Long-Term Glycemic Control Has a Nonlinear Association to the Frequency of Background Retinopathy in Adolescents With Diabetes

Follow-up of the Berlin Retinopathy Study

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OBJECTIVE — To assess the influence of long-term glycemic control on the development of background retinopathy in adolescents followed longitudinally from the onset of insulin-dependent diabetes mellitus (IDDM).

RESEARCH DESIGN AND METHODS — Repeated retinal fluorescein angiographies, in intervals of 1–2 years, were evaluated prospectively in 346 patients (190 males, 156 females; 19.8 [8.8–35.4] years of age; diabetes duration of 10.4 [1.1–27.4] years at their latest eye examination, median [range]). The influences of long-term HbA_{1c} (mean of 18 [1–95] determinations per person) and microalbuminuria (≥2 of ≥3 measurements ≥15 μg/min × 1.73 m^2) were studied by multiple linear regression, life-table analysis, and trend analyses.

RESULTS — The rate of background retinopathy per 100 patient-years increased with poorer glycemic control from 0.7 (long-term HbA_{1c} <7%) to 7.3 (HbA_{1c} >11%) following an exponential function. Life-table analysis after subdivision in HbA_{1c} quartiles of equal sizes (HbA_{1c} <8, 8–9, 9–10, and >10%) revealed an individual median expectation of background retinopathy after more than 25, 16.2, 12.7, or 12.0 years of diabetes, respectively. However, significant differences were found only between 8–9% and 9–10%, calculated either as prevalence, life-table analysis, or relative incidence, thus suggesting that a threshold model may also fit the data. After 12 years of diabetes, <25% of those patients exhibiting microalbuminuria (n = 18) were expected to be free from retinopathy compared with 81% of those with normoalbuminuria (n = 86).

CONCLUSIONS — Two statistical models are appropriate to explain the relationship between glycemic control and risk for background retinopathy: *1*) a continuous exponential relationship as described by the DCCT or 2) the presence of a threshold HbA_{1c} level at 9%. Thus, diabetes treatment in children should aim at long-term HbA_{1c} levels <9.0%, but every progress closer to normal may further reduce the risk.

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Received for publication 20 August 1993 and accepted in revised form 11 July 1994.

DCCT, Diabetes Control and Complications Trial; IDDM, insulin-dependent diabetes mellitus; UAE, urinary albumin excretion.

The recently published results of the multicenter, randomized Diabetes Control and Complications Trial (DCCT) (1) have confirmed previous studies (2–8) supporting that glycemic control is a major determinant of the prevalence and severity of microvascular complications in patients with insulin-dependent diabetes mellitus (IDDM). The secondary analyses of the DCCT data (presented in Fig. 5*A* of reference 1) support the hypothesis that there is a continuously increasing risk of progression to retinopathy with increasing mean glycated hemoglobin. Although this study has established the benefits of intensive therapy for adolescent and adult patients with IDDM, questions remain whether there is a specific glycated hemoglobin value at which the benefits of diabetes management are maximal (9).

Our present study in children and adolescents reports the long-term follow-up of the Berlin Retinopathy Study, started in 1977 as a retrospective analysis of the development of early retinopathy and followed prospectively and longitudinally until this day (10). In contrast to the DCCT approach, these patients represent an unselected cohort, following various treatment modalities and cared for with routine measures available in this institution in an urban setting. The outcome measure was the development of background retinopathy, detected by serial fluorescein angiographies (11), which were performed until the individuals left pediatric care. The distinct features of this study are a follow-up of the study cohort from onset of the disease (i.e., without retinopathy at baseline), treatment within a single institution over the total study period, and the use of the actuarial method of data analysis, which allows the inclusion of all available patient data.

RESEARCH DESIGN AND METHODS

— A single-center follow-up study was conducted. Patients were treated exclusively in our institution and were scheduled to be seen four times

a year. Prospective follow-up was started in 1977 in patients who were diagnosed in our institution before 1977 without retinopathy and all subsequently diagnosed patients from onset of the disease, i.e., without retinopathy at baseline. This is an ongoing study with patients entering continuously over time. The evaluation of our results was conducted in May 1993. Protocol and overall follow-up procedures have remained unchanged from the beginning with two exceptions: first, glycated hemoglobin became available in 1980 and was determined at every visit from then on, and second, microalbuminuria determinations became available in 1987. The total number of patients that entered the study (i.e., the number of patients seen in our hospital during this time period) was 634. The eye fundi were studied every 1 (1–10 microaneurysms in previous examination) to 2 (no changes) years by both ophthalmoscopy and fluorescein angiography in all children >15 years of age and/or having diabetes for >5 years. A first cross-sectional analysis had indicated even minimal structural changes almost exclusively after these respective limits (10). Between 1977 and the end of this study, ~2,000 (n = 1,997) fluorescein angiographies were performed with no major side effects, averaging 4 (1–14) [median (range)] per patient after informed consent was given by the patients and/or their parents (10). For this study, absolute findings of retinopathy from baseline (manifestation of disease; no morphological changes) were evaluated in three stages of retinopathy (10): 0, no changes; 1, minimal retinopathy (1–10 microaneurysms); 2, background retinopathy, including mild (11–50 microaneurysms and <25 leakages) and more advanced preproliferative changes. Development of background retinopathy terminated the observation period for this study, and no data beyond this event was included in the analyses. Proliferative changes without prior detection of background retinopathy were found in only four individuals. For the purpose of this study, they were included in stage 2. Therefore, the correct reference to stage 2 would have to be "background retinopathy (plus)". For easier reading, the "plus" will be omitted from the remaining text.

Four hundred and four patients met the above-mentioned criteria. Patients without glycated hemoglobin determined before detection of background retinopathy were excluded from analysis. Thus, data from 346 patients (190 males, 156 females; baseline data: 9 [1–18] years of age at diabetes manifestation; diabetes duration of 0 years, no retinopathy; data at onset of background retinopathy or last evaluation with fewer retinal changes: 19.8 [8.8–35.4] years of age, diabetes duration of 10.4 [1.1–27.4] years; median [range]) were available for the evaluation of the influence of HbA_{1c} on retinopathy. Patients usually left pediatric care between 18 and 22 years of age, and the observation was terminated at this time. Because of the unique situation of being the only diabetes center in the city of West Berlin, a city politically isolated until November 1989, virtually all children with diabetes in West Berlin were referred to us. Insulin was administered at least twice daily. Multiple injection or pump regimens were carried out by only a minority of prepubertal children. Their frequency increased with age, reaching up to 60% of patients >18 years of age. The long-term glycated hemoglobin was calculated from 14,033 determinations overall, averaging 18 (1–95) per patient over the total observation period starting in 1980. To eliminate possible distribution bias by some patients with more frequent clinic visits, we calculated a mean value for every patient-year and used these means per patient-years for calculation of the overall individual mean long-term glycemic control. Thus, we obtained a representative HbA_{1c} value for every year of each patient irrespective of the number of his clinical visits. HbA_{1c} values of the 1st year of diabetes were excluded because of the possible influence of different degrees of partial remission. The individual mean for every year was calculated up to the event in question (i.e., detection of background retinopathy or latest angiography) on the average for 5 (1–14) years per patient. The variation in the number of yearly means is explained by the different duration of follow-up of the patients. For example, a patient entering the study in 1992 will have only few HbA_{1c} determinations. In the life-table analysis used in the present study, the contribution of this patient data to the overall results would be minimal.

Glycated hemoglobin was originally determined by a microcolumn method after dialysis of the labile fraction (Panchem, Kleinwallstadt, Germany). In 1990, the glycated hemoglobin technique was changed to high-performance liquid chromatography (Diamat; Bio-Rad, Munich, Germany). Extensive duplicate analyses using both methods demonstrated a correlation coefficient of r = 0.987 (HbA_{1c} [Diamat] = 0.981 × $HbA_{1stable}$ [microcolumn] − 0.572). The upper normal limit of HbA_{1c} is 6.0%. The interassay coefficient of variation was between 1.0 and 3.6%.

Data on the urinary albumin excretion (UAE) in this study population has been available since 1987. UAE was determined in timed, overnight urine samples by radioimmunoassay (Pharmacia, Uppsala, Sweden) with an upper limit of normal (98th percentile) of 15 μg/min × 1.73 m^2 (12). Of 104 patients who had at least three UAE determinations during a period of ≥4 years (54 males, 50 females; at final evaluation: 18.0 [10.4–31.5] years of age, diabetes duration of 9.4 [3.1–18.7] years) before detection of background retinopathy, 86 were found to have normoalbuminuria, and 18 were found to have microalbuminuria (≥2 elevated UAEs).

Statistical analysis

The dynamics of the development of retinopathy were evaluated by life-table analysis (13). The statistical evaluation of the event- (i.e., the occurrence of background retinopathy) free survival in various subgroups of patients (degrees of

control or UAE) was performed using the Lee-Desu statistics program applying the technique of Cutler/Ederer for interval-censored data (14). Because the fluorescein angiographies were performed in 1-year intervals, the same interval was chosen for the risk estimation. Multiple stepwise regression analysis was used to identify factors exerting independent influences on the development of background retinopathy. The actual prevalence of retinopathy and its rates per 100 patient-years in the different subgroups were compared with trend analysis (15). Differences concerning age or diabetes duration were analyzed by the Mann-Whitney rank-sum test (14).

RESULTS — Although nearly twice as many patients were included in the present analysis compared with our previous report in 1986 (10), the median expectation by life-table analysis of the total cohort for the development of minimal retinopathy after 9.1 years of diabetes and background retinopathy after 14.3 years of diabetes is virtually identical in both studies.

The development of retinal changes was significantly related to the degree of long-term glycemic control. The rate of background retinopathy rises with increasing HbA_{1c} levels from 0.7 events per 100 patient-years in the group with long-term HbA_{1c} <7% to 7.3 events per 100 patient-years when the long-term HbA_{1c} was >11%. Logarithmic regression analysis indicated that this follows an exponential relationship (Fig. 1) as described in the DCCT study. However, the exponential relationship is due to the high incidence rate of retinopathy in one subgroup, i.e., patients with long-term HbA_{1c} levels >9%.

To analyze whether this influence of glycemic control follows a continuous relationship, we subdivided the total cohort into quartiles of long-term HbA_{1c} levels of <8, 8–9, 9–10, and >10%, resulting in four groups of approximately equal sizes (Fig. 2, Table 1). Assuming a linear model, a highly significant trend for

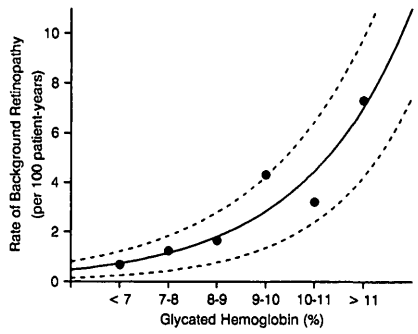

Figure 1—*Rate of development of background retinopathy per 100 patient-years in different classes of HbA_{1c}. The HbA_{1c} levels used for classification were calculated as mean HbA_{1c} of the individual annual means until the onset of background retinopathy or the latest eye exam with fewer changes (see METHODS). ●, the crude rates of background retinopathy; each corresponding to >300 patient-years. ———, a nonlinear regression following an exponential relationship between rate of retinopathy and long-term HbA_{1c} (r^2 = 0.92, P < 0.01). – – – –, the 95% confidence interval.*

the frequency of retinopathy was seen across groups (F = 37.2, P = 0.000). Interestingly, the predominant contrast was between individuals with long-term HbA_{1c} <9% and >9%, i.e., the two lower and upper quartiles (F = 41.1, P = 0.000). No contrast was found between the upper (F = 0.2, P = 0.678) or the lower quartiles (F = 0.9, P = 0.348), respectively, indicating a discontinuous relationship of control and retinopathy (Table 1). This finding was irrespective of the mode of data evaluation using either calculation of actual prevalence of background retinopathy at the time of the latest retinal examination, life-table analysis, or rates per 100 patient-years. No differences were found for diabetes duration between these four subgroups (P = 0.196).

However, glycemic control did not influence the duration of diabetes until the detection of background retinopathy, when those patients already suffering from this complication were analyzed (Fig. 3). Indeed, a significantly (P = 0.042) shorter diabetes duration until the onset of background retinopathy was found only in those four patients exhibiting long-term HbA_{1c} values >13%. In all other groups with mean HbA_{1c} levels between 6 and 13%, the median onset of background retinopathy was ~12 years, with wide variations, however, regardless of control (Fig. 3).

Furthermore, the association of microalbuminuria and background retinopathy was evaluated. For patients with microalbuminuria (n = 18), the calculated median expected onset of background retinopathy was significantly reduced from 14.7 years (in normoalbuminuric subjects [n = 86]) to 11.5 years (Fig. 4). While the chance to remain free from background retinopathy after 12 years of diabetes is <25% in patients with microalbuminuria, this figure was calculated to be 81% in those with normoalbuminuria, respectively. Stepwise multiple regression analysis for the total group of 346 patients revealed independent influences on the development of background retinopathy of glycated hemoglobin (P = 0.000) and diabetes duration (P = 0.000). About 25% of the variance (adjusted r^2 = 0.252) was explained by those factors. Other factors like age at manifestation, age at last follow-up, or gender did not contribute significantly to the ophthalmological findings. When the analysis was repeated in the subgroup of 104 patients with UAE determinations, the presence of microalbuminuria had an independent influence (P = 0.022) additional to HbA_{1c} and diabetes duration.

CONCLUSIONS — Many studies (5,16–19), including our own (3), indicate age-related factors such as diabetes duration as most important for the development of diabetic retinopathy. Our present study confirms previous reports (3,10,20,21) that early structural retinal changes can be detected by fluorescein angiography with a median probability after 9.1 years and clinically significant background retinopathy after 14.3 years of diabetes duration, respectively.

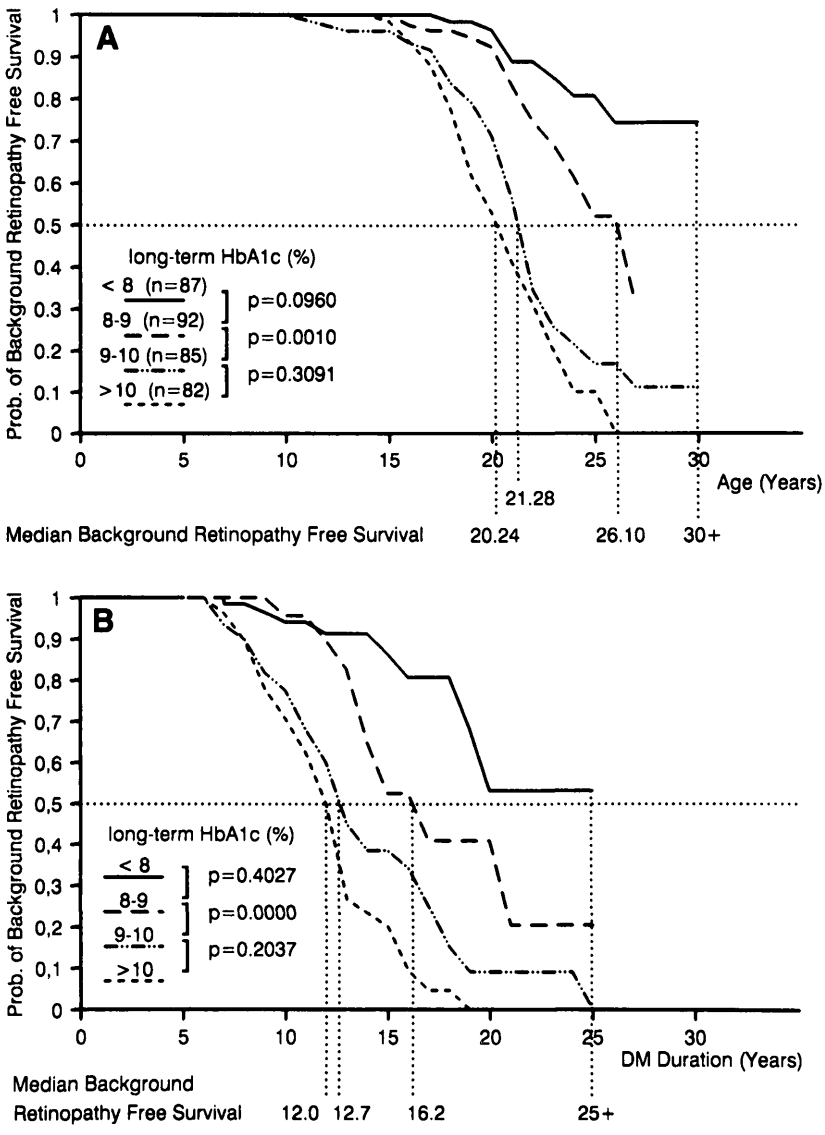

Figure 2—*Development of background retinopathy in patients achieving different degrees of long-term glycemic control (calculated as means of the individual annual mean HbA_{1c} values) regarding chronological age (A) and diabetes duration (B). For life-table analysis, statistical differences between the respective groups were calculated applying the Lee-Desu procedure. +, greater than calculated values.*

An unexpected, and somewhat intriguing, observation is our finding of a nonlinear, discontinuous relationship between long-term control and the development of background retinopathy. In HbA_{1c} quartile subgroups of the total cohort, no significant difference was found for the frequency of retinopathy between the two lower and the two higher quartiles using different methods of data analysis (Table 1). Only the difference between the second and the third quartile, i.e., between HbA_{1c} categories of 8–9 and 9–10%, was statistically significant. These findings were not influenced by potentially confounding factors, such as age or gender, which were similarly distributed in HbA_{1c} subgroups.

The overall influence of glycemic control on the frequency of retinopathy is in agreement with studies from the pre-HbA_{1c} era (22), as well as with cross-sectional studies (16,19), short-term (2–6 years) longitudinal studies (5–8), and the recent DCCT study (1). However, the DCCT study reports a continuous increase of the risk for retinopathy with higher HbA_{1c} levels in the group of patients with intensive treatment regimens. If the rates of background retinopathy during the 3,264 patient-years in the Berlin Retinopathy Study are calculated, a similar curve can be constructed from the present data (Fig. 1). According to this mode of statistical analysis, both studies strongly suggest that an exponential model may explain the relationship between glycemic control and risk for retinopathy. Also, in the DCCT, the published crude rates for the HbA_{1c} percentiles increased two- to three-fold between deciles of 8 and >9% (1), notwithstanding that the outcome measures of the DCCT study (≥3 step progression using photographic analysis of seven fundus fields) and the Berlin Retinopathy Study (detection of early background retinopathy by fluorescein angiography) are different. This trend of a nonlinear, steeper increase with HbA_{1c} levels >9% may be augmented in the present study by the higher prevalence of patients with poor glycemic control in our unselected cohort, compared with the well-controlled DCCT study population on intensified insulin regimens. Only 10% of the DCCT patients of Fig. 5*A* (1) had long-term control >9% (their last decile), while 167 of 346 (48%) of the Berlin patients met these criteria.

Also, however, the findings suggesting a threshold level are consistent with some other studies. Janka et al. (17) reported a substantial increase in the relative odds for a rapid progression from background to proliferative retinopathy after 4 years when the baseline HbA_{1c} was >9% but also suggested an exponential relationship. Klein et al. (23) found in their group of younger-onset patients (<30 years of age) similar 4-year incidences of proliferative retinopathy in the

Table 1—*Influence of long-term glycemic control on the development of background retinopathy*

HbA_{1c} category (%)	Prevalence		Life-table analysis		Retinopathy rate per 100 patient-years	
	n	*P*	*n*	*P*	*n*	*P*
≤8.0	9/87		25.0*		1.03	
		0.348		0.403		0.441
8.1–9.0	15/92		16.2		1.64	
		0.000		0.000		0.001
9.1–10.0	35/85		12.7		4.31	
		0.678		0.204		0.213
>10.0	36/82		12.0		5.40	
		0.000†		0.000†		0.000†

Data are *n* and *P* values. Prevalence is the absolute number of affected patients. Life-table analysis is the median expected onset in years of diabetes duration. Each HbA_{1c} quartile subsumes between 667 and 914 patient-years. *Median values greater than the calculated figures; †test for linear trend across all groups.

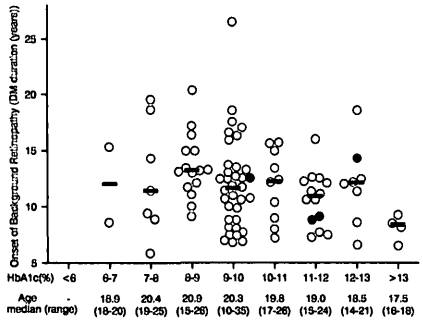

Figure 3—*Actual intervals (y-axis) between diabetes manifestation and the diagnosis of background retinopathy in patients achieving different levels of long-term glycemic control (calculated as means of the individual annual mean HbA_{1c} values). Each circle represents one patient whose background retinopathy has been determined by fluorescein angiography. In four patients (●), this event was missed and proliferative retinopathy was diagnosed without prior detection of background retinopathy.* ■, *the median onset of background retinopathy for each group. Medians and ranges for the chronological age at diagnosis of retinopathy are indicated for every subgroup. Except for the group with long-term HbA_{1c} values >13%, no statistical differences were seen between the groups with respect to age or diabetes duration (see text).*

two lower quartiles of glycated hemoglobin (relative risk 1.0 and 2.7, respectively), representing approximately half of the total population, followed by a notable increase in the third quartile (14.8), possibly describing a similar threshold phenomenon. However, in contrast to our study, only the glycated hemoglobin value at baseline was evaluated in their study, and no threshold was apparent for the incidence of newly developed retinopathy or the 4-year two-step progression (23). Roe et al. (24) demonstrated a significantly higher albumin excretion in adolescents with diabetes, exhibiting a mean HbA_{1c} level >9.0% during a period from 1 to 6 years. In the present study, microalbuminuria was associated with a reduced median background retinopathy-free survival, thereby further supporting the previously described close association of both vascular complications (22,25). Whether a similar nonlinear relationship exists for the development of proliferative retinal changes, nephropathy, or other neurovascular sequelae in children with diabetes remains to be elucidated.

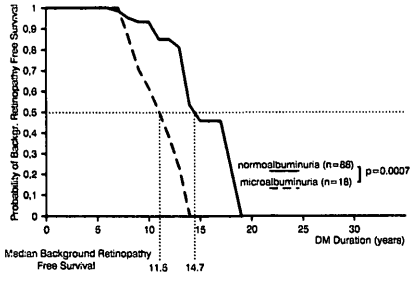

Figure 4—*Life-table analysis for diabetes duration until the development of background retinopathy in patients with normoalbuminuria and microalbuminuria. A subgroup of patients with a chronological age of ≥15 years and/or a diabetes duration of ≥5 years was analyzed when ≥3 UAE determinations had been performed over a period of ≥4 years. Microalbuminuria was diagnosed when ≥2 elevated UAEs were found.*

The second surprising finding was of glycemic control not influencing the actual latency period between the manifestation of diabetes and onset of background retinopathy. At first sight, the present calculations by life-table analysis would argue against this, because of a significantly increased median probability to develop background retinopathy earlier with poor or even fair control (Fig. 2). However, by definition, life-table analysis is event-oriented, meaning that the expected median survival is exclusively determined by the number of terminal events. In the context of this study, it is the smaller number of events, i.e., fewer manifestations of background retinopathy, in groups with better control that leads to the calculation of significantly longer expected latency periods in years of diabetes duration. However, when the prevalence of already existing background retinopathy is analyzed with regard to long-term glycemic control (Fig. 3), no difference in the actual intervals between diabetes manifestation and the onset of background retinopathy is observed with low or high long-term mean HbA_{1c} values. However, a later onset of background retinopathy would have to be expected, especially in the groups with better long-term control. Therefore, such analysis is especially vulnerable to small differences in the duration of follow-up present in our study. Nevertheless, it may be speculated that

poor control may determine a greater number of susceptible individuals to develop this complication. Whether or not this susceptibility is genetically determined, or long-term poor control merely overruns otherwise existing compensatory mechanisms, remains speculative (2,25).

Based on our data, two models are appropriate to explain the relationship between control and background retinopathy. Therefore, both models have to be proposed for discussion. From a statistical point of view, it is sufficient to find one model approximately explaining a given relationship. However, from a clinician's perspective, the question remains: if interventions for improvement of glycemic control lead to a constant rate of change in the eventual outcome or if achieving a cutoff point of control may lead to a dramatic change in the outcome (9). Our results are meant to provoke the thought of other models that may be appropriate to explain these relationships in a clinically relevant fashion.

Indeed, our study in children and adolescents confirms the close association between degree of control and retinopathy described in the DCCT study for adolescents and adults with IDDM. Even if lowering the HbA_{1c} to <9% has a more dramatic impact in risk reduction, every progress closer to normal may further reduce the risk. In fact, the benefits described in the DCCT study were observed with an average HbA_{1c} of 7.2% compared with 9.0% in the conventionally treated group (1). Several additional somatic and psychosocial factors, possibly even unrelated to the primary metabolic derangement, have to be suspected to contribute to the susceptibility for complications of an individual child or adolescent with diabetes. This makes a risk assessment based solely on glycated hemoglobin values questionable in pediatric care. Still, until better means of therapeutic approaches are found, this study supports the clinical recommendations (26–28) to achieve the best possible degree of long-term glycemic control for an individual patient with minimal risk for (and fear of) severe hypoglycemia. Every attempt should be made to keep the long-term HbA_{1c} level below 9%.

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