Risk of Developing Retinopathy in Diabetes Control and Complications Trial Type 1 Diabetic Patients With Good or Poor Metabolic Control

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OBJECTIVE — The study goal was to assess and predict the risk of developing retinopathy in type 1 diabetic patients with extreme metabolic control.

RESEARCH DESIGN AND METHODS — Based on material from the Diabetes Control and Complications Trial (DCCT) study (n = 1,441 patients), patients without retinopathy at baseline (DCCT primary cohort) were considered under good or poor metabolic control if the mean HbA_{1c} level (until the last visit) fell in the lower or upper 20% of the overall HbA_{1c} distribution, respectively. Retinopathy was recorded as either absent or present. Logistic regression was used to predict retinopathy from covariates used in the DCCT retinopathy study.

RESULTS — Among the 153 DCCT patients with "good metabolic control" (mean HbA_{1c} $\leq$6.87%), three-step change retinopathy developed in 15 (9.8%), and 138 (90%) remained free of retinopathy. Conversely, among the 166 patients with "poor metabolic control" (mean HbA_{1c} $\geq$9.49%), the complication did not develop in 71 (43%) and did develop in 95 (57%). Whereas occurrence of diabetic retinopathy was primarily due to metabolic control ($P < 0.0001$) and duration of participation in the study ($P < 0.0001$), two other covariates were found to be significant prognostic factors of the complication: HbA_{1c} at baseline (OR 1.37, $P < 0.001$) and BMI (OR 1.11, $P < 0.05$).

CONCLUSIONS — This study confirms that retinopathy develops in ~10% of patients with type 1 diabetes under good metabolic control, whereas >40% of patients with type 1 diabetes remain free of retinopathy despite poor metabolic control. After adjusting for metabolic control and duration of participation in the study, it was found that previous glycemic exposure (HbA_{1c}) and BMI may provide a possible explanation to such paradoxical clinical situations.

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The relationship between metabolic control of patients with type 1 or type 2 diabetes and the development of chronic adverse complications (retinopathy, nephropathy, or neuropathy) in such patients has always been the primary concern of clinicians, but also has been a much debated issue in the literature over the years (1–3). In a long-term study conducted between 1947 and 1973, Pirart (4) followed 4,400 diabetic patients and showed that patients with poor metabolic control did develop early, frequent, and severe irreversible complications. The Diabetes Control and Complications Trial (DCCT), published in 1993, was the first large, scientific, and rigorous clinical trial focusing on the problem (5). The study demonstrated a marked reduction in the development and progression of diabetic complications in intensively treated patients (mean HbA_{1c} ~7%) when compared with patients with conventional therapy (mean HbA_{1c} ~9%) (6,7). More recently, the U.K. Prospective Diabetes Study, based on 4,209 type 2 diabetic patients, confirmed that intensively handled patients had a 0.9% lower HbA_{1c} level than those who were treated conventionally (7.0 vs. 7.9%), resulting in a 25% reduction in microvascular complications (8–10).

These studies provide solid evidence that "good" metabolic control protects diabetic patients against chronic complications. Clinicians, however, faced with the individual variability of diabetic patients in their daily practices, often wonder why some patients under good metabolic control develop complications while others remain free of such complications, despite poorly controlled disease.

The present study revisited material from the DCCT database (7) made available by the National Technical Information Service of the Department of Commerce. The purpose was to assess the risk of developing diabetic retinopathy in patients with extreme (either good or poor) metabolic control but free of the complication at baseline and to search for potential prognostic factors associated with such outcomes.

RESEARCH DESIGN AND METHODS

— The DCCT recruited 1,441 type 1 diabetic patients according to the eligibility criteria in 29 clinical centers during the period 1983–1989. Follow-up was, on average, 6.5 ± 1.6 years, including a 2-year feasibility study (phase II) to assess specific operational objectives before launching the full-scale clinical

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Abbreviations: AIC, Akaike's Information Criterion; DCCT, Diabetes Control and Complications Trial; ETDRS, Early Treatment Diabetic Retinopathy Study; SNPDR, severe nonproliferative diabetic retinopathy.

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

trial (phase III). All type 1 diabetic subjects, in the age range of 13–39 years, with a disease duration of 1–5 years and no retinopathy at baseline ("primary prevention cohort") or with a disease duration of 1–15 years and minimal-to-moderate nonproliferative retinopathy at baseline ("secondary intervention cohort") were randomized into either "intensive" or "conventional" diabetes therapy. Detailed descriptions of the eligibility criteria and randomization procedures for subjects entering the DCCT have been published elsewhere (11,12). All eligibility determinations were completed within a 4-month period before random assignment to treatment.

Table 1—*Development of retinopathy in type 1 diabetic patients from the DCCT primary cohort with good and poor metabolic control*

	Three-step retinopathy			
Metabolic control*	Absent	Change	Sustained	SNPDR
Good (n = 153)	138	15	0	0
HbA_{1c} ≤6.87%	90.2%	9.80%	0%	0%
Poor (n = 166)	71	38	54	3
HbA_{1c} ≥9.49%	42.8%	22.9%	32.5%	1.8%

Data are n or %. *OR 12.3 (95% CI 6.83–23.5).

Definition of good and poor metabolic control

In the present study, "good metabolic control" was defined as the group of DCCT patients with a mean HbA_{1c} level (until last visit) ≤6.87%, a threshold corresponding to the 20th percentile of the overall distribution of HbA_{1c} mean level. Similarly, "poor metabolic control" was defined as the group of DCCT patients with a mean HbA_{1c} level (until last visit) ≥9.49%, which corresponded to the 80th percentile of the overall HbA_{1c} mean level distribution. Thus, patients with good and poor metabolic control were those in the lower and upper quintiles, respectively, of the HbA_{1c} distribution recorded in the DCCT study, regardless of the therapy they received. Because the present study was primarily concerned with the occurrence or nonoccurrence of diabetic retinopathy in patients with good or poor metabolic control but free of the complication at baseline, only patients in the DCCT primary prevention cohort, i.e., no retinopathy at baseline, were analyzed. There were 153 such patients in the good metabolic control group and 166 in the poor metabolic control group.

Definition of diabetic retinopathy

Development and progression of the diabetic retinopathy were defined as in the original study (13). Specifically, in the DCCT, seven-field stereoscopic color fundus photographs were taken on each eye for all patients by certified photographers every 6 months and were graded centrally according to the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol (14). The change in retinopathy severity on the ETDRS scale over time was the principal outcome measured. The occurrence of three steps or more in the ETDRS score compared with the ETDRS level at baseline was defined as "three-step change retinopathy." Cumulative incidence of progression by three or more steps on the scale at two consecutive visits (6 months apart) was defined as "sustained three-step progression." Severe nonproliferative diabetic retinopathy (SNPDR; level 53 or higher on the final EDTRS scale) was defined by severe retinal hemorrhages, venous beading, or moderate-to-severe intraretinal microvascular abnormalities.

Risk covariates

Occurrence of diabetic retinopathy in patients in the primary cohort with extreme metabolic control was studied in relation to a set of potential risk factors, namely those available in the database used in the original DCCT study on retinopathy (11,12,15). Quantitative variables included age at entry into the study (years), BMI (kg/m^2), calorie intake (kcal), duration of type 1 diabetes at baseline (months), mean education (years), full-scale IQ, HbA_{1c} at baseline (%), stimulated C-peptide concentration (pmol/ml), within-profile mean blood glucose level (mg/dl), dietary protein (g), total insulin dosage units/weight (kg), HDL and LDL cholesterol (serum, mg/dl), triglycerides (serum, mg/dl), and mean arterial blood pressure (mmHg). Duration (months) in the DCCT study and mean (+ SD) HbA_{1c} (%) level (until last visit) were also available. Categorical findings were gender (0 = male, 1 = female), adulthood (0 = less than 18 years, 1 = 18 years or older), family history of type 1 diabetes (0 = no, 1 = yes), marital status (0 = not married, 1 = married), and smoking status at baseline (0 = no, 1 = yes). In addition, the assigned therapy (0 = conventional, 1 = intensive) and phase of randomization (0 = phase II, 1 = phase III) were also known for each patient. Metabolic control was coded 0 for good and 1 for poor.

Statistical analysis

Results were expressed as the mean ± SD for quantitative variables and as proportions for categorical findings. A log-transform was applied to several variables to normalize their distributions. Prediction of diabetic retinopathy (recorded as 0 for absence and 1 for presence) from covariates was performed by logistic regression analysis assuming a common odds ratio for the cumulative logits. Odds ratios (with 95% CIs) were adjusted for extreme metabolic control. The combined predictive effects of the covariates in the model were quantified by the entropy r^2 equal to $(L_O - L_M)/L_O$, where L_O and L_M represent the maximized –2(log likelihood) of the null model and the fitted model, respectively. Akaike's Information Criterion (AIC = $L_M + 2 \times$ number of parameters) was also used for comparing models (the lower the AIC, the better the model). Results were considered significant at the 5% critical level ($P < 0.05$) after adjusting for multiple testing. All calculations were performed using SAS (version 6.12 for Windows; SAS Institute, Cary, NC) and S-PLUS (version 2000; Mathsoft, Cambridge, MA) statistical software packages.

RESULTS — Among the 153 diabetic patients with good metabolic control from the DCCT, 138 (90.2%) were free of diabetic retinopathy at the end of the study period, whereas 15 (9.8%) had three-step change retinopathy. Sustained three-step retinopathy or SNPDR did not develop in any of these patients (Table 1). Conversely, among the 166 patients with poor metabolic control from the DCCT, 71 (42.8%) did not develop the complication, whereas 38 (22.9%) had three-

Table 2—*Factors jointly predictive of retinopathy in type 1 diabetic patients from the DCCT primary cohort when adjusting for metabolic control, as obtained by multiple logistic regression* (n = 319)

Variable	Coefficient	*P*	Odds ratio
Intercept	−19.4 ± 3.40	<0.0001	
HbA_{1c} at baseline (%)	0.314 ± 0.093	0.0007	1.37 (1.15–1.65)
BMI (kg/m^2)	0.108 ± 0.053	0.0408	1.11 (1.01–1.24)
Duration of participation in the study (months)*	2.83 ± 0.625	<0.0001	1.04 (1.02–1.06)†
Metabolic control (0 = good, 1 = poor)	2.01 ± 0.358	<0.0001	7.48 (3.79–15.5)

Data are coefficient ± SE or odds ratio (95% CI). *Log-transform applied; †odds ratio on original scale (month).

step change retinopathy, 54 (32.5%) had sustained three-step progression retinopathy, and 3 (1.8%) had SNPDR (Table 1). Three-step change retinopathy had not developed in any patients in either group at the last visit. Thus, diabetic retinopathy was present in 9.8% of patients in the former group and 57.2% of patients in the latter group (OR 12.3, $P < 0.0001$). Because most patients with good metabolic control received the intensive treatment (93.5 vs. 6.5%) and most patients with poor metabolic control received the conventional treatment (93.4 vs. 6.6%), the difference observed between the two proportions merely confirms one of the salient results of the DCCT study (6).

Prediction of diabetic retinopathy

To predict the development of diabetic retinopathy from data available at baseline, all risk covariates were combined into a multiple logistic regression analysis, adjusting for extreme metabolic control (good or poor). It turned out that only three factors were significantly predictive of diabetic retinopathy: duration in the study, HbA_{1c} at baseline, and BMI. All other variables were not significant. The concordance between predicted probabilities and observed responses was 86.6%, AIC was 311.6, and the multiple entropy r^2 increased from 0.21 (when only extreme metabolic control was included in the model) to 0.34 for the full model. When restricting logistic regression to the four significant covariates, including extreme metabolic control (see Table 2), the percentage of concordance was still 85.2% and r^2 was equal to 0.30. AIC, however, decreased from 311.6 to 297.4, indicating a better model. From Table 2, it is seen that each additional percent of HbA_{1c} at baseline increases the risk of developing diabetic retinopathy by a factor of 1.4, whereas the actual impact of BMI (odds ratio 1.1) only becomes sensitive for higher values. BMI was 23.4 ± 3.0 kg/m^2 in patients with retinopathy and 22.8 ± 2.7 kg/m^2 in patients without retinopathy. Corresponding mean values for HbA_{1c} at baseline were 10.1 ± 1.85 and 8.52 ± 1.51%, respectively. The effect of duration in the study (78 ± 20 vs. 67 ± 17 months) remained highly significant, even after adjusting for the other variables. Finally, it should be remarked that poor metabolic control increased by ~7.5 times the risk of developing diabetic retinopathy when compared with good metabolic control, after adjusting for the other variables in the model.

Derivation of a risk function

A risk function was derived as follows (see Table 2): Rf = 0.314 × HbA_{1c} + 0.108 × BMI + 2.83 × log(duration in the study) + 2.01 × metabolic control, with a cutoff point of 19.4 ± 3.4. The greater the value of Rf, the higher the risk of developing diabetic retinopathy. To illustrate the effects of baseline covariates HbA_{1c} and BMI on the probability of developing diabetic retinopathy, we considered four fictitious patients and computed the risk function under good and poor metabolic control. The duration in the study was assumed to be 72 months in each case.

All results are shown in Table 3. Under good metabolic control, it is seen that a 2% difference in HbA_{1c} at baseline more than doubles the risk of developing retinopathy, whereas the effect of BMI is less apparent (~2%), as expected. If the BMI of patients I and III was 30 kg/m^2, then the corresponding probabilities would increase to 62 and 80%, respectively. Under poor metabolic control, the chances of not developing the complication can remain as high as 31%, even for elevated HbA_{1c} (11%), BMI (24 kg/m^2), and long duration in the study (72 months). Figure 1 shows nomograms for the probability of developing diabetic retinopathy under good metabolic control (Fig. 1*A*) and the probability of not developing the complication under poor metabolic control (Fig.

Table 3—*Probability of developing retinopathy in four fictitious type 1 diabetic patients under good (HbA_{1c} ≤6.87%) or poor (HbA_{1c} ≥9.49%) metabolic control, given HbA_{1c} and BMI at baseline and for a duration period of 72 months*

	Mean HbA_{1c} during 72 months	Risk score*	Probability of retinopathy†	
			Absence	Presence
Patient I				
Baseline HbA_{1c} = 8%	≤6.87%	17.0	92%	8.0%
Baseline BMI = 22 kg/m^2	≥9.49%	19.0	60%	40%
Patient II				
Baseline HbA_{1c} = 8%	≤6.87%	17.2	90%	10%
Baseline BMI = 24 kg/m^2	≥9.49%	19.2	55%	45%
Patient III				
Baseline HbA_{1c} = 11%	≤6.87%	17.9	82%	18%
Baseline BMI = 22 kg/m^2	≥9.49%	19.9	38%	62%
Patient IV				
Baseline HbA_{1c} = 11%	≤6.87%	18.1	79%	21%
Baseline BMI = 24 kg/m^2	≥9.49%	20.1	31%	69%

*Rf = 0.314 × HbA_{1c} + 0.108 × BMI + 2.83 × log(duration) + 2.01 × metabolic control (metabolic control is coded 0 for good and 1 for poor); †probabilities (×100%) are obtained as follows: calculate Rf_1 = 19.4 − Rf. Then, P(absence) = exp(Rf_1)/{1 + exp(Rf_1)} and P (presence) = 1 − P (absence).

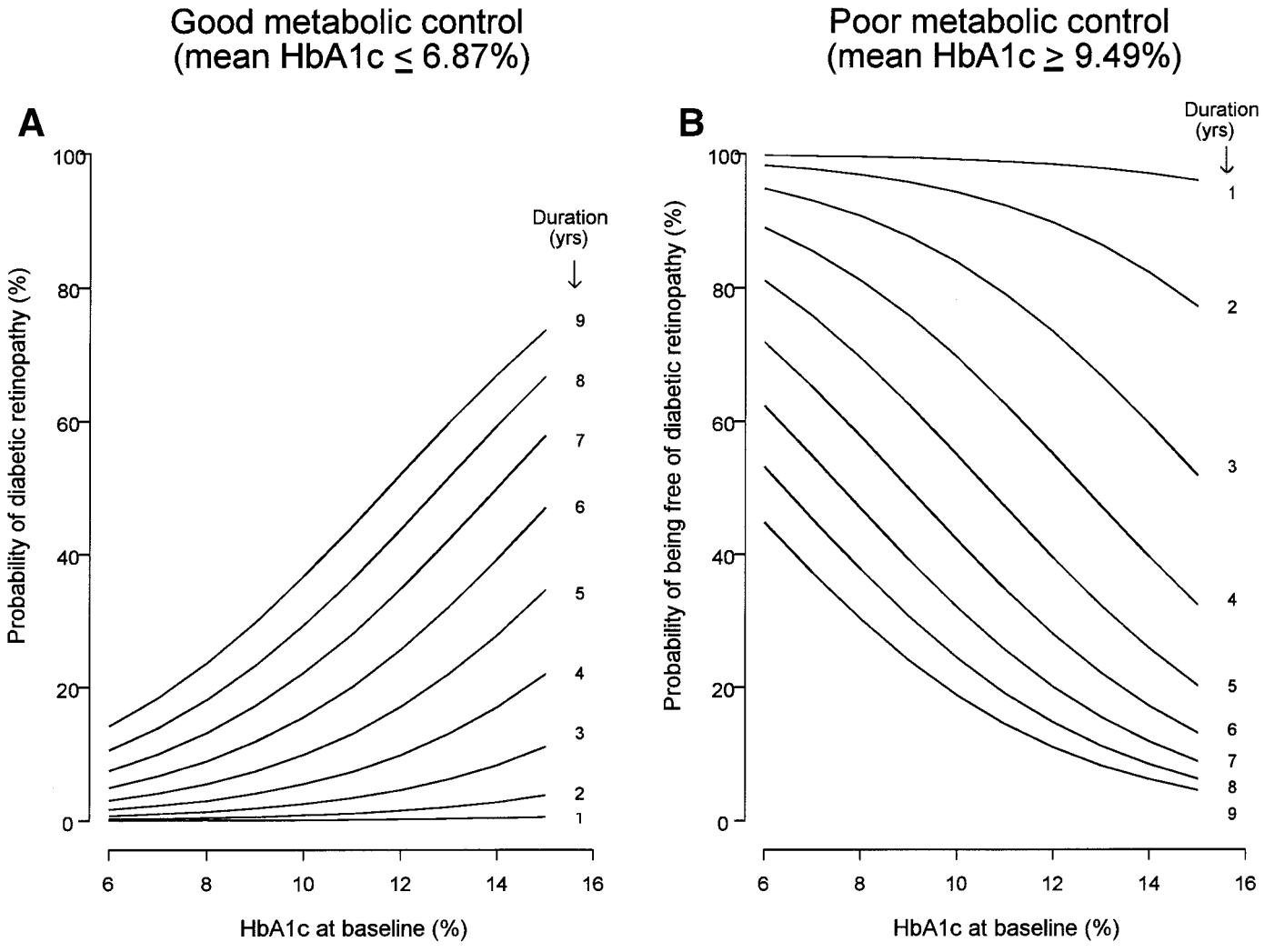

Figure 1—A: *Probability of developing retinopathy in type 1 diabetic patients as a function of HbA_{1c} level (%) at baseline and duration (years) of good metabolic control (HbA_{1c} ≤6.87%).* B: *Probability of not developing retinopathy in type 1 diabetic patients as a function of HbA_{1c} level (%) at baseline and duration (years) of poor metabolic control (HbA_{1c} ≥9.49%). In both cases, BMI is assumed to be equal to 22 kg/m^2.*

1*B*) for HbA_{1c} levels at baseline ranging from 6 to 16% and duration in the study between 1 and 9 years, with BMI set at 22 kg/m^2.

CONCLUSIONS — The development of retinopathy in type 1 diabetic patients with good metabolic control may be considered a failure of treatment, a matter of personal concern, or even more an unexpected and unexplained event by the clinician. Conversely, clinical experience shows that diabetic patients with poor metabolic control will often survive years of treatment without any minor or major complications (16,17). These opposite and paradoxical clinical evolutions in type 1 diabetic patients remain a source of debate and scientific query that long-term studies and clinical trials (4,5,8) have not entirely resolved. The present study revisited material from the DCCT database (7) to explore this problem in more detail.

DCCT patients were considered as being under good or poor metabolic control if their HbA_{1c} mean level was in the lower or upper 20% of the overall HbA_{1c} distribution observed in the DCCT population. Therefore, 60% of the DCCT material was not used in the present study. The choice of a 20% cutoff may be argued, but was believed to be a good compromise between obtaining a sufficient sample size to reach statistical conclusions and meeting clinical criteria defining good and poor metabolic control. HbA_{1c} thresholds were found to be 6.87 and 9.49% for patients with good and poor metabolic control, respectively, and did correspond to generally accepted lower and upper bounds.

Only patients without diabetic retinopathy at baseline (primary cohort) were included in the analysis because the study objective was to assess the risk of developing retinopathy in extreme metabolic control situations. The DCCT reported that the primary prevention cohort had substantially lower rates of retinopathy development than the secondary intervention cohort, in which patients had minimal-to-moderate nonproliferative retinopathy at baseline (6).

In patients with good metabolic control (HbA_{1c} ≤6.87%), the incidence of retinopathy was ~10%, confirming that such patients do not necessarily escape

the complication. In patients with poor metabolic control (HbA_{1c} ≥9.49%), 42.8% did not have diabetic retinopathy, whereas 22.9% had three-step change, 32.5% had sustained three-step retinopathy, and 1.8% with SNPDR (total 57.2%). Therefore, patients with poorly controlled diabetes can be exempt from the complication for a long period of time. By multivariate logistic regression analysis, only three variables were significantly related to the development of diabetic retinopathy after adjusting for metabolic control: duration of participation in the study, HbA_{1c} level, and BMI at baseline. Duration of participation in the study, which can be viewed as long-term glycemic exposure, has a marked adverse effect in both well-controlled and poorly controlled patients (see Fig. 1). It should be remarked, however, that in the DCCT primary cohort, patients with complications stayed significantly ($P < 0.0001$) longer in the study than patients without complications. This may have overestimated its prognostic effect in the group comparison. Although unknown at baseline, duration can be set arbitrarily for making short- or long-term predictions. HbA_{1c} at baseline plays a determinant role in the prediction of diabetic retinopathy, even after adjusting for metabolic control and duration in the study, confirming previous findings of the DCCT study (7). The appearance of BMI is novel but its actual prognostic impact is more limited (~1% risk increase by kg/m^2), unless it reaches scores indicative of obesity.

The present study confirms the puzzling but clinical reality that diabetic retinopathy can develop in patients with good metabolic control and remain absent in patients with poor metabolic control. Although extreme metabolic control is the major determinant of the risk of developing diabetic retinopathy in patients without the complication, the study emphasizes the role of baseline glycemic exposure (HbA_{1c}) in the prospective assessment of patient outcome. High baseline HbA_{1c} values increase the risk of developing the complication despite good metabolic control, whereas low values do prevent development of diabetic retinopathy in poorly controlled patients. The same argument applies, to a lesser extent, for BMI: high scores are deleterious and low scores are preventive. It is concluded that early control of the metabolic and clinical status of type 1 diabetic patients has major consequences on evolution of the disease, in agreement with recent guidelines on treatment strategies (18,19).

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