Metabolic Control of Diabetes Is Associated With an Improved Response of Diabetic Retinopathy to Panretinal Photocoagulation

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OBJECTIVE — To study the influence of glycemic control and the presence of microalbuminuria on the initial response to panretinal photocoagulation (PRP) in patients with a high-risk proliferative diabetic retinopathy (PDR).

RESEARCH DESIGN AND METHODS — This was a prospective cohort study with a two-by-two factorial design. We used full-scattered PRP to treat 115 eyes of type 2 diabetic patients who have high-risk PDR. HbA_{1c} (A1C) and albumin levels in 24-h urine were constantly monitored during the preenrollment, treatment, and posttreatment periods. At a follow-up visit 12 weeks after the last PRP session, the fundus was examined for characteristics of regression from high-risk PDR and the response to PRP was determined to be successful or unsuccessful. The eyes were categorized into four groups based on average A1C levels and the presence or absence of microalbuminuria. The data were analyzed using a logistic regression model. Our statistical analysis determined the probability of achieving a satisfactory response to PRP in association with A1C levels and the presence or absence of microalbuminuria.

RESULTS — Of the 115 eyes examined, 65 (56.5%) had a successful initial response to PRP and 50 (43.5%) did not. The probability of a satisfactory response to PRP was related to A1C levels ($P < 0.05$) but not to microalbuminuria and its interaction with hemoglobin glycosylation ($P \geq 0.05$).

CONCLUSIONS — Low levels of hemoglobin glycosylation (A1C <8%) during the pretreatment, treatment, and posttreatment periods are associated with a regression of proliferative diabetic retinopathy after PRP.

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Diabetic retinopathy has been the subject of in-depth study for the last 3 decades, during which time randomized and controlled multicenter clinical trials have provided important information about the natural history and treatment of the disease. Panretinal photocoagulation (PRP) is the treatment of choice for proliferative diabetic retinopathy (PDR) (1). However, some patients do not respond to PRP and eventually experience legal blindness (2).

Hyperglycemia is an important risk factor for the development of microvascular disease in diabetic patients. There is a direct relation between the degree of glycemic control and the incidence and progression of retinopathy (3–11). However, the influence of metabolic control of diabetes on the response of diabetic retinopathy to PRP has not been previously studied. Linking PRP effectiveness with metabolic control of diabetes may provide useful information for visual prognosis in diabetic patients.

Data from most studies suggest an association between diabetic nephropathy, as manifested by microalbuminuria, and diabetic retinopathy (12). There are no data, however, on whether the presence of microalbuminuria is a negative prognostic factor for the efficacy of PRP. The aim of this study was to assess the influence of the degree of glycemic control and microalbuminuria on the initial response to PRP in patients with high-risk PDR.

RESEARCH DESIGN AND METHODS

— This was a prospective cohort study with a two-by-two factorial design. From September 2000 to September 2004, we prospectively studied 115 eyes from 76 type 2 diabetic patients who had high-risk PRD as defined by the Diabetic Retinopathy Study (any one or more of the following criteria: *1*) neovascularization within 1 disc diameter of the optic disc with vitreous or preretinal hemorrhage, *2*) neovascularization within 1 disc diameter of the optic disc that covers >25% of the disc [more than the Diabetic Retinopathy Study standard photograph 10A] without vitreous or preretinal hemorrhage, or *3*) neovascularization elsewhere [on the retina] of >50% disc diameter with vitreous or preretinal hemorrhage) (13).

One surgeon treated the patients with full-scattered PRP in three divided sessions at 2-week intervals using argon green laser. Focal macular photocoagulation was performed in cases with clinically significant macular edema as defined by the Early Treatment Diabetic Retinopathy Study: *1*) thickening of the retina at or within 500 μm of the center of the macula, *2*) hard exudates at or within 500 μm of the center of the macula if associated with thickening of the adjacent retina, and *3*) a zone or zones of retinal thickening 1 disc diameter or larger, any

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Abbreviations: PDR, proliferative diabetic retinopathy; PRP, panretinal photocoagulation; VEGF, vascular endothelial growth factor.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

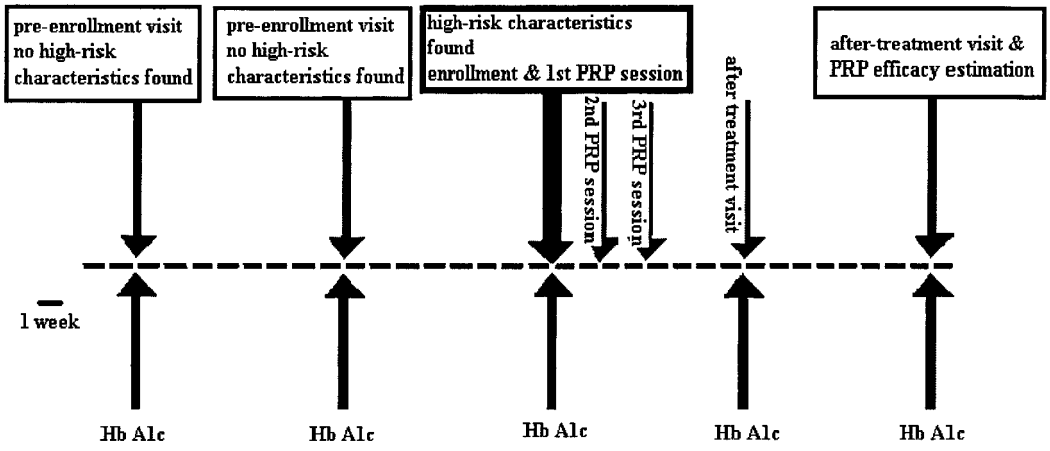

Figure 1—*Study protocol.*

part of which is within 1 disc diameter of the center of the macula (14).

The participants were selected from type 2 diabetic patients who had severe nonproliferative or early proliferative retinopathy and were followed in our outpatient clinic every 8 weeks. The metabolic control of diabetes was also monitored at each preenrollment visit using blood A1C levels. The enrollment took place just after high-risk retinopathy was diagnosed and only if the patient had previously attended at least two preenrollment visits (Fig. 1). None of the eyes had prior retinal photocoagulation or cryopexy of any kind. Increased duration of diabetes is one of the risk factors for the progression of diabetic retinopathy (7,8). To eliminate a presumed influence of the duration of diabetes on PRP effectiveness, we matched patients with regard to the duration of their diabetes. Only patients with type 2 diabetes of ≥15 years' duration were included (Table 1); 7 patients with diabetes of <15 years' duration were excluded from the study. To exclude any influence of other metabolic disorders that affect the progression of diabetic retinopathy, patients with renal insufficiency (expressed as gross proteinuria), systemic hypertension (systolic blood pressure >140 mmHg and diastolic blood pressure >85 mmHg, actively treated or not), anemia (hematocrit <40% for men and <37% for women), or hyperlipidemia (total cholesterol levels >220 mg/dl, actively treated or not) were not included (7–11). We excluded 22 patients with high-risk PDR in at least one eye because of these metabolic disorders. Because cataract surgery accelerates the progression of diabetic retinopathy, patients with prior intraocular surgery of any kind were not enrolled in the study (15). Eyes presenting with a vitreous hemorrhage massive enough to preclude the requisite therapy in compliance with the treatment protocol were also excluded from the study. If the fellow eye developed high-risk retinopathy characteristics, it was included in the study only if ≥6 months had passed since the first eye's last treatment.

Plasma A1C levels were continuously monitored every 8 weeks until the last posttreatment visit (Fig. 1), and the average of the five A1C measurements was used as an index of metabolic control. According to the American Diabetes Association standards of medical care for patients with diabetes (16), A1C levels should ideally be <7%, but levels <8% are acceptable. This A1C cutoff was used for our patients' categorization. Thus patients with average plasma A1C levels <8% were considered to have acceptably controlled diabetes ($A1C^-$), and those with average plasma A1C levels ≥8% were considered to not have acceptably controlled diabetes ($A1C^+$). Patients with a significant switch in diabetes metabolic control (defined as a >1 unit difference in A1C levels between any two of the five A1C measurements) were excluded from the study. To estimate the relation of the PRP response to microalbuminuria, we monitored the levels of albumin in 24-h urine twice during the observation period (Fig. 1). Microalbuminuria was defined as albumin levels in urine >30 mg/24 h in both measurements, and patients were marked as M/alb^+ in the presence of microalbuminuria and as M/alb^- in the absence of microalbuminuria. Therefore, the patients could be divided into four (2 × 2) groups using combinations of $A1C^+/^-$ and $M/alb^+/^-$.

Table 1 —*Therapeutic response of study patients classified according to A1C levels and the presence or absence of microalbuminuria*

	Group 1	Group 2	Group 3	Group 4
n	19	18	12	21
Sex (M/F)	11/8	8/10	7/5	10/11
Mean age (years)	67.6 (62–76)	66.2 (56–73)	66.9 (62–71)	67.1 (59–73)
Diabetes duration (years)	16.9 (15–20)	17.0 (15–20)	17.3 (16–20)	18.0 (15–21)
A1C (%)	≥8	≥8	<8	<8
Microalbuminuria	Yes	No	Yes	No
Response of eyes to treatment				
Total treated	31	29	20	35
Successful	10 (32)	15 (43)	15 (80)	25 (71)
Unsuccessful	21 (68)	14 (57)	5 (20)	10 (29)

Data are mean (range) or *n* (%).

At the time when high-risk retinopathy characteristics were observed and 12 weeks after the last PRP session, the patients underwent a full ophthalmic examination, including best-corrected Snellen visual acuity, slit lamp examination, fundus biomicroscopy, applanation tonometry, red-free or color digital photography, and video fluorescein angiography. The fundus was examined for signs of regression to high-risk PDR 12 weeks after the last PRP session, as recommended by the American Academy of Ophthalmology (resolution or regression of neovascularization, with the remaining new vessels appearing inactive; marked reduction of preexisting vitreous hemorrhage; or no evidence of new hemorrhage) (17), and the response to PRP was accordingly characterized as satisfactory or unsatisfactory.

The study was scheduled as blind. The retina specialist who performed PRP and estimated laser therapy results was not aware of each patient's metabolic control status. The Ethics Committee of the University Hospital of Larissa approved this protocol.

The data were analyzed using a logistic regression model. In this model, the probability of demonstrating a satisfactory response to PRP was investigated in association with A1C and microalbuminuria. Based on this model, the odds ratios (ORs) of a satisfactory response for $A1C^+$ relative to $A1C^-$ and M/alb^+ relative to M/alb^- were estimated. Proportions were compared using the *Z* test. The analysis was performed using GLIM (18) and SPSS 11.

RESULTS — Over the course of the study, 6 patients dropped out, leaving 70 patients (36 men and 34 women) who complied with the therapy and observation regimen. The patients' mean age was 67 years (range 56–76 years) and the mean duration of diabetes was 17.3 years (range 15–21 years) (Table 1).

We prospectively studied and treated 115 eyes with high-risk PDR; of those, 65 (56.5%) had a satisfactory initial response to PRP and 50 (43.5%) did not ($P > 0.05$). The treatment effect in relation to metabolic control was investigated by comparing the four groups that were defined based on the average A1C levels plus the presence or absence of microalbuminuria (Table 1).

The statistical analysis revealed that the probability of a satisfactory response to PRP depended on A1C levels ($P < 0.05$). The OR of a satisfactory response to PRP among $A1C^+$ compared with $A1C^-$ patients was 0.28 (CI 0.13–0.62). Consequently, the odds of a satisfactory response to PRP was 72% less for $A1C^+$ compared with $A1C^-$ patients. On the other hand, the probability of a satisfactory response to PRP did not depend on microalbuminuria ($P \geq 0.05$) or its interaction with hemoglobin ($P \geq 0.05$); the probability of a satisfactory response to PRP was 33% less for M/alb^+ compared with M/alb^- patients (OR 0.67 [0.31–1.48]; NS). It is possible that this finding might change if a larger number of eyes or patients were studied.

CONCLUSIONS — Many epidemiological studies have demonstrated a strong relation between hyperglycemia and the development and progression of diabetic retinopathy. PRP is a treatment of choice for PDR, but it is not always effective. In our study, a satisfactory initial therapeutic response was observed in 65 (56.5%) of the 115 eyes treated. This is a lesser response than that reported by Doft and Blankenship (satisfactory PRP results in 70% of 50 treated eyes) (10), but similar to that cited by Vander et al. (2), where 35 (59.3%) of 59 diabetic eyes presented a favorable early response to PRP. However, neither of the above-mentioned studies (2,19) provided information on the metabolic control status of diabetic patients responsive and nonresponsive to treatment. Elevated A1C levels have been found to be a potent predictor of progression to PDR and severe visual loss in type 1 and 2 diabetic patients (3–11). Furthermore, the positive association between high glycosylation levels and the incidence of severe visual loss and vitrectomy was proven in the Early Treatment Diabetic Retinopathy Study (7,10). Our results indicate that the beneficial effect of PRP is accomplished more easily in the eyes of patients with well-controlled diabetes.

The interaction of advanced glycation end products and their receptors and the increased activity of the polyol pathway have been implicated as mediators of increased microvascular permeability, ischemia, and angiogenesis (20–22). Retinal ischemia promotes angiogenesis, triggering the upregulation of various growth factors, especially the vascular endothelial growth factor (VEGF) (23). The cause of the upregulation of VEGF by high glucose levels remains speculative, but multiple factors may be implicated. It has been suggested that high glucose concentrations, through an increased flux of glucose via the sorbitol pathway, may trigger hypoxia-like alterations in the cellular redox status (24). Because tissue hypoxia is a major regulator of VEGF production, the hypoxia-like redox imbalance may inappropriately upregulate VEGF expression. In addition, glucose degradation products and advanced glycation end products are known to induce VEGF expression in vitro, although the in vivo relevance of these pathways remains to be demonstrated. Laser burns destroy the ischemic retinal tissue that is a source of intraocular VEGF (25,26), which is followed by alterations in gene expression, as has been observed in mice retina after PRP. Specifically, genes inhibiting VEGF expression (e.g., angiotensin II type 2 receptor) were found to be upregulated, whereas genes promoting VEGF expression (e.g., fibroblast growth factors 14 and 16, interleukin-1β, calcitonin receptor-like receptor, and plasminogen activator inhibitor 2) were found to be downregulated (27). These changes may lower the intraocular VEGF levels and hence favor the initial therapeutic response to PRP. It is possible that the beneficial effect of PRP, exerted through the modulation of intraocular growth factors, is adversely impacted by chronic hyperglycemia, leading to unsuccessful therapeutic results. The intraocular VEGF levels could be a useful marker of the pathophysiological mechanism if it was technically and ethically easily achieved. VEGF levels in the plasma have not been measured because they do not reliably reflect intraocular changes (28,29).

In our study, we found that the presence of microalbuminuria did not correlate with the initial response of PDR to PRP. Increased urinary albumin excretion is the earliest clinical finding of diabetic nephropathy and a surrogate marker of renal microvascular disease. Hyperglycemia is an important risk factor for the development of microvascular disease in diabetic patients. A direct relation between the degree of glycemic control and the incidence and progression of retinopathy and nephropathy has been noted in patients with type 2 diabetes (5,30). Albuminuria was established as a predictor of diabetic retinopathy in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (12) but in a recent study was confirmed in only Hispanic patients (31). The association between the development of diabetic retinopathy and nephropathy suggests common pathogenetic factors that may underlie the development of

both complications (32). However, different local mechanisms may be involved, and the change of local conditions in retina after PRP seems to be crucial for the therapeutic result.

In conclusion, good metabolic control in diabetic patients with high-risk PDR is associated with a greater regression of proliferative retinopathy than in subjects with not acceptably controlled diabetes. Our finding that well-balanced glycemic control supports a positive therapeutic result is encouraging; however, further studies are required to confirm these results and elucidate the local mechanisms through which hyperglycemia influences the response of high-risk PDR to PRP.

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