Understanding Metabolic Memory: The Prolonged Influence of Glycemia During the Diabetes Control and Complications Trial (DCCT) on Future Risks of Complications During the Study of the Epidemiology of Diabetes Interventions and Complications (EDIC)

*John M. Lachin[1] and David M. Nathan,[2] on behalf of the DCCT/EDIC Research Group**

Diabetes Care 2021;44:2216–2224 | https://doi.org/10.2337/dc20-3097

The Diabetes Control and Complications Trial (DCCT, 1983–1993) showed that intensive therapy (mean HbA_{1c} 7.2%) compared with conventional therapy (mean HbA_{1c} 9.0%) markedly reduced the risks of retinopathy, nephropathy, and neuropathy, and these reductions in complications were entirely attributable, statistically, to the difference in mean HbA_{1c} levels. The DCCT cohort has been followed in the Epidemiology of Diabetes Interventions and Complications (EDIC) study (1994 to date). Early in EDIC, mean HbA_{1c} levels in the former intensively and conventionally treated groups converged. Nevertheless, the beneficial effects of DCCT intensive versus conventional therapy on microvascular complications not only persisted but increased during EDIC. The differences in complications during EDIC were wholly explained, statistically, by differences between groups in HbA_{1c} levels during DCCT. These observations give rise to the concept of metabolic memory. Subsequent similar findings from the UKPDS gave rise to a similar concept, which they called the legacy effect. In this report, we present the evidence to support metabolic memory as both a biological and epidemiological phenomenon and discuss potential underlying mechanisms. We also compare metabolic memory and the legacy effect and conclude that the two are likely biologically similar, with comparable effects on long-term outcomes. The long-term influence of metabolic memory on the risk of micro- and macrovascular complications supports the implementation of intensive therapy, with the goal of maintaining near-normal levels of glycemia, as early and as long as safely possible in order to limit the risk of complications.

The Diabetes Control and Complications Trial (DCCT) (1983–1993) (1) provided a comprehensive study of type 1 diabetes complications and their relationship with

[1]*Biostatistics Center, The George Washington University, Rockville, MD*
[2]*Massachusetts General Hospital Diabetes Center, Harvard Medical School, Boston, MA*

Corresponding author: John M. Lachin, jml@bsc.gwu.edu

Received 21 December 2020 and accepted 16 May 2021

Clinical trial reg. nos. NCT00360893 and NCT00360815, clinicaltrials.gov

This article contains supplementary material online at https://doi.org/10.2337/figshare.14611245.

**A complete list of the members of the DCCT/EDIC Research Group can be found in N Engl J Med 2017;376:1507–1516.*

This article is part of a special article collection available at https://care.diabetesjournals.org/collection/long-term-effects-of-earlier-glycemic-control.

See accompanying articles, pp. 2212, 2225, and 2231.

levels of glycemia. The DCCT, a randomized controlled trial, tested the "glucose hypothesis" that hyperglycemia is a direct cause of the development and progression of microvascular complications. Over its mean 6.5 years of therapy, the DCCT convincingly demonstrated that intensive treatment, which achieved glycemic levels as close to the nondiabetic range as safely possible (i.e., HbA_{1c} ~7%), reduced the risks of development and progression of early stages of retinopathy, nephropathy, and neuropathy by 34%–76%, compared with conventional treatment with its attendant higher levels of glycemia (HbA_{1c} ~9%) (1). The risk for microvascular complications was strongly associated with HbA_{1c} levels during DCCT, and the reduction in complications with intensive versus conventional therapy was entirely attributable to the separation between the two treatment groups in mean HbA_{1c} levels (2–4).

The DCCT was followed by the Epidemiology of Diabetes Interventions and Complications (EDIC) observational study of the DCCT cohort (1994 to date) (5). During EDIC, HbA_{1c} levels of the former randomly assigned DCCT treatment groups rapidly converged, yet the beneficial effects of prior DCCT intensive versus conventional treatment on diabetes complications persisted and even increased (6–8). This gave rise to the concept named "metabolic memory" (8) in which a prior period of hyperglycemia increases the long-term risk of complications. Conversely, a period of near-normal glycemia produces long-term beneficial effects on complications, with such effects persisting even though subsequent levels of glycemia may have risen.

Approximately 5 years following the initial observation of metabolic memory, the UK Prospective Diabetes Study (UKPDS) described a similar long-term benefit of former intensive versus conventional therapy in type 2 diabetes that was referred to as a "legacy effect" (9). There are subtle differences in the way that the two terms have been applied.

Herein, we review the salient evidence supporting the phenomenon of metabolic memory, describing the role of glycemia over time in the emergence and progression of both micro- and macrovascular complications. Data supporting the role of early glycemic levels as the major mediator of the development and progression of diabetes complications, an effect that persists for 10 or more years after the initial period of glycemic exposure, are presented. We also compare and contrast the manifestations of metabolic memory in how they may differ from those of the legacy effect. Finally, we review the current understanding of the potential mechanisms of metabolic memory.

Methods

DCCT (1983–1993)

The design and methods of the DCCT have been described in detail (1). Between 1983 and 1989, 1,441 subjects 13–39 years of age were recruited in 29 medical centers in the U.S. and Canada. Of these, 715 were members of the primary prevention cohort with 1–5 years' duration of type 1 diabetes, no retinopathy, and albumin excretion rate (AER) $<$40 mg/24 h and 726 were members of the secondary intervention cohort with 1–15 years' duration of diabetes, mild to moderate nonproliferative diabetic retinopathy, and AER $<$200 mg/24 h. Subjects were free of hypertension, symptomatic neuropathy, and macrovascular disease and had calculated LDL cholesterol levels $<$190 mg/dL. Owing to these exclusions, participants were generally young and healthy with a "glucocentric" risk profile. The overall mean HbA_{1c} at baseline was 9.1%, 47% were female, 14% were adolescents (age 13–18 years), and 96.5% were White.

Subjects were randomly assigned to intensive therapy, with three or more daily insulin injections or use of an insulin pump, that aimed at normoglycemia with avoidance of hypoglycemia, or to conventional therapy, usually with two daily insulin injections, aimed at the absence of symptoms of hyperglycemia and frequent or severe hypoglycemia. HbA_{1c} was measured quarterly, retinopathy assessed semiannually, and AER measured annually from a 4-h timed urine collection. AER and HbA_{1c} were measured centrally, and retinopathy was assessed by central grading of fundus photographs according to the final Early Treatment Diabetic Retinopathy Study (ETDRS) scale of severity (10).

The principal outcome was a three-step or more (3+ step) progression of retinopathy on the ETDRS scale that was confirmed on two successive 6-monthly evaluations. Microalbuminuria was defined as an AER $\geq$40 mg/24 h ($\geq$28 μg/min) and albuminuria as AER $\geq$300 mg/24 h ($\geq$208 μg/min) during the DCCT. Additional descriptions of methods are provided in the individual cited references.

EDIC

DCCT randomized treatment and data collection ended in 1993, at which time 1,422 (99.4%) of the surviving 1,430 subjects completed a DCCT closeout assessment visit. Thereafter, conventional treatment group subjects were trained in intensive therapy and all subjects were referred to their own health care providers for diabetes care. EDIC was initiated in 1994; 1,375 of the 1,425 surviving members (96%) enrolled and as of 2019 have been followed for an additional 26 years.

The DCCT methods of evaluation were also employed during the EDIC study (5) with central grading of fundus photographs and central laboratory measurements of AER and HbA_{1c}. HbA_{1c} was measured annually during EDIC, and the updated mean HbA_{1c} over DCCT and EDIC combined was calculated by weighting the values by the months since the last measurement; namely, 3 months during DCCT and 12 during EDIC.

Retinopathy was assessed every 4 years. During EDIC, *further* retinopathy progression was defined as a 3+ step progression of the level of retinopathy *from that at the end of the DCCT*, which did not need to be sustained at a subsequent visit as in the DCCT owing to less frequent examinations. A 4-h timed urine collection was obtained every other year. Microalbuminuria was defined as an AER $\geq$30 mg/24 h during EDIC (the contemporaneously established definition) rather than $\geq$40 mg/24 h as in the DCCT. Analyses of further progression of retinopathy and new onset of nephropathy during EDIC were adjusted for the values or status at DCCT closeout.

The statistical methods are described in Supplementary Material.

DCCT Results

DCCT Treatment Group Differences and the Role of Hyperglycemia in the Development and Progression of Complications

The distribution of the mean HbA_{1c} for subjects in the intensive and conventional treatment groups over up to 9.5 years (mean 6.5 years) of treatment in the DCCT and an additional 26 years of follow-up in EDIC is shown in Fig. 1.

During the DCCT, subjects in the intensive treatment group maintained a mean HbA_{1c} of 7.2% vs. 9.0% among those in the conventional treatment group.

Of note, the cumulative incidence of sustained 3+ step progression of retinopathy severity, the primary DCCT outcome, did not differ between treatment groups in either the primary or secondary cohort during the first 4 years of treatment (1) (see Supplementary Fig. 1). Afterward, the cumulative incidence in retinopathy in the conventional treatment group increased at a much higher rate than that in the intensive treatment group, ultimately with a 76% (Supplementary Fig. 1*A*) and 54% (Supplementary Fig. 1*B*) risk reduction in the primary and secondary cohorts, respectively. Thus, the implementation of a difference in levels of glycemia may not result in a discernible difference in risks of microvascular complications for several years. In retrospect, this may be the first suggestion of metabolic memory. The same delayed effect of glycemic separation was also observed for other, more severe levels of retinopathy (10).

While the history of pre-DCCT HbA_{1c} levels was unknown, it is noteworthy that subjects within the highest quintiles of HbA_{1c} and the longest preexisting duration of diabetes on entry in the DCCT had the highest absolute risk of sustained 3+ step retinopathy progression (rate per 100 patient-years) in both the conventional and intensive treatment groups (2) (see Supplementary Fig. 2). Although the risks were markedly reduced with intensive therapy, they were not completely eliminated. Thus, glycemic exposure prior to entry into the DCCT appears to have had a prolonged effect on the risk of retinopathy progression in both treatment groups, and this risk was not diminished until >4 years of intensive therapy.

During the DCCT, the mean level of HbA_{1c} was the principal determinant of risk of progression of complications. The risk increased exponentially with increasing HbA_{1c} and to the same degree in both groups (2), with no glycemic (HbA_{1c}) threshold in the relationship detectable above the nondiabetes range of HbA_{1c} (3). The difference in risk of outcomes with intensive versus conventional treatment group was almost entirely explained by the HbA_{1c} differences between the groups (4). For example, compared with the conventional treatment group, the intensive group had a 73% reduction in the risk of sustained 3+ step progression with a χ^2 test value of 96.7. Adjustment for the updated mean HbA_{1c} as a time-dependent covariate, i.e., assuming no difference between groups in HbA_{1c} over time, reduced the group difference to $\chi^2 = 3.72$, representing a 96.2% reduction in the χ^2 test value [(100)(96.7 − 3.72)/96.7)]. Thus, the difference in mean glycemia between the treatment groups statistically explained virtually all of the beneficial effects of intensive therapy on retinopathy progression. Similarly for the other outcomes, 91.8%–99.9% of the risk reduction with intensive versus conventional treatment was explained by the group difference in the mean HbA_{1c} levels during the DCCT (4) (Table 1).

EDIC Results

The Role of Prior DCCT Treatment Group and HbA_{1c} in Further Progression of Complications During the First 8 Years of EDIC Follow-up

The DCCT closeout visit in 1993 constituted the baseline visit for EDIC. At that time, participants had a mean age of 33 years and diabetes duration of 12 years. Subsequently, the surviving DCCT cohort has been followed with an annual assessment visit during EDIC, herein up to 26 years by 2019. Over this period, on average, 93% of the survivors have been followed annually.

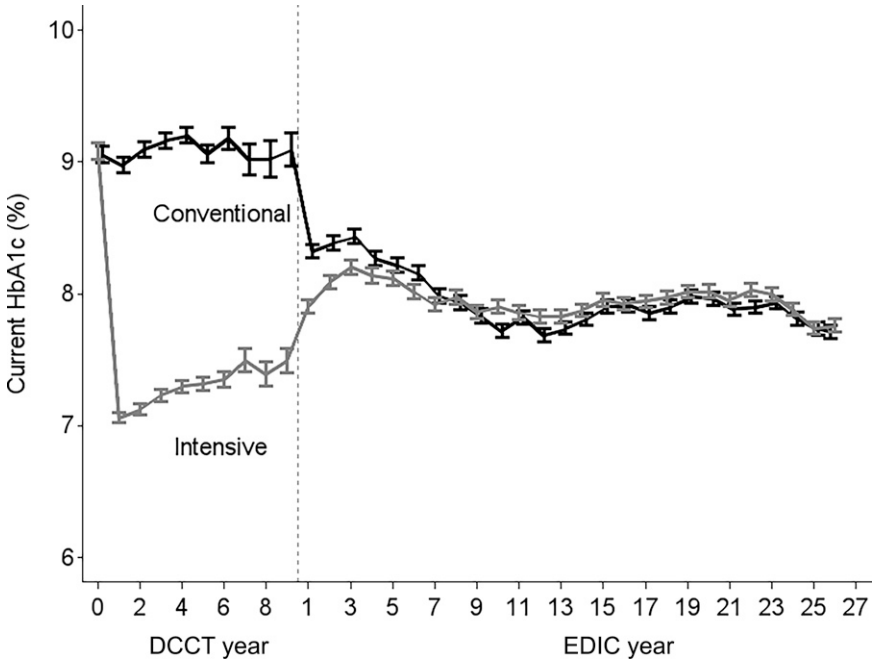

Figure 1—The mean ± SE HbA_{1c} over the average of 6.5 years of follow-up in the DCCT (9.5 years maximum) and up to 26 years of follow-up in EDIC for subjects in the DCCT originally assigned to intensive and conventional treatment groups. Adapted with permission from the American Diabetes Association (25).

Table 1—Adjusted risk reduction with intensive versus conventional treatment in DCCT combined primary and secondary cohorts and % of the group test value explained by the log of the current mean HbA_{1c}

Complication	Risk reduction, % (95% CI)	*P* value	% explained by HbA_{1c}
Retinopathy[a]			
Single 3+ step progression	57 (48, 65)	<0.0001	95.8
Sustained 3+ step progression	73 (65, 80)	<0.0001	96.2
SNPDR	64 (42, 77)	<0.0001	99.9
Any laser	61 (34, 77)	0.0003	99.5
CSME	29 (−5, 52)	0.084	99.9
Nephropathy[b]			
Microalbuminuria[c]	40 (23, 53)	<0.0001	99.2
Albuminuria	59 (28, 77)	0.0016	96.7
Neuropathy at 5 years[d]	68 (50, 80)	<0.0001	91.8

CSME, clinically significant macular edema; SNPDR, severe nonproliferative diabetic retinopathy. [a]From a relative risk (hazards) estimate in a proportional hazards model adjusted for the ETDRS level of retinopathy at baseline and the pre-DCCT glycemic exposure represented by the preexisting duration of diabetes separately for the primary and secondary cohorts and the level of log(HbA_{1c}) on eligibility screening. [b]From a Cox proportional hazards model adjusted for primary vs. secondary cohort on entry, the log(AER) on entry, and the pre-DCCT glycemic exposure. Microalbuminuria, AER >40 mg/24 h; albuminuria, AER >300 mg/24 h. [c]Subjects with microalbuminuria on entry deleted from analysis. [d]From an odds ratio in a logistic regression model, adjusted for primary vs. secondary cohort and the pre-DCCT glycemic exposure represented by the preexisting duration of diabetes separately for the primary and secondary cohorts and the level of log(HbA_{1c}) on eligibility screening.

During EDIC, the mean of the annual HbA_{1c} values in the two groups became almost identical, with values of 8.2% vs. 8.0% over the first 8 years of follow-up in the former conventional and intensive treatment groups, respectively (Fig. 1). This negligible difference in HbA_{1c} between the original DCCT treatment groups during EDIC has persisted to date. Since the difference in progression of complications in the intensive versus conventional treatment groups during DCCT was closely tied to the differences in HbA_{1c}, it was reasonable to expect that the merger of the HbA_{1c} levels would result in similar rates of progression of complications during EDIC.

However, analyses showed that prior intensive versus conventional therapy during DCCT actually reduced the risk of 3+ steps further progression of retinopathy during the first 4 years of EDIC from the level present at the end of the DCCT by 72% ($P < 0.001$) (6). Prior intensive therapy also reduced the risks of new severe nonproliferative retinopathy, clinically significant macular edema, and any laser therapy by 76%, 77%, and 77%, respectively; all $P < 0.002$. Subsequent analyses showed similar persistent effects of intensive versus conventional therapy on progression of nephropathy over these 4 years (7).

Further analyses after 8 years of EDIC follow-up showed increasing treatment group differences in the risk of further progression of retinopathy by at least 3 steps from the level at DCCT closeout and the development of macroalbuminuria (AER >300 mg/24 h) among those free of albuminuria at the end of the DCCT (8) (Fig. 2). For both retinopathy and nephropathy, the risk reduction with intensive therapy during EDIC was greater than that initially observed during DCCT (6–8). The vast majority of the differences in complications between the former DCCT intensive and conventional treatments over the first 8 years in EDIC was attributable to the original treatment group differences in the mean level of HbA_{1c} during the DCCT (Table 2).

Metabolic Memory

The findings during the DCCT and the first 8 years of EDIC led to the hypothesis that pathologic changes persist

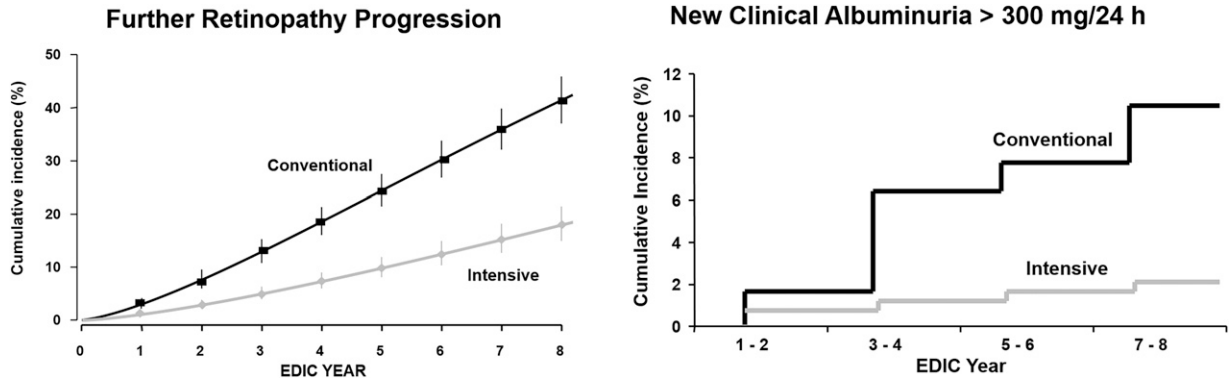

Figure 2—Cumulative incidence of further progression of retinopathy by at least 3 steps from the level at the end of the DCCT during the subsequent 8 years of follow-up during EDIC. Subjects experiencing laser therapy during the DCCT were excluded from analysis. Cumulative incidence of new albuminuria (AER >300 mg/24 h) during 8 years of follow-up during EDIC. Subjects developing albuminuria during the DCCT were excluded from analysis. Reprinted with permission from the *Journal of the American Medical Association* (9).

beyond a period of hyperglycemia that contribute to the long-term risk of complications, a phenomenon termed *metabolic memory* (8). Further analyses showed that metabolic memory has two principal manifestations. One is a biological effect on the day-to-day *incidence* (risk or hazard) of progression that is a manifestation of underlying biological effects associated with the history of prior poor glycemic control. The other is an epidemiological effect on the *cumulative incidence* of progression that reflects the population public health impact on the absolute risk of progression expressed as the number or percentage of subjects with progression over a specified period of time. In the cumulative incidence calculations, the prior differences in incidence (risk) are perpetuated into the future.

There is also a statistical relationship between the past incidence and the cumulative incidence at a given point in time. The cumulative incidence at any time t, say P_t, a proportion, is a direct exponential function of the area under the incidence curve up to time t, (AUC_t), where $P_t = 1 - \exp(-AUC_t)$. As an analogy to banking, incidence, reflecting the biological manifestations of metabolic memory, is like the interest rate compounded daily, whereas the cumulative incidence, reflecting the epidemiological manifestations of metabolic memory, is the total accrued value (your bank account balance) at a point in time.

How Long Does Metabolic Memory Persist?

We assessed the longevity of the metabolic memory effect by examining the DCCT/EDIC outcomes over ~26 years of EDIC follow-up (Table 3). Figure 3 presents the incidence and cumulative incidence curves for further 3+ step progression of retinopathy. (Curves for other outcomes are presented in Supplementary Material.)

The smoothed incidence (hazard) function of further 3+ step progression over these 26 years yields an aggregate 44% reduction in the risk (incidence) ($P < 0.0001$) (Table 3). During the first 5 years of EDIC, the incidence of further retinopathy progression (Fig. 3, left) was up to three times higher in the former conventional than in the intensive treatment group. However, over the subsequent 5–10 years of follow-up, the difference in risk narrowed (11), the incidences in the two groups being nearly identical over the subsequent 11–26 years of follow-up, reflecting a waning of metabolic memory.

A further analysis of retinopathy progression over the first 10 years of EDIC, with the end of DCCT serving as the baseline, showed a 52% risk reduction in the original intensive therapy group ($P < 0.0001$) (11), whereas an analysis over 11–26 years of follow-up showed only an 18% reduction ($P = 0.18$). Clearly, the biological effect of metabolic memory waned after year 10 of EDIC. Nevertheless, there was a continuing expanding reduction in the cumulative incidence (epidemiologic metabolic memory) over the latter period (Fig. 3, right).

Note that the area under the incidence curve (AUC) is substantially different between the treatment groups up to 10 years. Thereafter the increment in the AUC beyond 10 years is the same in the two groups. Thus, the AUC up to 10 years following the end of DCCT differs between groups but thereafter increases by about the same amount over time in each group, such that the cumulative incidence in the conventional group continues to increase faster than in the intensive group. Indeed, even if the incidences beyond 26 years of follow-up remain equal in the two groups, the cumulative incidence in the intensive group will never catch up with that in the conventional group.

Thus, the biological manifestations of metabolic memory on the risk of further retinopathy progression appear to be operant for at least 10 years after the end of the DCCT, with attenuation (*metabolic amnesia*) occurring thereafter. Nevertheless, the epidemiological manifestations reflect a continuing beneficial effect on cumulative incidence, translating into a continued benefit in the population.

Table 3 provides a summary of similar analyses for other outcomes. For micro- and macroalbuminuria, over all of EDIC, there were 29% and 47% risk reductions with intensive therapy, respectively, with higher (54% and 73%) risk reductions during years 1–10 (12) and lesser, nonsignificant, risk reductions during years 11–26. By visual inspection of

Table 2—Adjusted odds reduction of complications at EDIC years 4 and 8 in the former DCCT intensive versus conventional treatment groups in the DCCT combined primary and secondary cohorts and % of group test value explained by the log of the current mean HbA_{1c}†

Complication[a]	Odds reduction, % (95% CI)	*P* value	% explained by DCCT HbA_{1c}[e]
Retinopathy at 4 years[b]			
Further 3+ step progression	72 (59, 81)	<0.001	97.7
New SNPDR[c]	76 (52, 88)	<0.001	98.8
New laser	77 (45, 91)	0.002	94.3
New CSME[c]	77 (52, 89)	<0.001	98.0
Nephropathy at 8 years[d]: new albuminuria	84 (67, 92)	0.0016	98.8

P value: the likelihood ratio χ^2 test statistic value. CSME, clinically significant macular edema; SNPDR, severe nonproliferative diabetic retinopathy. †From 6,8,11,12. [a]Logistic regression model adjusted for primary vs. secondary cohort and diabetes duration on DCCT entry, separately for each, and the level of HbA_{1c} on eligibility screening. [b]Adjusted for the ETDRS level of retinopathy at the close of the DCCT. Subjects with prior laser therapy were excluded. [c]Subjects with a history of this level of retinopathy during the DCCT were excluded. [d]Also adjusted for the log(AER) at the close of the DCCT. Subjects with each level of nephropathy during the DCCT were excluded from analysis. For these renal outcomes during EDIC, events were defined from assessments at year 1 or 2 of EDIC and at years 3–4, 5–6, and 7–8, as the measurements were performed in one-half of the cohort every year. [e]The percentage of an effect (e.g., DCCT treatment group) mediated (explained) by another factor (e.g., DCCT mean HbA_{1c}) is computed as the percentage reduction in the magnitude of the effect test statistic from a regression model without and then with adjustment for the other factor.

Table 3—The % reduction in the hazard rate (95% CI) and *P* value for the assessment of the difference between the original DCCT intensive versus conventional treatment groups for complications during EDIC follow-up‡

Outcome (reference)*	Over 26 years of EDIC follow-up	EDIC years 1–10	EDIC years 11–26	Approximate year of equivalence
3+ step progression (11)	44 (35, 53), $P < 0.0001$	52 (42, 60), $P < 0.0001$	18 (−10, 39), $P = 0.18$	11
PDR (11)	40 (23, 52), $P < 0.0001$	55 (36, 69), $P < 0.0001$	19 (−13, 42), $P = 0.21$	17
Ocular surgery (13)†	40 (25, 51), $P < 0.001$	59 (29, 77) $P = 0.002$	35 (19, 49), $P < 0.001$	23
Microalbuminuria (12)	29 (9, 45), $P = 0.007$	54 (35, 67), $P < 0.0001$	−16 (−70, 21), $P = 0.46$	9
Macroalbuminuria (12)	47 (26, 63), $P < 0.001$	73 (52, 84), $P < 0.001$	7 (−52, 42), $P = 0.78$	10
Any CVD (14)†	12 (−12, 32), $P = 0.286$	41 (5, 64), $P = 0.029$	−2 (−37, 24), $P = 0.912$	12
MACE (14)†	15 (−20, 40), $P = 0.348$	41 (11, 81), $P = 0.024$	−6 (−56, 29), $P = 0.789$	11

‡Complications with up to 26 years' EDIC follow-up: 3+ step further progression of retinopathy, proliferative diabetic retinopathy (PDR), ocular surgery, microalbuminuria (sustained AER >30 mg/24 h), macroalbuminuria (AER >300 mg/24 h), any CVD event, and MACE. Also shown is the approximate time in EDIC at which the incidence rate equated (i.e., waned) by visual inspection. Any CVD defined as MACE or confirmed angina or revascularization (angioplasty, stent, or bypass) or "silent" myocardial infarction based on a centrally read electrocardiogram. All CVD events were adjudicated by a committee masked to treatment assignment and HbA_{1c} values. Weibull regression models for interval-censored data were used for analyses of 3+ step progression and proliferative diabetic retinopathy and Cox proportional hazards models for other outcomes. For each outcome, separate models assessed associations over all 26 years, just the first 10 years of follow-up, and years 11–26. *For each outcome the references cited presented the most recent assessments of metabolic memory at the time of those analyses. All analyses have been updated here to include outcomes through year 26 of EDIC. †For these outcomes, the prior published article did not present separate analyses within the first and second EDIC periods.

the incidence curves for micro and macroalbuminuria, the incidences are equivalent for about ∼9–10 years, at which time metabolic amnesia occurs. However, owing to the biological effects of metabolic memory evident over the first 10 years of EDIC, there is a continuing epidemiological benefit (difference in cumulative incidence) over the remainder of EDIC (see Supplementary Fig. 3 in Supplementary Material).

Clinical Consequences of Metabolic Memory: The Cumulative Effect on More Severe Complications

Previous analyses of other more severe outcomes (ocular surgery [13] and any cardiovascular disease [CVD] and major adverse cardiovascular event [MACE] [14,15]) used the total experience over DCCT and EDIC combined so as to increase power. Updated analyses presented here only include cases that occurred during EDIC so as to provide a precise assessment of metabolic memory (and subsequent amnesia).

Over the 26 years of EDIC (Table 3), there was a substantial 40% reduction in the risk of ocular surgery with intensive versus conventional therapy. The risk over the first 10 years in EDIC was reduced by 59% and over the subsequent 16 years was reduced by 35%, the difference being significant over both periods. By visual inspection, the (biological) metabolic memory for ocular surgery did not wane until 23 years of EDIC follow-up. Likewise, there was a 40% reduction in the risk of development of proliferative diabetic retinopathy, with a 55% risk reduction over the first 10 years of EDIC, but only 19% over the next 16 years ($P = 0.21$) and waning by 17 years.

The updated analyses herein over 26 years of EDIC follow-up no longer show an overall significant risk reduction in CVD or MACE with intensive versus conventional therapy, the respective risk reductions being 12% and 15%. While the analysis over the first 10 years of EDIC alone showed a significant 41% reduction in the risk of both outcomes ($P < 0.03$ for both), over 11–26 years of EDIC the metabolic memory had completely waned, with risk reductions of −2% and −6% (Table 3). Nevertheless, the cumulative incidence (or epide-

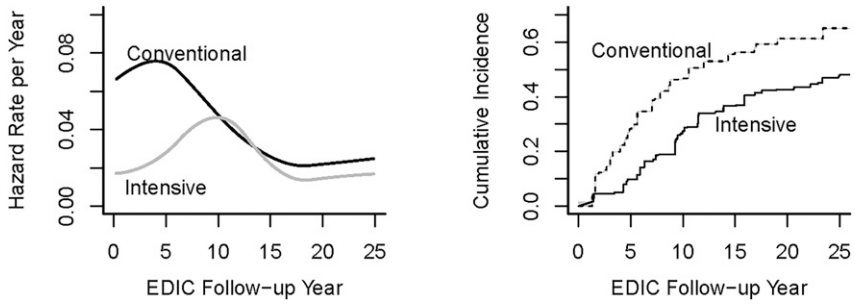

Figure 3—The smoothed estimate of the day-to-day incidence (hazard) rate of sustained 3+ step progression of retinopathy within the former intensive vs. conventional treatment groups over 26 years of EDIC follow-up (left), which represents biological metabolic memory, and the cumulative incidence of 3+ step progression (right), representing epidemiological metabolic memory or the legacy effect. The cumulative incidence functions were computed using the Turnbull estimate for interval-censored data, smoothed using natural cubic splines, and differentiated to yield the smooth hazards estimate.

miological manifestation of metabolic memory) within the conventional group remained higher than that in the intensive group over years 11–26 but with a small, 1%–4%, difference between the curves. Of note, the increasing application of improved methods of reducing CVD risk, such as more aggressive control of blood pressure and use of statins, may also have played a role in reducing the relative beneficial effects of the original glycemic separation (16).

Other Results

Potential Mechanisms for Metabolic Memory

DCCT/EDIC investigators have also conducted two ancillary studies to search for pathophysiologic explanations or mechanisms for metabolic memory. One explored the formation of glycated proteins with slow turnover (17,18) and the other epigenetics (19). Several reviews (20,21) have examined and proposed other putative mechanisms of metabolic memory, including potential effects of oxidative stress in addition to advanced glycation and epigenetics.

Glycation and Glycoxidation.

In a sample of 216 DCCT subjects, a skin biopsy was obtained ~1 year before the end of the DCCT and advanced glycation end product (AGE) formation was measured in dermal collagen (17). Levels of furosine (glycated collagen) and carboxymethyl-lysine (CML), among others, were significantly lower in the intensive than in the conventional treatment group. When examined jointly with the DCCT HbA_{1c}, the levels of the AGEs were significantly and more strongly associated with complications than the DCCT mean HbA_{1c} (18). The collagen AGE levels explained 97.7% of the original DCCT group difference in the risk of retinopathy progression at 4 years of EDIC and 94.5% of the association of the DCCT mean HbA_{1c} with the risk of such progression. More importantly, while the DCCT mean HbA_{1c} was strongly associated with progression of retinopathy and nephropathy at 10 years of EDIC follow-up, these associations were negated completely after adjustment for dermal furosine and CML levels (P = 0.987 for retinopathy and 0.964 for nephropathy) (18).

Type 4 collagen has a very long half-life, estimated at 15 years, and the formation of other long-lived glycated proteins during the DCCT could be the mechanism by which the difference in HbA_{1c} between treatment groups during the DCCT had such persistent long-term effects on microvascular complications. That CML is a product of lipoxidation as well as glycoxidation suggests that hyperglycemia and associated metabolic derangements may lead to complications.

Epigenetics.

Epigenetics is another potential mechanism for metabolic memory that has been supported recently by another DCCT/EDIC ancillary study (19). That study assessed the association of epigenetic DNA methylation (DNAme) with metabolic memory in 499 randomly selected DCCT participants who were followed during EDIC. DNAme was measured in the blood DNA of saved genetic samples collected at DCCT closeout, and we assessed its association with the past history of glycemia and with subsequent development of complications over an 18-year period of follow-up in EDIC. DNAme was associated with the mean HbA_{1c} during DCCT at 186 cytosine-guanine dinucleotides (CpGs) at a false discovery rate $<$15%, including 43 at a false discovery rate $<$5%, many of which were located in genes related to complications. Further exploratory studies of biological function showed that these CpGs were enriched in binding sites for the C/EBP transcription factor, as well as enhancer/transcription regions in blood cells and hematopoietic stem cells, and open chromatin states in myeloid cells. Further mediation analyses showed that several CpGs in combination explained 68%–97% of the association of mean DCCT HbA_{1c} with the risk of complications during EDIC. Thus, prior history of hyperglycemia may induce persistent DNAme changes at key loci, including *TXNIP*, in various target cells, and in hematopoietic stem cells, which are epigenetically retained in differentiated myeloid (and other) cells. These epigenetic modifications may facilitate metabolic memory, probably through modifying enhancer activity at nearby genes. The results suggest that DNAme may play a role in mediating the association between HbA_{1c} and the future development of complications.

The Legacy Effect

Approximately 5 years after the description of metabolic memory by DCCT/EDIC (8), the UKPDS in type 2 diabetes described a similar phenomenon that they termed a *legacy effect* (10). The UKPDS intervention trial compared intensive therapy with sulfonylurea or insulin versus conventional therapy in nonobese patients with recent-onset diabetes who were treated for 6–20 years (median 10 years), ending in 1997. The intensive group maintained an HbA_{1c} 0.9% lower than did the conventional group and at study end had a significantly lower risk of any diabetes-related end point, the primary outcome (12% risk reduction, P = 0.03), and an almost significant reduction in the risk of myocardial infarction (16% risk reduction, P = 0.052).

Following the end of the intervention trial, a 10-year observational follow-up was launched (10). During the first year following the active interventions (1998), the HbA_{1c} levels in the former intensive and conventional groups merged and remained equal over the next 9 years, analogous to the EDIC experience. After the additional 10 years (2007), with a combined follow-up of up to 30 years, the risk reduction for any diabetes-related end point with the original intensive versus conventional treatment remained significant (9%, P = 0.04) and that for myocardial infarction became significant (15%, P = 0.01).

The UKPDS (10) did not present an analysis of the cumulative incidence of new events during the 10-year follow-up. However, the risk reductions over the 30 years of treatment and extended follow-up (9% and 15%, respectively) are close to those over the 20-year treatment phase (12% and 16%). Under a proportional hazards model this implies that the cumulative incidence function over the 10-year follow-up would continue to increase and widen between groups, as was observed in the analyses of metabolic memory.

The UKPDS referred to these long-term differences as a legacy effect (10), stating, "Benefits persisted despite the early loss of within-trial differences in glycated hemoglobin levels between the intensive-therapy group and the conventional-therapy group—a so-called legacy effect." This description is clearly similar to that used previously to refer to metabolic memory. Thus, both "metabolic memory"

and "legacy effect" represent persistent long-term effects of the past history of glycemia on the risks of progression of complications, potentially mediated by the same biological mechanisms.

Discussion

The phenomenon that we have named metabolic memory might never have been discovered had it not been for the deliberate training of the original DCCT conventional treatment group in intensive therapy at the end of the DCCT, coupled with the cessation of DCCT-provided intensive therapy in the intensive group, and the referral of both groups to non-study (community) care. This resulted in the disappearance of the separation in glycemia that had been maintained during the 6.5 years of DCCT, with HbA_{1c} remaining essentially equivalent between the two original DCCT treatment groups during the observational long-term follow-up of the DCCT cohort during the EDIC study. This unintended experiment has shown that a period of high or low glycemia has long-term adverse or beneficial effects, respectively, on the risks of micro- and macrovascular complications. Metabolic memory may persist for 10 years or more before waning.

Although the biological mechanism(s) that causes vascular injury based on antecedent levels of HbA_{1c} has not been clearly established, metabolic memory applies to all of the outcomes considered, including retinopathy, nephropathy, neuropathy, and CVD. Although neuropathy was only fully assessed at two times during EDIC, the second assessment at 13/14 years of EDIC (22) also showed a beneficial metabolic memory effect of the original intensive therapy. The long-term effects of metabolic memory also translated into major clinical benefits including reduced ocular surgery and development of stage 3 chronic kidney disease (13,23) and mortality (24).

In retrospect, at the conclusion of the DCCT one would have expected the HbA_{1c} in the two former treatment groups not to equate instantly but, rather, to do so slowly, and without a precipitous change in risk in the former groups. However, the persistence of metabolic memory for at least 10 years after DCCT end, depending on the outcome, is remarkable. Waning of the metabolic memory effect can be manifest by an eventual decline in the risk in the former conventional group resulting from a lowered HbA_{1c} to ~8%, an eventual increase in the risk in the former intensive group resulting from an increased HbA_{1c}, or both.

It is not clear how or whether these findings could ever be replicated in an epidemiologic surveillance study. Subjects would need to have a $\geq$1% change (either up or down) in HbA_{1c} values at a specific time, without any uniform intervention, and would need to have the change maintained over time with prolonged surveillance of outcomes before and after the change point.

Nevertheless, in a recent review, Miller and Orchard (25) presented additional analyses of the Pittsburgh Epidemiology of Diabetes Complications (EDC) cohort and concluded that "there is no need to invoke a 'metabolic memory' phenomenon to explain the persistence of a lower incidence of complications in the DCCT intensive therapy group compared with conventional therapy group, which can be fully explained by cumulative glycemic exposure." The fundamental issue is the assertion that the risk of outcomes is dependent solely on the cumulative level of glycemia and that the pattern of glycemia is irrelevant, i.e., whether the cumulative level "results from a high exposure for a short time or a lower exposure for a longer time." We took exception to this statement (26), noting that cumulative glycemic exposure includes long-term effects, such as metabolic memory, and as a result early implementation of intensive therapy will have greater beneficial long-term effects. Miller and Orchard then replied (27) that owing to a greater period of diabetes prior to entry in their cohort compared with that for the DCCT cohort (18 vs. 4 years, respectively) it is not feasible to replicate the DCCT/EDIC experience.

In support of the metabolic memory phenomenon, an independent analysis of the publicly available DCCT data (28) derived and applied a mathematical model to explore metabolic memory and determine its "shape" over time. The authors endorsed the existence of metabolic memory and concluded that its duration was as long as 8 years.

Conclusion

Considering our current understanding of the central role of glycemia in the pathogenesis of microvascular and cardiovascular complications in type 1 diabetes, no one would intentionally replicate the sequence of intensive therapy during DCCT followed by less aggressive care in EDIC. However, our discovery of metabolic memory and its long-term aggregate expression further reinforces our original recommendation that individuals with type 1 diabetes should implement intensive insulin therapy as early and as long as safely possible from the time of diagnosis. Recognizing the toxic and prolonged effects of early periods of hyperglycemia provides the rationale for this approach, as it maximizes the benefits of intensive therapy. Moreover, the prolonged benefit of early tight glycemic control may buffer the adverse effects of any subsequent periods of hyperglycemia.

Funding. DCCT/EDIC has been supported by cooperative agreement grants (1982–1993, 2012–2017, and 2017–2022) and contracts (1982–2012) with the Division of Diabetes, Endocrinology, and Metabolic Diseases of the National Institute of Diabetes and Digestive and Kidney Diseases (grants U01 DK094176 and U01 DK094157) and through support by the National Eye Institute, the National Institute of Neurological Disorders and Stroke, the General Clinical Research Center Program (1993–2007), and Clinical and Translational Science Center Program (2006–present) (Bethesda, MD). Industry contributors have provided free or discounted supplies or equipment to support participants' adherence to the study: Abbott Diabetes Care (Alameda, CA), Animas Corporation (West Chester, PA), Bayer Diabetes Care (Tarrytown, NY), Becton Dickinson (Franklin Lakes, NJ), Eli Lilly and Co. (Indianapolis, IN), Extend Nutrition (St. Louis, MO), Insulet Corporation (Bedford, MA), LifeScan, Inc. (Milpitas, CA), Medtronic Diabetes (Minneapolis, MN), Nipro Home Diagnostics, Inc. (Fort Lauderdale, FL), Nova Diabetes Care (Billerica, MA), Omron (Shelton, CT), Perrigo Diabetes Care (Allegan, MI), Roche Diabetes Care (Indianapolis, IN), and Sanofi U.S. (Bridgewater, NJ).

Industry contributors have had no role in DCCT/EDIC.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

References

1. Nathan DM, Genuth S, Lachin J, et al.; Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on

the development and progression of long-term complications in insulin-dependent diabetes mellitus.N Engl J Med 1993;329:977–986
2. The Diabetes Control and Complications Trial Research Group. The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the diabetes control and complications trial. Diabetes 1995; 44:968–983
3. The Diabetes Control and Complications Trial Research Group. The absence of a glycemic threshold for the development of long-term complications: the perspective of the Diabetes Control and Complications Trial. Diabetes 1996; 45:1289–1298
4. Lachin JM, Genuth S, Nathan DM, Zinman B; DCCT/EDIC Research Group. Effect of glycemic exposure on the risk of microvascular complications in the diabetes control and complications trial–revisited. Diabetes 2008;57:995–1001
5. Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group. Epidemiology of Diabetes Interventions and Complications (EDIC). Design, implementation, and preliminary results of a long-term follow-up of the Diabetes Control and Complications Trial cohort. Diabetes Care 1999;22: 99–111
6. Diabetes Control and Complications Trial/Epidemiology of Diabetes Intervention and Complications Research Group; Lachin JM, Genuth S, Cleary P, Davis MD, Nathan DM. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. N Engl J Med 2000;342:381–389
7. Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group Effect of intensive therapy on the microvascular complications of type 1 diabetes mellitus. JAMA 2002;287:2563–2569
8. Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Sustained effect of intensive treatment of type 1 diabetes mellitus on development and progression of diabetic nephropathy: the Epidemiology of Diabetes Interventions and Complications (EDIC) study. JAMA 2003;290:2159–2167
9. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HAW. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577–1589
10. Diabetes Control and Complications Trial Research Group. Progression of retinopathy with intensive versus conventional treatment in the Diabetes Control and Complications Trial. Ophthalmology 1995;102:647–661
11. The Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group. Effect of intensive diabetes therapy on the progression of diabetic retinopathy in patients with type 1 diabetes: 18 years of follow-up in the DCCT/EDIC. Diabetes 2015;64:631–642
12. de Boer IH, Sun W, Gao X, et al.; DCCT/EDIC research group. Effect of intensive diabetes treatment on albuminuria in type 1 diabetes: long-term follow-up of the Diabetes Control and Complications Trial and Epidemiology of Diabetes Interventions and Complications study. Lancet Diabetes Endocrinol 2014;2:793–800
13. DCCT/EDIC Research Group; Aiello LP, Sun W, Das A, et al. Intensive diabetes therapy and ocular surgery in type 1 diabetes. N Engl J Med 2015;372:1722–1733
14. Lachin JM, Orchard TJ; DCCT/EDIC Research Group. Update on cardiovascular outcomes at 30 years of the diabetes control and complications trial/epidemiology of diabetes interventions and complications study. Diabetes Care 2014;37: 39–43
15. Nathan DM, Clearly PA, Backlund J-YC, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Intervention and Complications Study (DCCT/EDIC) Research Group-Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005;353:2643–2653
16. Bebu I, Braffett BH, Pop-Busui R, Orchard TJ, Nathan DM; DCCT/EDIC Research Group. The relationship of blood glucose with cardiovascular disease is mediated over time by traditional risk factors in type 1 diabetes: the DCCT/EDIC study. Diabetologia 2017;60:2084–2091
17. Monnier VM, Bautista O, Kenny D, et al. Skin collagen glycation, glycoxidation, and crosslinking are lower in subjects with long-term intensive versus conventional therapy of type 1 diabetes: relevance of glycation collagen products versus HbA1c as markers of diabetic complications. DCCT Skin Collagen Ancillary Study Group. Diabetes Control and Complications Trial. Diabetes 1999;48:870–880
18. Genuth S, Sun W, Cleary P, et al.; DCCT Skin Collagen Ancillary Study Group. Glycation and carboxymethyllysine levels in skin collagen predict the risk of future 10-year progression of diabetic retinopathy and nephropathy in the diabetes control and complications trial and epidemiology of diabetes interventions and complications participants with type 1 diabetes. Diabetes 2005;54:3103–3111
19. Chen Z, Miao F, Braffett BH, et al.; DCCT/EDIC Study Group. DNA methylation mediates development of HbA1c-associated complications in type 1 diabetes. Nat Metab 2020;2:744–762
20. Cooper ME, El-Osta A, Allen TJ, et al. Metabolic karma—the atherogenic legacy of diabetes: the 2017 Edwin Bierman Award Lecture. Diabetes 2018;67:785–790
21. Testa R, Bonfigli AR, Prattichizzo F, La Sala L, De Nigris V, Ceriello A. The "metabolic memory" theory and the early treatment of hyperglycemia in prevention of diabetic complications. Nutrients 2017;9:437
22. Martin CL, Albers JW; DCCT/EDIC Research Group. Neuropathy and related findings in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study. Diabetes Care 2014;37: 31–38
23. de Boer IH, Sun W, Cleary PA, et al.; DCCT/EDIC Research Group. Intensive diabetes therapy and glomerular filtration rate in type 1 diabetes. N Engl J Med 2011;365:2366–2376
24. Writing Group for the DCCT/EDIC Research Group; Orchard TJ, Nathan DM, Zinman B, et al. Association between 7 years of intensive treatment of type 1 diabetes and long-term mortality. JAMA 2015;313:45–53
25. Miller RG, Orchard TJ. Understanding metabolic memory: a tale of two studies. Diabetes 2020;69:291–299
26. Lachin JM, Nathan DM, Zinman B, Bebu I. Comment on Miller and Orchard: understanding metabolic memory: a tale of two studies. Diabetes 2020;69:291–299 (Letter). Diabetes 2020;69:e7–e8. DOI: https://doi.org/10.2337/db20-0311
27. Miller RG, Orchard TJ. Response to comment on Miller and Orchard: understanding metabolic memory: a tale of two studies. Diabetes 2020;69:291–299 (Letter). Diabetes 2020;69:e9. DOI: https://doi.org/10.2337/dbi20-0021
28. Lind M, Odén A, Fahlén M, Eliasson B. The shape of the metabolic memory of HbA_{1c}: re-analysing the DCCT with respect to time-dependent effects. Diabetologia 2010;53: 1093–1098