Lingering Effects of Hyperglycemia in Recently Diagnosed Diabetes During Long-term Follow-up of the DCCT/EDIC and UKPDS Cohorts: More Evidence That Early Control Matters

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The Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study (UKPDS) have given us fundamental insights into the natural history and management of diabetes (1,2). These include strong evidence that *1*) enhanced glycemic management can limit some of the complications of diabetes, *2*) there is a dose-response relationship between HbA_{1c} levels and the risk of complications, and *3*) a treatment target of $<7.0\%$ (<53 mmol/mol) HbA_{1c} is realistic and appropriate. Continued observation of the randomized cohorts after the planned end of study has further shown that cardiovascular events and mortality, which could not be shown to be improved during the randomized treatment phases, were significantly reduced long after glucose control equalized in the two arms (3–5). In both studies glycemic control as assessed by HbA_{1c} accounted statistically for most of the difference in outcomes.

In three articles in this issue of *Diabetes Care* the DCCT and UKPDS investigators provide more information on the long-term effects of enhanced glycemic control early in the natural history of diabetes (6–8). In the first of two articles based on more than 20 years of additional observation of the DCCT cohorts in the Epidemiology of Diabetes Interventions and Complications (EDIC) study, Lachin and Nathan (6) report new analyses of data on microvascular complications. These add to previously reported evidence for persistence of lower rates of progression of microvascular disease in the originally intensively managed cohort, despite convergence of HbA_{1c} values in the two groups soon after cessation of the randomized comparison of treatments. The investigators have previously termed this phenomenon "metabolic memory." Here they further report a gradual waning of outcome differences after $\sim$10 years. They emphasize a distinction between the incremental effect on microvascular complications, which slowly declines, and the cumulative effect over the whole period of observation, which results in lasting differences between the randomized cohorts. The authors also review some molecular mechanisms that might mediate these effects.

In the second article, Lachin et al. (7) report modeled estimates of the effects of earlier versus later improvements in glycemic control on outcomes during 20 years of observation in EDIC. They compare the effects of differently timed 10-year periods of HbA_{1c} 7.0% (53 mmol/mol) contrasted with HbA_{1c} 9.0% (75 mmol/mol) throughout. The models estimate that 7.0% followed by 9.0% would yield a $>50\%$ reduction of hazard for cardiovascular events during the 20 years of observation, while for 9.0% followed by 7.0% the reduction would be just 12%. Similarly, they estimate that earlier control of HbA_{1c} for 10 years would reduce new incidence of estimated glomerular filtration rate <60 mL/min/1.73 m^2 by $>60\%$, while later reduction would lead to just 20% reduction of hazard.

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Lind et al. (8), in an article reporting several models of data from the UKPDS, describe similarly persistent effects of prior glycemic exposure on later outcomes. The UKPDS group previously reported that intensive management reduced the long-term incidence of several outcomes that were not definitely reduced at the time the randomized difference in treatment strategy ended (5). The current epidemiologic projections suggest that improving glycemic control during the first 10 years of the study had a greater effect on later myocardial infarction and all-cause mortality than did any similar improvement beginning in the second 10 years. They estimated that maintaining a 1.0% (11 mmol/mol) reduction of HbA_{1c} from diagnosis could reduce risk of death by 19% compared with 2.7% when this improvement was delayed for 10 years. This observation they describe as another aspect of what they have termed the "legacy effect."

These latest reports add significantly to prior descriptions of the long-term effects of a limited period of glycemic control (9–12). Prospective collection of posttrial information over decades has allowed each of these studies to accumulate a critical mass of information on long-term outcomes long after cessation of the original 6.5 and 10 years of intensive versus standard glycemic intervention in the DCCT and UKPDS.

Although both addressed the question of whether enhanced glycemic control could alter outcomes, the studies differed in many ways. The DCCT enrolled young people (mean age 26 years) with type 1 diabetes with a mean of duration of 6 years. A difference of nearly 2.0% (22 mmol/mol) HbA_{1c} was maintained in the randomized treatment phase over 6.5 years. The end point of emphasis was progression of new or established retinopathy. There were too few cardiovascular events for analysis due to the age of the population. In contrast, the UKPDS enrolled an older population (mean age 56 years) within a year after diagnosis of type 2 diabetes, randomizing those with elevated fasting plasma glucose after 3 months of lifestyle therapy. A between-treatment difference of almost 1.0% (11 mmol/mol) HbA_{1c} was then maintained for 10 years, but with worsening levels in both arms over time. The leading end points used to assess treatment differences were composites of medical events, including any diabetes-related event (including cardiovascular and microvascular outcomes), deaths from diabetes-related causes, and deaths from any cause (2).

Notwithstanding these differences, the studies' similar approaches to long-term follow-up allow construction of a simple model of the natural history of diabetes-related outcomes, linking glycemic control to the late complications. This model considers the effects of hyperglycemia within categories that differ both in scale and timing (Table 1). Effects at the molecular level have been described, including structural changes of proteins through glycation and oxidation and epigenetic effects on DNA through methylation of nucleotides. Some alterations may be short-lived, such as glycation of hemoglobin due to replacement of erythrocytes every few months. Changes to longer-lasting proteins such as collagen could contribute to persisting but slowly waning effects. The time course of epigenetic changes is uncertain but could be prolonged if modified stem cell lines persist. Molecular changes may not be apparent for some time, yet eventually lead to changes of tissue structure and function that may have short- or long-term effects. For example, circulating endothelial progenitor cells of marrow origin, responsible for vascular repair, are markedly reduced in type 1 diabetes before complications can be detected (13). Clinically detectable changes may also have long-term effects. Thus, changes to retinal vessels including increased permeability, development of microaneurysms, and capillary loss are early features of diabetic retinopathy. Albuminuria due to increased permeability of vascular membranes is a functional change that signals risk of further progression of diabetic nephropathy. After varying periods of time, cumulative tissue injury can lead to detectable and usually irreversible organ dysfunction and, eventually, impairment of critical functions such as myocardial performance. Medical outcomes of clinical trials are often late-developing critical organ-specific events such as myocardial infarction, hospitalization for heart failure, renal dialysis or transplantation, or lower extremity amputation. Dysfunction of a single organ may have harmful effects elsewhere, such as the deleterious effect of impaired renal function on cardiovascular risk (14). Cumulative damage to multiple organs eventually leads to impaired quality of life and mortality.

A mechanistic question that arises from the DCCT/EDIC and UKPDS follow-up reports concerns the nature of the continuing differences in harm after glycemic control equalizes. Clearly, any irreversible harm that has been identified during the primary study will persist and by itself may have a continuing effect on health-related quality of life

Table 1—Classification of damage secondary to hyperglycemia

Classification	Examples	Time for development	Reversibility
Molecular changes	Glycated hemoglobin	Weeks to months	Weeks to months
	Other modified proteins	Months to years	Partial
	Methylated nucleotides	Years	Uncertain
Tissue injuries	Retinal vessels	2–5 years	Partial
	Glomerular membranes	2–5 years	Partial
	Nerve fibers	2–5 years	Partial
	Arterial wall damage	5–10 years	Limited
Organ dysfunction	Reduced visual acuity	>10 years	Limited
	Reduced eGFR	>10 years	Limited
	Peripheral neuropathy	>10 years	Limited
	Impaired cardiac performance	>10 years	Limited
Clinical events	Vision loss	>10 years	No
	Kidney failure	>10 years	No
	Foot ulceration	>10 years	Limited
	Stroke, myocardial infarct	>10 years	No
	Heart failure	>10 years	Limited
Late impairments	Frailty, reduced mobility	>20 years	Progressive
	Cognitive decline	>20 years	Progressive
	Institutionalization	>20 years	No
	Premature death	>20 years	No

Examples within categories are shown with some associated characteristics.

and function. But if all effects of glycemic differences dissipate after the active treatment period, the curves reflecting cumulative outcomes in the treatment groups will become parallel (Fig. 1*A*); i.e., there would be no difference in the incidence of new events. In this scenario, the relative risk of a given event would decline over time but a numerical between-treatment difference would persist.

However, this is not the pattern generally observed during follow-up of these studies, and there could be a persisting biologic effect on new outcomes. This would lead to continued separation of the curves over time (Fig. 1*B*). The question is, what biologic effects are in play? One possible explanation is that a significant part of the difference in damage to tissues and organ dysfunction between the intervention and control groups at the end of the main study has remained undetected. In this case an excess of new events in the former control group may reflect a greater predisposition to these events in that group that would become apparent as tissue injury reaches a detectable threshold over time. This alone could account for a continuing divergence of event curves. The difference in progression of retinopathy in the DCCT/EDIC persisted for years but waned eventually, possibly reflecting loss of an advantage in prevalence of underlying tissue injury, and perhaps also due to a ceiling effect, as the maximum population incidence is reached later in the intervention group. Such biologic effects may explain the clear difference in total mortality reported by the DCCT/EDIC investigators >20 years after cessation of intensive glycemic therapy, as well as the appearance of protection against death at the end of the follow-up period of UKPDS (4,5).

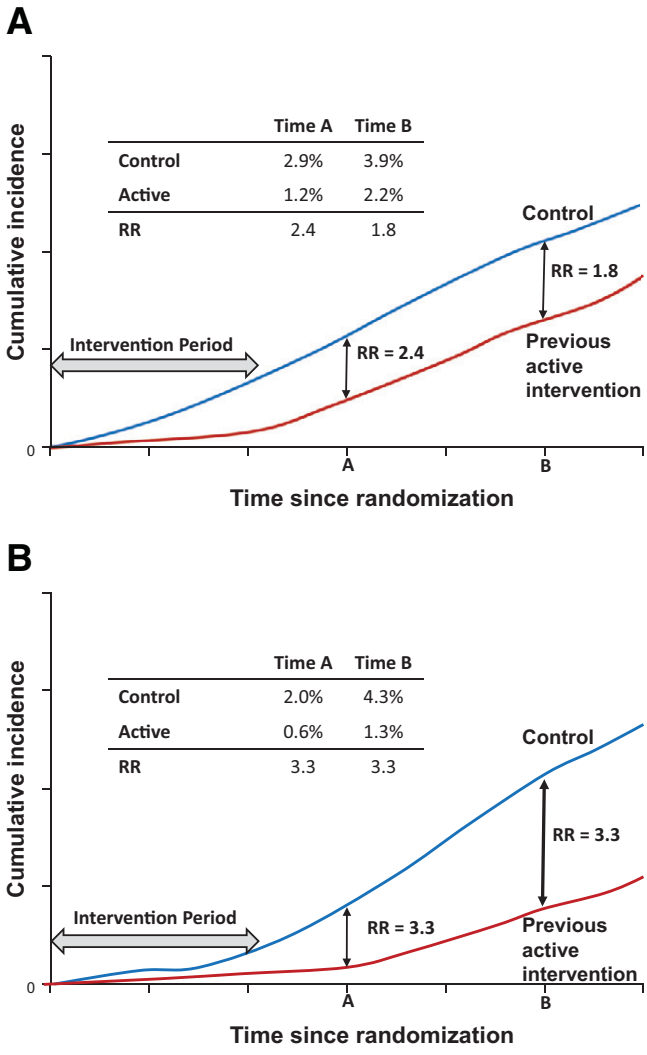

Figure 1—Alternative patterns of effects of hyperglycemia during randomized intervention and after its cessation. *A*: If intervention does not change biology. Shown are cumulative incidence curves for an active intervention and a control group, assuming the intervention has no persisting biologic effect. Risk of an event is reduced only during the intervention, with similar postintervention incidence in both groups. Shown are nonproportional curves with declining relative benefit after the intervention period but persisting cumulative effect. *B*: If intervention changes biology. Shown are curves for an intervention that irreversibly alters biology with persistence of incremental effects after cessation of the intervention. Risk of an event is reduced at any point over the passive follow-up period. Proportional curves reflect higher annual event rates in the control arm during observation, with the same relative benefit at any point of time. RR, risk ratio.

While the relative contributions of different mechanisms to the lingering benefits of intensive glycemic management cannot be estimated at present, the main observation is clinically important. The DCCT/EDIC and UKPDS investigators agree that the first few years after a diagnosis of diabetes are the most important for limitation of later complications (6,7). This strongly emphasizes an important clinical message. Good glucose control must start early, as well as continue long. This would apply to both type 1 and type 2 diabetes, which in this way appear to be more alike than different. Are we doing enough to keep HbA_{1c} ≤7.0% (53 mmol/mol) in the first 10 years of diabetes? Even in the very young and in frail older individuals this is increasingly possible while maintaining quality of life and not impairing the risk-to-benefit ratio. Many people living with diabetes are not succeeding in this quest, yet could with better support. Could some of the extensive resources now applied to management in the last 5 years of life be reallocated to the 10 years following diagnosis of diabetes, when glycemic control matters most and is easiest to attain? The continuing reports from the DCCT/EDIC and UKPDS studies are challenging us to do better.

Duality of Interest. All authors contributed to both the conception and writing of this article. The authors report no direct dualities of interest that are relevant to this work but note that they have together worked and published on nearly all the therapies used to enhance glucose control and with the manufacturers of those therapies. No other potential conflicts of interest relevant to this article were reported.

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