Effect of Intensive Therapy on the Microvascular Complications of Type 1 Diabetes Mellitus

The Writing Team
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The purpose of this report is to summarize and integrate the findings of the Diabetes Control and Complications Trial (DCCT), a randomized controlled clinical trial, and the succeeding observational follow-up of the DCCT cohort in the Epidemiology of Diabetes Interventions and Complications (EDIC) study, regarding the effects of intensive treatment on the microvascular complications of type 1 diabetes mellitus. The DCCT proved that intensive treatment reduced the risks of retinopathy, nephropathy, and neuropathy by 35% to 90% compared with conventional treatment. The absolute risks of retinopathy and nephropathy were proportional to the mean glycosylated hemoglobin (HbA_{1c}) level over the follow-up period preceding each event. Intensive treatment was most effective when begun early, before complications were detectable. These risk reductions, achieved at a median HbA_{1c} level difference of 9.1% for conventional treatment vs 7.3% for intensive treatment have been maintained through 7 years of EDIC, even though the difference in mean HbA_{1c} levels of the 2 former randomized treatment groups was only 0.4% at 1 year ($P<.001$) (8.3% in the former conventional treatment group vs 7.9% in the former intensive treatment group), continued to narrow, and became statistically nonsignificant by 5 years (8.1% vs 8.2%, $P=.09$). The further rate of progression of complications from their levels at the end of the DCCT remains less in the former intensive treatment group. Thus, the benefits of 6.5 years of intensive treatment extend well beyond the period of its most intensive implementation. Intensive treatment should be started as soon as is safely possible after the onset of type 1 diabetes mellitus and maintained thereafter, aiming for a practicable target HbA_{1c} level of 7.0% or less.

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THE MICROVASCULAR COMPLICATIONS of type 1 diabetes mellitus were rarely noted prior to the discovery of insulin.[1] The introduction of insulin therapy allowed patients to live long enough to develop diabetic retinopathy and diabetic nephropathy.[2] A long-standing debate ensued as to whether these complications were caused by the metabolic abnormalities of diabetes, in particular hyperglycemia, and whether they could therefore be prevented or at least significantly moderated by improved blood glucose control.[3-6] Although a body of observational evidence and experimental animal evidence incriminated hyperglycemia,[7] small randomized controlled trials conducted in the 1970s and early 1980s failed to conclusively prove the validity of the so-called glucose hypothesis.[7]

In 1975, the National Commission on Diabetes recommended to Congress that a randomized controlled trial be conducted with the power to test the glucose hypothesis definitively. Once the ability was achieved to maintain near normal glycemia with multiple daily injections of insulin or continuous subcutaneous insulin infusion, to monitor chronic integrated glucose levels with glycosylated hemoglobin (HbA_{1c}), and to assess quantitatively retinopathy and nephropathy noninvasively, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) initiated a trial in 1982. After 1 year of protocol development by the study investigators,[8] the Diabetes Control and Complications Trial (DCCT) began recruiting subjects in

A complete list of the Diabetes Control and Complications Trial Research Group appears in *N Engl J Med.* 1993;329:977-986. **A complete list of the Epidemiology of Diabetes Interventions and Complications Research Group** appears in *Diabetes Care.* 1999;22:99-111.

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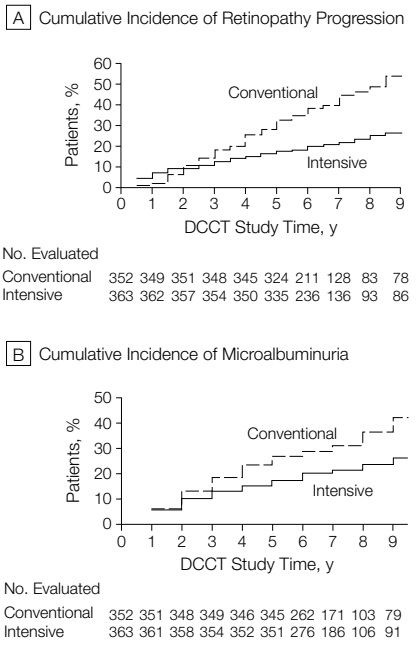
Table 1. Baseline Characteristics of DCCT/EDIC Cohort of Type 1 Diabetic Patients*

Characteristic	Primary Prevention		Secondary Intervention	
	Conventional (n = 378)	Intensive (n = 348)	Conventional (n = 352)	Intensive (n = 363)
Age, mean (SD), y	26 (8)	27 (7)	27 (7)	27 (7)
Female	172 (46)	176 (51)	163 (46)	169 (47)
Diabetes duration, mean (SD), y	2.6 (1.4)	2.6 (1.4)	8.6 (3.7)	8.9 (3.8)
HbA_{1c}, mean (SD), %	8.8 (1.7)	8.8 (1.6)	8.9 (1.5)	9.0 (1.5)
Microaneurysms only	0	0	204 (58)	243 (67)
Mild NPDR	0	0	81 (23)	65 (18)
Moderate NPDR	0	0	67 (19)	55 (15)
Urinary AER, mean (SD), mg/d	12 (8)	12 (9)	19 (24)	21 (25)

*Data are No. (%) unless otherwise indicated. DCCT indicates Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications; HbA_{1c}, glycosylated hemoglobin; NPDR, nonproliferative diabetic retinopathy; and AER, albumin excretion rate. Data from The DCCT Research Group.[9]

Figure 1. Comparison of Conventional and Intensive Therapy in Cumulative Incidence of Retinopathy Progression and Microalbuminuria Secondary Intervention Cohorts



Modified from The DCCT Research Group.[9] Cumulative incidence of sustained 3-step progression of 2 cohorts of the Diabetes Control and Complications Trial (DCCT). A, The Early Treatment Diabetic Retinopathy Study scale cohort (conventional vs intensive, $P<.001$). B, The development of microalbuminuria cohort (conventional vs intensive, $P=.001$).

1983. By the close of enrollment in 1989, 1441 participants ages 13 to 39 years, including adolescents ages 13 to 18 years, with baseline characteristics detailed in TABLE 1 were enrolled.[9] The participants included 726 patients with no evidence of retinopathy and a urine albumin excretion rate (AER) of less than 40 mg/d in a primary prevention cohort and 715 patients with mild to moderate retinopathy (no more than a grade of 47/47 on the Early Treatment Diabetic Retinopathy Study [ETDRS] final scale) and AER of less than 200 mg/d in a secondary intervention cohort. Only 10% of the latter had AER of 40 to 199 mg/d. The primary and secondary cohorts were each randomized to either intensive treatment (3-4 injections of insulin or continuous subcutaneous insulin infusion and 4 self-monitored blood glucose tests daily) or conventional treatment (1-2 injections of insulin and either home urine glucose testing several times per day, or later in the study, self blood glucose testing once per day).

Summary of Salient DCCT Results

The DCCT ended in 1993, after a mean duration of follow-up of 6.5 years.[9] The salient results for the secondary intervention cohort are shown in FIGURE 1. Intensive treatment (median HbA_{1c}, 7.3%) compared with conventional treatment (median HbA_{1c}, 9.1%) reduced the progression of retinopathy (3-step increase on the ETDRS scale) by 76% in the primary prevention cohort and by 54% in the secondary intervention cohort.[9,10] Patients in the primary prevention cohort with duration of diabetes of less than 2.5 years at entry into the trial had 89% reduction in the risk of retinopathy compared with 70% in patients with duration of more than 2.5 years ($P<.001$).[11]

Epidemiological analysis of the DCCT data demonstrated a strong exponential relationship between the risk of retinopathy and the mean HbA_{1c} measured quarterly in the trial.[12] For each 10% decrease in HbA_{1c}, such as from 9.0% to 8.1% or from 8.0% to 7.2%, there was a 39% decrease in risk over the range of HbA_{1c} values.[12] The overall risk gradients were very similar in the 2 treatment groups and statistically indistinguishable.[12] This provided strong supporting evidence that intensive treatment decreased the risk of retinopathy by lowering blood glucose. Additional analyses also revealed no glycemic threshold at which the risk of retinopathy was eliminated above the nondiabetic range of HbA_{1c} (4.0%-6.05%).[13] Although the absolute risk of retinopathy was relatively low in the lower end of the diabetic HbA_{1c} range, reduction of HbA_{1c} at all diabetic levels further decreased the risk. The risk of retinopathy at any mean HbA_{1c} level also increased with the duration of follow-up during the DCCT (FIGURE 2).[12] For example, the same risk of retinopathy was reached within 2.5 years at an HbA_{1c} level of 11% as was reached in 9 years at an HbA_{1c} level of 8% (Figure 2). Both degree and duration of glycemic exposure are important determinants of the risk of retinopathy.

The appearance and progression of diabetic nephropathy was assessed by yearly measurement of AER and creatinine clearance. Intensive treatment had a similar beneficial effect on diabetic nephropathy as it had on retinopathy (Figure 1B).[9,14] In the combined cohorts, intensive treatment decreased the development of microalbuminuria (defined in 1982 by the DCCT as 40–299 mg/d) by 39% and the development of clinical albuminuria (≥300 mg/d) by 56%. As was the case for retinopathy, the risk of developing nephropathy was exponentially related to the mean HbA_{1c}.[13] For each 10% decrease in HbA_{1c}, there was a 25% de-

crease in the risk of microalbuminuria.[13] No glycemic threshold for nephropathy was detected above the nondiabetic range of HbA_{1c} by any form of modeling of the data.[13] The DCCT found no influence of intensive treatment on glomerular filtration rate, as measured by iodine 125 (^{125}I)-iothalamate clearance, or creatinine clearance.[14] However, these values remained within the normal range for most subjects during the DCCT.

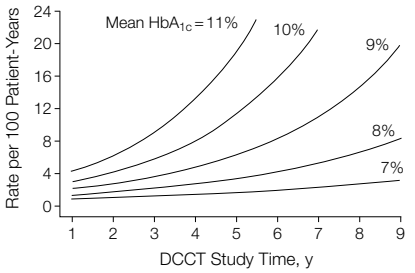
Neuropathy, whether assessed by a neurologist's standardized clinical examination, nerve conduction studies, or autonomic nerve function testing, was also benefited by intensive treatment.[15-17] At 5 years of DCCT follow-up, the prevalence of confirmed clinical neuropathy in those without this complication at study baseline was reduced by 69% and 57% in the primary and secondary cohorts, respectively.[9]

In addition to these direct effects, intensive therapy had other effects that indirectly benefited complications. Intensive treatment preserved endogenous insulin secretion, assessed by stimulated plasma C-peptide levels, compared with conventional treatment; the risk of losing C-peptide responses to stimulation was reduced 57% by intensive treatment.[18] Intensively treated patients with preserved insulin secretion had 35% and 23% reductions in risk of retinopathy and nephropathy, respectively, and 65% reduction in risk of severe hypoglycemia, compared with those devoid of detectable endogenous insulin secretion.[18]

Transition From the DCCT to the Epidemiology of Diabetes Interventions and Complications

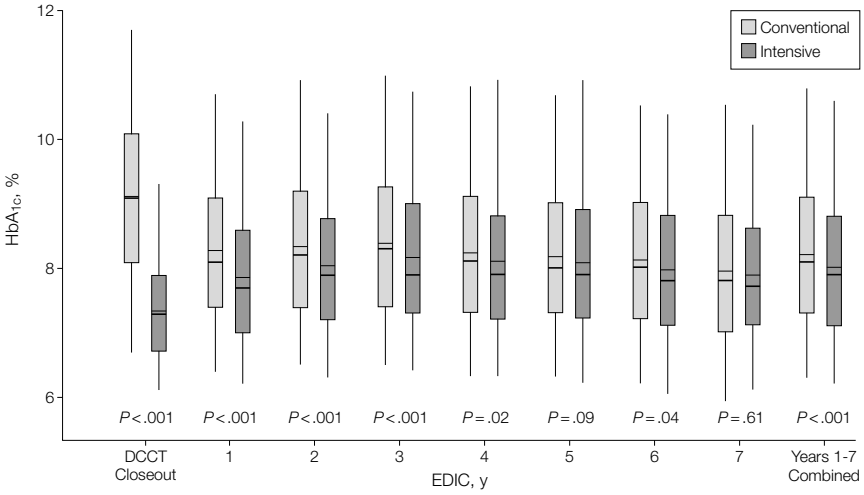
The randomized controlled clinical trial phase of the DCCT was stopped prematurely after a mean follow-up time of 6.5 years, when the benefits of intensive treatment were deemed incontrovertible by the data safety and quality committee and highly unlikely to be reversed with time. Participants who had been assigned to intensive treatment were encouraged to continue, and participants originally assigned to conventional treatment were advised to change to intensive treatment. They were provided the opportunity to implement intensive treatment with NIDDK resources and DCCT staff during a closeout period. Within a year, the observational phase of the DCCT/Epidemiology of Diabetes Interventions and Complications (EDIC) study commenced.[19] A total of 1375 of the DCCT subjects (95%) (half from each treatment group) volunteered to participate in EDIC. A total of 1294 to 1335 patients have been examined annually in the EDIC clinics with structured interviews to determine diabetes treatment regimens and HbA_{1c} has been measured centrally using the DCCT assay. One fourth of the cohort has fundus photographs annually and one half has measurement of albumin excretion rate, serum creatinine, and creatinine clearance annually. At the end of EDIC year 1, 95% of the former intensive treatment group and 75% of the former conventional treatment group reported that they were using intensive treatment (as defined above) and had mean HbA_{1c} levels of 7.9% and 8.3%, respectively (FIGURE 3). The HbA_{1c} levels converged further and have remained similar during the ensuing 7 years. The overall mean HbA_{1c} levels for the entire EDIC follow-up thus far are 8.3% for the former conventional treatment group and 8.1% for the former intensive treatment group. The percentage of

Figure 2. Risk of Retinopathy Progression vs Mean Glycosylated Hemoglobin (HbA_{1c}) and Time in Study Conventional Treatment Group



Reprinted with permission from *The American Diabetes Association*.[12] Absolute risk of retinopathy progression as a function of the updated mean HbA_{1c} during the study and the follow-up time estimated from a Poisson model in the conventional treatment group of the Diabetes Control and Complications Trial (DCCT).

Figure 3. Distribution of Glycosylated Hemoglobin (HbA_{1c}) According to Original Diabetes Control and Complications Trial (DCCT) Treatment Assignment at DCCT Closeout and in Each Epidemiology of Diabetes Interventions and Complications (EDIC)



The box plots represent the 2nd and 3rd quartiles of the distribution; the heavy horizontal lines, the medians; the thin horizontal lines, the means; and the whiskers, the 5th and 95th percentiles. *P* values are from Wilcoxon rank sum test.

former conventional treatment patients using intensive treatment has risen to 83% at 7 years. At the seventh annual examination, 27% of former conventional treatment group and 41% of former intensive treatment group participants are using continuous subcutaneous insulin infusion, while 44% and 49% of these respective treatment groups report that they are self-monitoring blood glucose at least 4 times per day.

Summary of EDIC Results

During EDIC, similar application of therapy and similar HbA_{1c} levels in the 2 originally randomized treatment groups has permitted study of the long-term impact of the significant glycemic differences that did exist during the DCCT. The results of such intention-to-treat analyses after 4 years of EDIC have been reported[20] and are intriguing. With regard to retinopathy, the reduction in risk observed with intensive treatment at the DCCT closeout examination was the same or greater after 4 years of EDIC; the benefit derived from intensive therapy did not wane.[20] In analyses using the DCCT closeout examination as a new baseline state for EDIC, further progression of retinopathy during the first 4 years of EDIC was 66% to 77% less in the former intensive group than in the former conventional group by all measurements used (TABLE 2).[20] The benefit is particularly significant because it included an effect on severe degrees of retinopathy. Significantly fewer former intensive group patients than former conventional group patients have required photocoagulation therapy during EDIC to preserve vision. The decrease in HbA_{1c} from about 9% to approximately 8% has not dramatically reduced the progression of retinopathy in the former conventional treatment group; nor has the increase in HbA_{1c} from about 7% to approximately 8% dramatically accelerated retinopathy in the former intensive treatment group. Even after 7 years of EDIC follow-up, the cumulative incidence of further 3-step progression on the ETDRS scale from the level at the end of the DCCT is still significantly less in the former intensive treatment group than in the former conventional treatment group (FIGURE 4).

The course of nephropathy in the 2 former DCCT treatment groups has mimicked that of retinopathy in the initial 4 years of EDIC (Table 2).[20] The development of microalbuminuria and albuminuria in those without these nephropathic outcomes at DCCT closeout were 53% and 86% reduced, respectively. Moreover, at the fifth- and sixth-year examination of 1298 EDIC participants, the prevalence of microalbuminuria in those without it at DCCT closeout remains less in the former intensive treatment group than conventional treatment group (4.5% vs 12.3% for a risk decrease of 67%; $P<.001$). In subjects with either normal albuminuria or microalbuminuria at DCCT closeout, the risk reduction in subsequent development of clinical albuminuria (≥300 mg/d) in the former intensive treatment group was 84% ($P<.001$). Furthermore, using an aggregate end point of serum creatinine (2.0 mg/dL [176.8 µmol/L]), chronic dialysis therapy, or renal transplantation, only 6 of the original intensive treatment group vs 17 of the original conventional group have reached that outcome. Hypertension is an almost invariable important consequence of diabetic nephropathy. While there was no treatment group difference in the prevalence of hypertension observed at the end of the DCCT (12% in the conventional group vs 11% in the intensive group), by 6 years in EDIC the prevalence of hypertension in the conventional group has become significantly greater than in the intensive group (33% vs 25%, $P<.001$).

Table 2. Incidence of Worsening of Retinopathy Between the End of the DCCT and After 4 Years of the EDIC Study*

	No. of Patients	No. (%) of Patients Who Progressed	Adjusted Odds Reduction, % (95% CI)	*P* Value
Retinal Change				
3-Step progression from no retinopathy				
Conventional therapy	109	18 (16)	66 (26-84)	.006
Intensive therapy	173	11 (6)		
Severe nonproliferative retinopathy or worse				
Conventional therapy	556	53 (10)	76 (52-88)	<.001
Intensive therapy	589	11 (2)		
Proliferative retinopathy				
Conventional therapy	564	48 (9)	74 (46-87)	<.001
Intensive therapy	590	10 (2)		
Clinically significant macular edema				
Conventional therapy	564	45 (8)	77 (52-89)	<.001
Intensive therapy	582	9 (2)		
Laser therapy (focal or scatter)				
Conventional therapy	544	35 (6)	77 (45-91)	.002
Intensive therapy	575	6 (1)		
Renal Change				
Microalbuminuria†				
Conventional therapy	573	63 (11)	53 (26-70)	.002
Intensive therapy	601	31 (5)		
Albuminuria‡				
Conventional therapy	637	33 (5)	86 (60-95)	<.001
Intensive therapy	639	4 (1)		

*DCCT indicates Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications; and CI, confidence interval. Data from The DCCT/EDIC Research Group.[20]
†Albumin excretion rate (AER) was 40 to 299 mg/d in participants with AER of less than 40 mg/d at DCCT closeout examination.
‡The AER was 300 mg/d or more in participants with AER of less than 300 mg/d at DCCT closeout examination.

Comment

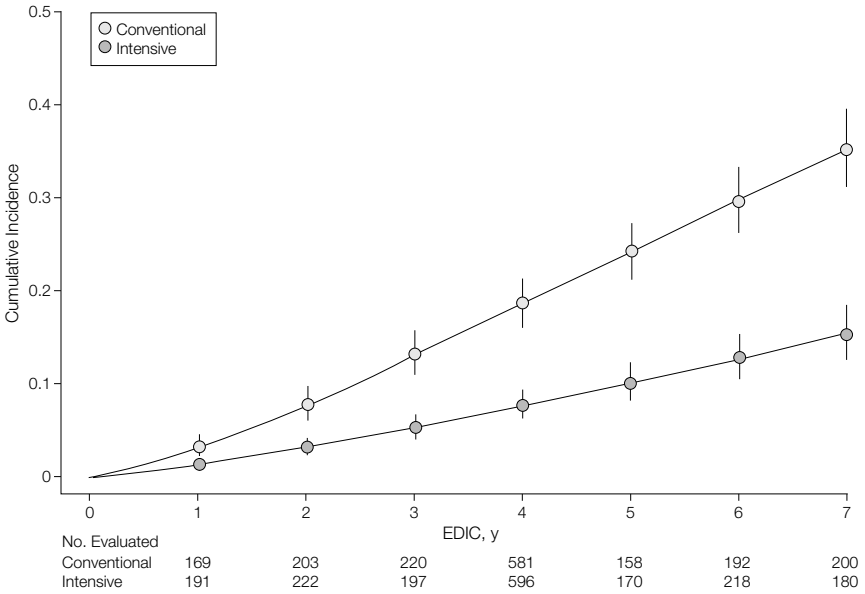
The overall DCCT/EDIC results consistently demonstrate that the delete-

rious microvascular effects of hyperglycemia, as evidenced by retinopathy and nephropathy, persist for a considerable period after glucose levels have decreased. Moreover, the benefits of intensive therapy may persist beyond the period of strictest intervention. Taken together, the long-term benefits of DCCT intensive therapy when compared with conventional therapy have persisted and increased further during EDIC follow-up. The EDIC observations are also consistent with earlier observations made during the DCCT period of study. The entry level of HbA_{1c} at DCCT baseline was identified as a risk factor for the subsequent development of retinopathy during the DCCT.[12] Moreover, although the mean HbA_{1c} levels of the 2 DCCT treatment groups reached their maximum separation by 6 months postrandomization, it took 3 to 4 years of different treatment regimens with separation of HbA_{1c} levels by 2.0%, before the cumulative incidence curves of retinopathy and nephropathy in the intensive treatment and conventional treatment groups began to diverge distinctly (Figure 1).[9] In the case of retinopathy, this delay may partly be accounted for by the phenomenon of early worsening that occurred during the first 6 to 12 months of intensive therapy in 13% of the DCCT patients.[21] These findings indicate that hyperglycemia has long-term chronic effects on the underlying pathophysiolgy of microvascular complications, not acute effects. It takes time for improvements in control to negate the long-lasting effects of prior prolonged hyperglycemia, and once the biological effects of prolonged improved control are manifest, the benefits are long-lasting.

What is the overall biological significance of the continued beneficial effect of DCCT intensive treatment during the subsequent 6 years of EDIC? Assuming that the predictive association of risk of retinopathy with the preceding mean HbA_{1c} level over time (Figure 2) reflects a causal relationship, then the total glycemic exposure of a diabetic patient will determine the degree of retinopathy observed at any one time,[12,22] and better than the most recent glycemic exposure. Our observations suggest a mechanism whereby damage from hyperglycemia may compound itself over time (ie, that the absolute rate of progression will be proportional at any time to the amount of retinopathy already present at that time). If so, the difference in the degree of compounding and the net retinopathic damage produced in the groups previously maintained for 6.5 years during the DCCT at 2 very different HbA_{1c} levels would not be expected to dissipate quickly after the glycemic exposure levels came much closer together during EDIC. If this interpretation is correct, then the DCCT intensive treatment for 6.5 years will only delay the natural progression of microvascular complications associated with conventional therapy and a mean HbA_{1c} level of 9%. The cumulative incidence of retinopathic and nephropathic events in the 2 former treatment groups will ultimately begin to converge though never completely equalize, if their mean HbA_{1c} levels remain similar. It is also possible that introduction of DCCT intensive treatment early in the course of type 1 diabetes mellitus (average duration of diabetes at DCCT baseline was 5.5 years [Table 1]) disrupted the pathogenic process at a critical time. Specifically, maintenance of a mean HbA_{1c} level of 7.0% during the early years may have disrupted the pathogenic process for enough time to slow the rate of progression indefinitely, compared with that of individuals in whom a greater momentum of microvascular complications was maintained by a mean HbA_{1c} level of 9.0% over the same DCCT time period. Clearly, further long-term follow-up will be needed to shed more light on the meaning of these combined DCCT/EDIC observations.

In any case, these observations should stimulate even greater efforts to under-

Figure 4. Estimated Cumulative Incidence of Progression of Retinopathy 3 Steps on the ETDRS Scale From the Level at DCCT Closeout Over 7 Years of EDIC



ETDRS indicates Early Treatment Diabetic Retinopathy Study; DCCT, Diabetes Control and Complications Trial; and EDIC, Epidemiology of Diabetes Interventions and Complications. At each EDIC year, approximately one fourth of the treatment groups were examined by fundus photography, except for year 4 when approximately 85% were examined. Risk reduction with intensive therapy is 62% (95% confidence interval, 51%-70%; $P<.001$). The curves show the cumulative incidences estimated by a proportional hazards regression model for interval-censored event times that are assumed to follow an underlying Weibull distribution. Error bars represent 95% confidence intervals.

stand the pathogenesis of microvascular complications. There is no doubt that hyperglycemia is critically involved, but the exact mechanisms remain uncertain. Numerous good candidate mechanisms have been unearthed.[23] These include the formation of advanced glycation end products (AGEs); increases in reactive oxygen species; increased activation of protein kinase C with its multiple possible consequences; excess formation of polyols, such as sorbitol; local excess or deficiency of nitric oxide; overproduction of various growth factors; and interactions among all of these. It is still unclear whether the same pathophysiology underlies all the long-term complications.

The DCCT provided some support for a pathophysiologic mechanism involving AGEs. In a DCCT ancillary cross-sectional study, the risk of retinopathy and nephropathy complications was associated with the level of AGEs in skin collagen.[24] The level of AGEs was lower in participants who had been assigned to intensive treatment than in those assigned to conventional treatment. Furthermore, the association between complications and AGEs was independent of HbA_{1c} levels and AGEs explained at least as much of the variance in the risk of complications as did HbA_{1c} levels.[24] The specific AGEs measured, pentosidine and carboxymethyllysine, have relatively long half-lives and the collagen had altered physicochemical properties.[24] Structural and functional consequences of AGEs that may underlie various complications, and their persistent or even compounding effects, could explain how the damage produced by a given degree of hyperglycemia might outlast the presence of that degree of hyperglycemia.

Regardless of the mechanism, the combined DCCT/EDIC results provide a firm basis for clinical guidelines in the treatment of type 1 diabetes mellitus. The greater benefit of intensive treatment in patients of the primary prevention cohort, with shorter duration of disease and the potential to preserve endogenous insulin secretion, support early implementation and continuation of intensive therapy aimed at maintaining near normal glycemia. The persistent benefit afforded by intensive treatment, even into a period of less intensive treatment, should not be interpreted to mean that intensive treatment need only be given for a limited period of time because, as noted above, the effect may be only one of delay rather than elimination of the risk of complications.

The more time patients are exposed to chronically elevated plasma glucose levels, reflected in elevated HbA_{1c}, the greater their risk of microvascular complications (Figure 2). Conversely, the longer patients can maintain a target HbA_{1c} level of 7.0% or less, which is achievable with current methods, the greater their protection from those complications. However, using intensive treatment regimens[25] that are still current led to a 3-fold increase in severe hypoglycemic events[9,26,27] and to excess weight gain in the DCCT.[28] Clearly, improvements in methods for achieving glycemic control are still needed. In the interim, every effort must be made to eliminate preventable severe hypoglycemic episodes that result from unsafe patient behavior and decisions, and to avoid inordinate weight gain. Irregular food intake, failure to check blood glucose before planned or unplanned vigorous exercise or before operating a motor vehicle, and excess alcohol ingestion have been identified as risk factors for hypoglycemia[29] and serious sequelae and must be scrupulously avoided. Mealtime bolus doses of rapid acting insulin must be based on the preinjection blood glucose level and the anticipated amount of carbohydrate intake and upcoming exercise. Thorough diabetes education and its regular reinforcement should be provided by diabetes nurse and dietitian educators. These professionals can negotiate individualized care plans with patients, give them training in self-management, and provide stimulation, motivation, and positive reinforcement for good self-care behavior, such as frequent self blood glucose monitoring and regular eating habits. While these measures can interfere with patients' lifestyles, they are the current price that must be paid to delay or reduce the risk of microvascular complications until truly physiologic insulin delivery becomes available.

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Books are not absolutely dead things, but do contain a potency of life in them to be as active as that soul was whose progency they are; nay they do preserve as in a vial the purest efficacy and extraction of that living intellect that bred them.
—John Milton (1608-1674)