultats : L’amélioration du contrôle métabolique a induit une rétinopathie modérée non proliférante sansœdème maculaire chez 4 patients, qui a régressé sans traitement. Chez 19 patients, une maculopathie diabétique symptomatique s’est développée avecœdème maculaire, résolue par coagulation fœcale chez 3 patients. Parmi les 16 patients restants, 14 ont développé une rétinopathie proliférante (dont 7 malgré un prêtraitement par coagulation fœcale, en grille ou dispersée), et ont été traités par une coagulation panrétinienne complète. Chez 7 des 14 patients avec rétinopathie proliférante, une hémorragie vitrénienne est survenue nécessairement nécessitant une vitrectomie pars plana. Une protéinurie, une polyneuropathie et une altération visuelle avant le traitement laser étaient des marqueurs de mauvais pronostic. Une acuité visuelle > 0,3 dans au moins un œil a été préservée chez 22 des 23 patients.

Conclusions : Chez les patients avec diabète de type 1 et détérioration précoce de la rétinopathie diabétique, le bénéfice d’une photoocoagulation laser standard est limité, particulièrement en présence d’unœdème maculaire symptomatique.

Mots-clés : rétinopathie proliférante, diabète sucré, complications, contrôle métabolique, contrôle glycémique, JGF-1.
The clinical course of mild to moderate non-proliferative diabetic retinopathy (NPDR) with macular edema is characterized by a relatively slow progression rate: only 4% of patients progress to severe visual loss or vitrectomy within 5 years, if laser treatment is withheld [1, 2]. However, NPDR can accelerate acutely, as was documented in the Diabetes Control and Complications Trial DCCT [3]. In that study, so-called “early worsening of diabetic retinopathy” [4] was observed in certain patients in response to a sudden and sustained reduction in the average blood glucose level, as evidenced by a decline in glycated hemoglobin (HbA1c) within several weeks [4].

Contrary to widely held beliefs, early worsening (EW) is neither rare nor is it always benign. For example, 148 out of the 1441 patients had experienced EW at the beginning of the DCCT, compared to 271 patients exhibiting sustained progression of diabetic retinopathy at the end of the DCCT [3]. Only 5 of these 148 patients with “early worsening” had received laser photocoagulation [3], suggesting that EW in that study was mild and merely transient [5, 6]. The contrary, however, has also been observed: rapid and irreversible EW with progression of NPDR to proliferative retinopathy, hemorrhages and blindness [7-9].

The natural history of EW in type-1 diabetes mellitus, hence, remains to be determined. According to the DCCT report [3], higher HbA1c at baseline and greater reduction of this level within 6 months, as well as greater severity of baseline retinopathy are predictors of “early worsening”. Acute macular edema is one of its most severe complications [3, 6-9, 10].

Except for the study by Favard et al. [10], advocating aggressive, extensive photocoagulation and early vitrectomy, laser photocoagulation treatment in this condition has rarely been elucidated. Since the classic retinopathy studies [11, 12] have assessed standard treatment strategies mostly in type-2 diabetic patients, and have not accounted for abrupt lowering of average glycaemia, their results may not apply to early worsening of diabetic retinopathy in type-1 diabetic patients. The following study was, therefore, undertaken to investigate the outcome of standard laser photocoagulation treatment for “early worsening” in type-1 diabetic patients.

## PATIENTS AND METHODS

### Patients

A review of 700 charts of type-1 diabetic patients attending the university diabetes outpatient clinic revealed 23 patients with “early worsening” (EW), of whom datasets were available. They had been under continuous care of the university diabetes outpatient clinic for 13-184 months (median 40 months), during a 16-years period from 1983-1999. Seventeen of the patients were females; all of them had a history of prolonged periods of extremely poor control (due to negligence, bulimia, of fear of hypoglycaemia), as documented by HbA1c-levels > 10% on repeated occasions. Two patients (1 female) had Mauriac’s syndrome [13], and 13 had micro- or macroproteinuria indicative of incipient of overt diabetic nephropathy.

More than half of the patients (14/23) had signs or symptoms of peripheral diabetic neuropathy, which, synchronously with EW, in 4 of them transiently painfully exacerbated [6, 14]. When exhibiting EW, the patients were aged 15-43 (median 25) years, and diagnosed with type-1 diabetes mellitus since 5-25 (median 13) years. Prior to EW they had either no retinopathy at all, or mild to moderate NPDR. None of them had been treated with laser photocoagulation before.

### Definitions

Early worsening (EW) was defined as incidence, or any one-step progression of diabetic retinopathy, if it had occurred within 6 months [3] after a reduction in HbA1c by > 2% over 6 months.

Retinopathy status was defined according to the current German standard [15], based on ETDRS criteria [16, 17] as: nonproliferative diabetic retinopathy (NPDR) of mild, moderate or severe stage; proliferative diabetic retinopathy (PDR) with low risk, high risk, or in regression; focal, diffuse, or ischaemic diabetic maculopathy (DMP), with/without clinically significant macular edema (CSME).

Type-1 diabetes mellitus was defined as insulin-requiring diabetes mellitus with onset below 30 years of age.

Diabetic polyneuropathy was defined as history of foot ulcer or neuropathic pain, and reduced vibration sensation, according to International Guidelines [18].

Diabetic nephropathy was defined as presence of either microproteinuria (40-499 mg/l), or macroproteinuria (> 500 mg/l) [19].

Hypertension was defined as blood pressure > 140/90 mm Hg, or taking antihypertensive medication.

### Methods

Patients were repeatedly screened for retinopathy by 45° fundus photography [20] during their visits to the diabetes outpatient clinic. The current German standards require screening every 3-6 months [15], however, since 1995, patients potentially at risk for EW were attempted to be screened in shorter intervals (1 months). Any symptoms (e.g. blurred vision) or abnormality on screening prompted examination by an ophthalmologist specialising in retinology. Except for 4 patients with very little EW (mild NPDR), all patients underwent slit-lamp biomicroscopy, an 5 to 7 fields
30° stereo fundusphotography; fluorescein angiography was performed in 14 patients [15]. Best corrected visual acuity was assessed with standardised chart lighting at 5 m distance.

Laboratory assessments

Proteinuria was measured by nephelometry, the upper normal limit being 40 mg/l [19]. HbA1c was measured by HPLC-method from capillary blood, the normal range being 4.2-5.6% in our laboratory [21]. The correlation between HbA1c and average blood glucose level was calculated using the formula of Goldstein et al. [22].

Treatment

Laser photocoagulation was performed according to ETDRS-guided German standards [15-17], with Argon green 514 nm wavelength. The size, power, duration and number of burns was chosen according to the treatment strategy. Focal coagulation consisted of 15-200 burns of 100-200 um spot size, while panretinal coagulation consisted of mild to full scatter coagulation of about 600 to 2 000 burns of 500 um diameter, which was filled in by additional 500 to 1 000 burns if necessary.

Follow-up: observation time from reduction of HbA1c until end of the study ranged from 12 to 120 months (median 36 months).

Statistics: Data are given as numbers, medians (with range), or means (with standard eviation), as indicated. Descriptive analysis was carried out by x 2 test with Yates correction, if appropriate. A p< 0.05 was considered significant.

RESULTS

At baseline, 16 patients displayed no retinopathy at all, or NPDR with/without DMP, and 7 patients displayed PDR. Tightening of diabetes control reduced HbA1c by > 2% within 6 months, equivalent to a mean reduction rate of 1.6 (SD 0.8) % per month. This is about half the maximum possible decay rate of HbA1c [21]. In all patients, retinopathy became florid (early worsening EW), which lasted for 0-14 months (median 5 months) after improving glycaemia. According to the severity, and the response to laser treatment, respectively, the patients could be grouped into 4 distinct categories of EW. Clinical details of the patient groups I-IV are summarized in the Tables I, II and III.

Group I comprised of 4 patients (17%), in whom EW lead to mild NPDR, without macular involvement or visual loss; laser coagulation was not required. In 19 of the 23 patients (83%), laser treatment was required because EW had induced focal or diffuse CSME. Focal coagulation was applied successfully in 3 of these 19 patients (Group II), while it had to be extended to scatter treatment in 9 of the 19 patients (Group III). Two out of 9 patients of Group III nevertheless progressed to severe NPDR, and 7 progressed to high-risk PDR requiring panretinal coagulation; vision had deteriorated in most of them already before laser coagulation was initiated. Group IV comprised of 7 patients who had abstained from any laser coagulation because spontaneous regression of EW [5, 6] was awaited. In all of them, macular edema and high-risk PDR developed, needing immediate panretinal coagulation. Of the 14 cases with high-risk PDR and panretinal coagulation (i.e. 7 out of 9 patients of group III, plus all of the 7 patients of group IV), 7 required pars plana vitrectomy because of vitreous haemor-

<table>
<thead>
<tr>
<th>Category of EW</th>
<th>patients</th>
<th>age, yrs</th>
<th>DD yrs</th>
<th>prot. mg/l</th>
<th>prevalence of</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>m/f</td>
<td></td>
<td></td>
<td></td>
<td>neuropathy</td>
</tr>
<tr>
<td>Group I (n = 4) NPDR, no DMP, no LC</td>
<td>2/2</td>
<td>(19-33)</td>
<td>6 (5-13)</td>
<td>&lt;40</td>
<td>1/4</td>
</tr>
<tr>
<td>Group II (n = 3) NPDR with DMP, resolved by focal LC</td>
<td>1/2</td>
<td>34 (31-37)</td>
<td>15 (10-19)</td>
<td>&lt;40</td>
<td>1/3</td>
</tr>
<tr>
<td>Group III (n = 9) NPDR with DMP, not resolved by focal LC</td>
<td>3/6</td>
<td>25 (21-43)</td>
<td>12 (10-25)</td>
<td>200 (40-500)</td>
<td>7/9</td>
</tr>
<tr>
<td>Group IV (n = 7) PDR with DMP, no focal LC</td>
<td>0/7</td>
<td>24 (15-20)</td>
<td>13 (6-17)</td>
<td>600 (40-1200)</td>
<td>5/7</td>
</tr>
</tbody>
</table>

median (range); EW = early worsening, DD = diabetes duration, prot = proteinuria (normal < 40mg/l), NPDR = nonproliferative diabetic retinopathy, PDR = proliferative diabetic retinopathy, DMP = diabetic maculopathy, LC = laser coagulation.
rhage (3 of them from Group III with focal, and 4 from Group IV without any coagulation pretreatment).

Patients progressing to PDR, at baseline more often presented with diffuse rather than focal maculopathy, and greater visual loss prior to laser coagulation, than patients who did not progress to PDR. Patients progressing to PDR also more frequently had micro- or macroproteniuria (11 out of 14 vs. 2 out of 9), or peripheral polyneuropathy (11 out of 14 vs. 2 out of 9) than patients who did not progress to PDR (chi-squared 5.0, df 1, p < 0.05). The time interval between the start of tightening glycaemic control and starting laser coagulation was not different between groups I to IV (Table II).

PDR seemed to occur somewhat later in patients of group III (pretreated with focal laser coagulation: median 11 (range 6-31) months) than in patients of group IV (no pretreatment with focal coagulation: median 5 (range 1-14) months).

Vitrectomy retained visual acuity 0.2 to 1.0 in 5 out of 8 operated eyes, and < 0.1 in the remaining 3 eyes after 6-120 (median 39) months of follow-up. Overall, visual acuity > 0.3 in at least one eye was preserved in 22 of the 23 patients at the end of follow-up after 12-120 (median 36) months.

### DISCUSSION

In the present study, most patients with EW progressed to severe CSME, high-risk PDR, and loss of vision, despite ETDRS-guided laser photocoagulation treatment. This confirms previous observations [9, 10, 24], but is inconsistent with both, the good response of EW to laser photocoagulation in the DCCT [3], and

<table>
<thead>
<tr>
<th>Category of EW</th>
<th>before EW</th>
<th>after EW</th>
<th>reduction per month</th>
<th>time to LC, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPDR, no DMP, no LC</td>
<td>12.0 (SD 1.8)</td>
<td>8.0 (SD 1.9)</td>
<td>1.3 (SD 1.1)</td>
<td>n.a</td>
</tr>
<tr>
<td>NPDR with DMP, resolved by focal LC</td>
<td>11.4 (SD 0.5)</td>
<td>8.4 (SD 0.8)</td>
<td>1.4 (SD 0.5)</td>
<td>5</td>
</tr>
<tr>
<td>NPDR with DMP, not resolved by focal LC</td>
<td>13.0 (SD 2.4)</td>
<td>8.2 (SD 1.9)</td>
<td>1.9 (SD 0.9)</td>
<td>4 (0-7)*</td>
</tr>
<tr>
<td>PDR with DMP, no focal LC</td>
<td>13.3 (SD 2.9)</td>
<td>8.5 (SD 1.7)</td>
<td>1.3 (SD 0.5)</td>
<td>5 (1-14)*</td>
</tr>
</tbody>
</table>

### TABLE II. Treatment characteristics.

<table>
<thead>
<tr>
<th>Category of EW</th>
<th>best corrected visual acuity</th>
<th>vitrectomies, number</th>
</tr>
</thead>
<tbody>
<tr>
<td>before EW</td>
<td>at start of LC</td>
<td>at follow-up</td>
</tr>
<tr>
<td>NPDR, no DMP, no LC</td>
<td>1.0 (1-1)</td>
<td>n.a</td>
</tr>
<tr>
<td>NPDR with DMP, resolved by focal LC</td>
<td>1.0 (1-1)</td>
<td>0.9 (0.8-1.0)</td>
</tr>
<tr>
<td>NPDR with DMP, not resolved by focal LC</td>
<td>1.0 (1-1)</td>
<td>0.6 (0.3-1.0)</td>
</tr>
<tr>
<td>PDR with DMP, no focal LC</td>
<td>1.0 (1-1)</td>
<td>0.4 (&lt; 0.03-0.8)</td>
</tr>
</tbody>
</table>

median (range). Abbreviations: EW = early worsening, NPDR = nonproliferative diabetic retinopathy, PDR = proliferative diabetic retinopathy, DMP = diabetic maculopathy, LC = laser coagulation.
the spontaneous resolution of PDR from EW in 2 case reports [5, 6]. However, these papers rarely reported on symptomatic macular edema, that heavily complicated EW in most of the present patients. In the study by Favard et al. [10], about 75% of cases had developed macular edema during a reduction in HbA1c by 2% within 3 months. Patient characteristics play an important role in the retinal response to acutely lowering hyperglycaemia. In the present study, factors predisposing for high-risk PDR, e.g. increased severity of retinopathy, decreased visual acuity (or extensive macular edema), higher glycosylated hemoglobin, history of neuropathy [2] and nephropathy, were common in patients with a poor outcome of EW. The duration of diabetes and of extreme hyperglycaemia, respectively, is important as well. We have found no EW in a control group of type-1 diabetic patients matched for age, sex, initial HbA1c to the study patients, in whom HbA1c was lowered at maximum by 3.8% per month. However, these patients neither had retinopathy, nor proteinuria, nor neuropathy, and the mean duration of diabetes was only 6 months (data unpublished). Likewise, in the present study cases with mild EW had shorter median duration of diabetes than cases with severe EW (Table 1).

The present paper, like previous ones on the same subject [7, 8, 10], has some limitations: it is not a controlled trial, but an observational study without control group, and the number of cases is small. There are two main reason for these shortcomings: firstly, the relatively low incidence of EW, and secondly the particular characteristics of most patients with EW, who are often incompliant with the self-management of their diabetes treatment, or affected by psychiatric disorders [10], which precludes proper clinical trials on them.

Nevertheless, some important information on the clinical course of EW can be extracted from the present findings. The features of EW resemble strongly to the florid diabetic retinopathy with macular edema, that has been described already in the 70es as relatively resistant to photocoagulation treatment [25, 26], and confirmed twenty years later by Favard et al. [10]. Polkinghorne et al. were the first to suggest a modification of the standard photocoagulation strategy in this condition, starting with peripheral panretinal coagulation for eyes with extensive capillary closure, but no new vessels, before treating macular edema [24]. Likewise, Lee et al. [27] have combined macular grid and peripheral panretinal coagulation in cases of diffuse diabetic macular edema, while Favard et al. [10] have advocated extensive coagulation plus early vitrectomy. These approaches deserve further study.

As reported previously, in 5 of our patients serum IGF-1 had been shown to increase before EW developed [13, 28]. Upregulation of serum IGF-1 concentration, hence, appears to be another risk factor for progressive diabetic retinopathy, and explains the favourable response of florid retinopathy to pituitary ablation [26]. Upregulation of serum IGF-1 promotes macular edema, presumably – like insulin itself [29] – by enhancing vascular endothelial growth factor gene expression in the retina. This mechanism is facilitated by capillary leakage [30], and associated with incipient or overt diabetic nephropathy. While most of the proteinuric patients in the present study developed PDR, patients without proteinuria developed only NPDR of less severity.

In consideration of the limited success of laser coagulation treatment, prevention of EW may be a better option to protect visual acuity. Three potential preventive strategies deserve consideration: very slow reduction of average hyperglycemia, pharmacological blockade of growth factors, prophylactic laser coagulation before retinopathy has started to progress.

– A reduction of average glycaemia, or of HbA1c, respectively, much slower than in the present study could protect against EW. We have observed occasionally, in high-risk patients that diabetic retinopathy progressed only minimally or not at all, when HbA1c was reduced by only 0.3% per month (unpublished). Although the DCCT analysis [3] was unable to confirm this theory (because of methodological shortcomings, as we believe) such gradual lowering of HbA1c equivalent to a reduction in average blood glucose concentration by 0.5 mmol/l per month [22] could be beneficial. It would require less insulinemia [29], and would trigger less IGF-1 upregulation [28], respectively; as a result less formation of edema and neovascularisation would be stimulated. Exogenous IGF-1 affects diabetic retinopathy in a dose-dependent manner [31].

– Pharmacological blockade of IGF-1 or other growth factors [30, 32] would be an interesting alternative. Recent studies with octreotide to inhibit IGF-1 are promising [33]. Other agents, like suramin [34] or pegvisomant [35] may be worth trying.

– Thirdly, prophylactic or more aggressive laser ablation of peripheral (ischaemic) retina [10, 24, 27], prior to any edema formation, could reduce the susceptibility of the retina for the action of endogenous angiogenic growth factors. This approach seems plausible for the patients in this study, since 83% of them finally required laser treatment. Very early laser coagulation of diabetic macular edema has been discussed recently by Ferris and Davis [36], and has been rejected for eyes with visual acuity 20/20 or better; however, their conclusions may not apply to EW as they did not consider this particular condition.

In summary, in 19 out of 23 type-1 diabetic patients with early worsening of diabetic retinopathy, diabetic maculopathy, severe macular edema, and florid proliferative retinopathy developed after a sustained improvement in HbA1c. Standard, ETDRS-guided laser coagulation was of limited benefit to
restore visual function or to prevent neovascularisations. Strategies to avoid early worsening, rather than to treat it by laser coagulation should, therefore, be devised preferentially.

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REFERENCES