Diabetologia (2021) 64:2131–2137
https://doi.org/10.1007/s00125-021-05539-8

REVIEW

The legacy effect in diabetes: are there long-term benefits?

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Received: 11 March 2021 / Accepted: 27 May 2021 / Published online: 14 August 2021

Abstract

In this narrative review, we summarise the evidence for and against the glycaemic legacy effect from the long-term follow-up of major diabetes trials and observational cohort studies. We provide a summary of the pathophysiological basis for the legacy effect and discuss some translational research. Results from trials of early diabetes and observational cohort studies suggest that a long-term effect of early glycaemic control exists; however, long-term follow-up from trials in participants with established diabetes is not supportive. Additionally, findings for the legacy effect are more conclusive for microvascular complications than macrovascular events. Overall, these results suggest that the glycaemic legacy effect is a long-term benefit (or risk) conferred to individuals in the early stages of diabetes and which is muted over time as individuals' vasculature changes and they develop complications from diabetes.

Keywords Cardiovascular disease · Diabetes mellitus · Diabetic complications · Diabetic nephropathies · Diabetic retinopathy · Glycaemic control · Review

Abbreviations

ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACCORDION	ACCORD Follow-on
ADN	Advanced Diabetic Nephropathy
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation
ESRD	End-stage renal disease
KPNC	Kaiser Permanente Northern California
RRR	Relative risk reduction
UKPDS	UK Prospective Diabetes Study
VADT	Veterans Affair Diabetes Trial

Introduction

In clinical practice, it is common to assume that the major effect of a treatment is an immediate change to a clinical outcome, especially since evidence for this is widespread. For example, glucose-lowering medications reduce blood sugar levels within hours of ingestion or administration. However, in complex chronic diseases such as diabetes, decades-old literature has established that there are long-term benefits of previous periods of euglycaemia and long-term harms associated with previous periods of hyperglycaemia, a phenomenon known as the legacy effect, or metabolic memory. In this review, we will summarise the evidence for this legacy effect of glycaemic control, starting with a review of the observational evidence from randomised trials, real-world cohorts and other studies, and ending with a brief review of the pathophysiological basis underlying the legacy effect.

RCTs: observational follow-up

Every major diabetes trial has investigated the presence of the legacy effect in the post-trial observational follow-up period. Because of their strong initial study design and successful longitudinal follow-up these studies provide the strongest evidence for and against the legacy effect of glycaemic control in diabetes. We will review the three major trials involving participants with recently diagnosed diabetes, all of which favour a legacy effect, and then we will review the three major trials involving participants with established diabetes that provide mixed evidence for the legacy effect. A summary of these findings can be found in Table 1.

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Table 1 Summary of results from RCTs and follow-up studies

Study	Study duration (years)	No. of participants	Mean HbA_{1c} at end of trial	Study findings	Follow-up study period post-trial (years)	Significant legacy effect finding
DCCT	6.5	1441 with recently diagnosed T1D	Intensive: 7.4% (57 mmol/mol) Control: 9.1% (76 mmol/mol)	Decreased rates of microvascular disease in intensive arm No difference in macrovascular disease	17–30	Decreased rates of microvascular disease and macrovascular disease in intensive control arm at follow-up
UKPDS	5	4209 with newly diagnosed T2D	Intensive: 7.0% (53 mmol/mol) Control: 7.9% (63 mmol/mol)	Decreased risk of microvascular disease in intensive arm Non-significant reduction in macrovascular disease	10	Decreased rates of microvascular disease, reduction in MI and mortality in intensive control arm at follow-up
Steno-2	7.8	160 with T2D and microalbuminuria	Intensive: 7.9% (63 mmol/mol) Control: 9.0% (75 mmol/mol)	Decreased rates of microvascular disease in intensive arm	5.5	Decreased rates of microvascular disease, lower rates of CV events, CV mortality and all-cause mortality in intensive control arm at follow-up
ADVANCE and ADVANCE-ON	5	11,140 with pre-existing diabetes (mean duration 8 years)	Intensive: 6.5% (48 mmol/mol) Control: 7.3% (56 mmol/mol)	Decreased rates of microvascular disease in intensive arm No significant difference in macrovascular disease	5.4	Lower rates of ESRD in intensive control arm at follow-up
ACCORD and ACCORDION	3.5	10,251 with pre-existing diabetes (mean duration 10 years)	Intensive: 6.4% (46 mmol/mol) Control: 7.5% (78 mmol/mol)	Increased mortality in intensive control arm Decreased rates of non-fatal CV events	4	No effect on primary outcome of CV events Decreased rates of retinopathy in intensive control group
VADT	5.6	1791 with pre-existing diabetes (mean duration 11.5 years)	Intensive: 6.9% (52 mmol/mol) Control: 8.4% (68 mmol/mol)	No significant difference in macrovascular events between arms	10–15	Reduction in macrovascular events in intensive control arm at 10 years follow-up but effect was lost at 15 years
ADN CKD 3–4	2	120 with pre-existing diabetes and advanced nephropathy (mean duration 15 years)	Intensive: 7.3% (56 mmol/mol) Control: 8.3% (67 mmol/mol)	Decreased rate of progression to ESRD in intensive arm	2	No significant difference in progression to ESRD between arms at follow-up

Study duration is presented as mean, except for ADVANCE (median), ACCORD (study stopped at 3.5 years due to increased mortality in intensive control group) and ADN CKD 3-4 (median 2 years)
ADVANCE-ON, ADVANCE Observational Study; CV, cardiovascular; MI, myocardial infarction; T1D, type 1 diabetes; T2D, type 2 diabetes

Early diabetes The first compelling data for the legacy effect emerged from the long-term follow-up of the DCCT, conducted from 1983 to 1989, known as the Epidemiology of Diabetes Interventions and Complications (EDIC) study. The trial randomised 1441 participants with newly or recently diagnosed type 1 diabetes to receive either intensive glycaemic control (i.e. external insulin pump or three insulin injections daily) or standard glycaemic control (i.e. two insulin injections daily) [1]. The investigators originally found that intensive control significantly decreased rates of microvascular complications but no significant difference in macrovascular disease [1]. After decades of follow-up, which was completed by 97% of the original participants, despite the HbA_{1c} levels converging in the two study arms 1 year after the study conclusion, the intensive control arm continued to have a significantly lower rate of microvascular complications. Furthermore, a new significant decrease in macrovascular complications emerged (relative risk reduction [RRR] 42% [95% CI 9, 63] for CVD; $p = 0.02$) [2–4]. This effect was seen at 17 years of follow-up and persisted for at least 30 years (RRR 30% [95% CI 7, 48] for CVD; $p = 0.02$), while the HbA_{1c} remained the same in both groups [5].

Similar results were found in the type 2 diabetes population in the pivotal UK Prospective Diabetes Study (UKPDS). Individuals with newly diagnosed type 2 diabetes were randomised to undergo intensive vs conventional glycaemic control ($N = 4209$; median age 53 years) and after the trial ended there was a 25% (95% CI 7, 40; $p = 0.0099$) RRR in microvascular complications and a 16% difference in macrovascular complications (approaching statistical significance, $p = 0.052$) [6]. Similar to the DCCT, differences in glycaemic control were lost at 1 year after the study conclusion. However, a 24% ($p = 0.001$) reduction in microvascular events persisted in the intensive control arm for 10 years after the study ended, by which time a 15% reduction in myocardial infarction ($p = 0.01$) and 13% reduction in mortality ($p = 0.007$) had emerged [7].

Lastly, in the Steno-2 trial, 160 participants with type 2 diabetes and microalbuminuria (mean age 55 years) were randomised to undergo intensive vs conventional glycaemic control and were followed for a total of a mean 13.3 years [8]. Again, despite convergence in glycaemic control after the end of the study, participants in the intensive control arm had a lower risk of cardiovascular events (HR 0.41 [95% CI 0.25, 0.67]; $p = 0.02$), cardiovascular mortality (HR 0.43 [95% CI 0.19, 0.94; $p = 0.04$) and all-cause mortality (HR 0.54 [95% CI 0.32, 0.89]; $p = 0.02$) [8].

Established diabetes The evidence for the legacy effect becomes less clear for individuals with established diabetes on examination of data from the major diabetes trials that compared intensive with standard glycaemic control. The results most consistent with the early diabetes trials came from the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial. In this trial, 11,140 participants (mean age 66 years) with pre-existing diabetes (mean duration 8 years) were randomised to undergo intensive glycaemic control with a goal HbA_{1c} of 48 mmol/mol (6.5%) vs standard glycaemic control. This study found significant reductions in microvascular disease (HR 0.86 [95% CI 0.77, 0.97]; $p = 0.01$), mostly due to a difference in nephropathy rates (HR 0.79 [95% CI 0.66, 0.97]; $p = 0.006$) [9]. The reduced rate of end-stage renal disease (ESRD) was maintained in the post-trial follow-up (HR 0.54 [95% CI 0.34, 0.85]; $p = 0.007$), again despite convergence of HbA_{1c} levels after the study period ended [10]. However, there are several caveats to these findings that may diminish their significance (e.g. the post-trial follow-up study did not measure nephropathy, which would have provided important process measure data to explain results). Additionally, there were few ESRD events and no difference in renal death, raising the possibility that the difference may be related to survivorship bias.

In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, findings were different from those of other studies. In this trial, 10,251 participants (mean age 62.2 years; median diabetes duration 10 years) were randomised to undergo either intensive glycaemic control (target HbA_{1c} 42 mmol/mol [6.0%]) or standard glycaemic control (HbA_{1c} 53–63 mmol/mol [7.0–7.9%]) [11]. The study was stopped after 3.5 years due to a significant increase in the rate of death in the intensive arm. In observational follow-up, intensive glycaemic control did not have an effect on the primary outcome of cardiovascular events (HR 0.95 [95% CI 0.87, 1.04]; $p = 0.27$) [12, 13]. However, in a subgroup analysis (the ACCORD Follow-on [ACCORDION] eye study), participants in the intensive glycaemic control group displayed a 45% decreased progression of retinopathy (adjusted OR 0.42 [95% CI 0.28, 0.63]; $p < 0.0001$), suggesting a possible legacy effect on microvascular outcomes [13]. Importantly, the participants in the ACCORDION eye study had to have survived the 4 year follow-up period and were slightly younger, with a shorter duration of diabetes and lower baseline HbA_{1c}, than the average participant in the ACCORD trial.

Another conflicting result came from follow-up of the Veterans Affair Diabetes Trial (VADT). In observational studies following the VADT, which randomised 1791 individuals with longstanding diabetes to undergo intensive vs conventional glycaemic control, a significant reduction in macrovascular events (HR 0.83 [95% CI 0.70, 0.99]; $p = 0.04$) was seen in the intensive-control arm in an analysis performed after about 10 years of follow-up [14]. However, at the 15 year follow-up, when data were adjusted for the most recent HbA_{1c} values, no significant reduction in macrovascular complications (HR 0.91 [95% CI 0.78, 1.06]; $p = 0.23$) was evident [15]. Unfortunately, results from the VADT trial on the long-term effects of intensive glycaemic control on microvascular diabetic complications have not been published.

Lastly, a smaller trial (Advanced Diabetic Nephropathy [ADN] CKD 3-4 Trial) enrolled 120 participants (mean age 57.5 years; mean diabetes duration 15 years) with advanced diabetic nephropathy and randomised them to undergo intensive control (integrated intensive diabetes and renal care with behavioural/dietary and pharmacological interventions) vs standard care [16]. After 2 years of follow-up, participants in the intensive control arm showed less progression towards ESRD (HR 0.13 [95% CI 0.02, 0.54]). About 60% of these participants were then followed after the trial to monitor for a legacy effect of diabetes control. The trial did not find a significant difference in outcomes in the follow-up period (23.7% advanced to ESRD in the intervention group vs 20.6% in the control group) [17].

In summary, the results from the observational follow-up of the clinical trials suggest that the duration of diabetes may modify the legacy effect, with longer durations of diabetes dampening any effects. Additionally, the long-term effects of glycaemic control likely have a greater effect on microvascular complications than macrovascular complications.

Real-world observational cohort studies

More evidence to elucidate the concept of the legacy effect comes from retrospective real-world cohort studies. These studies have been completed after major trials to examine whether the legacy effect exists in cohorts outside of clinical trial populations and to examine the extent of this effect on long-term microvascular and macrovascular outcomes.

Several studies have been conducted using data from the Kaiser Permanente Northern California (KPNC) Diabetes Registry. In a cohort study using KPNC data, following 34,737 individuals with newly diagnosed diabetes (mean age 56.8 years) for a mean of 13 years, participant outcomes were correlated to HbA_{1c} values over each year of the study. The study found that when compared with an HbA_{1c} <48 mmol/mol (6.5%), higher HbA_{1c} values during the first year after diabetes diagnosis were associated with an increased future risk of microvascular diabetic complications and mortality, even when corrected for HbA_{1c} values after the first year [18]. Additionally, longer periods of early exposure to an HbA_{1c} >64 mmol/mol (8.0%) were associated with increased microvascular events and increased mortality [18]. These findings suggest that very early glycaemic control after a diagnosis of diabetes can have long-term effects on complications up to 10 years from diagnosis and echo the results of the DCCT and UKPDS trials.

In another longitudinal study using KPNC data, 28,016 individuals with newly diagnosed diabetes (mean age 56.2 years) were found to fit into several different HbA_{1c} trajectories over the course of 10 years [19]. After adjustment for demographic factors, the study found that individuals whose HbA_{1c} was initially high and then later decreased had a 27% higher mortality rate (HR 1.27 [95% CI 1.03, 1.58]) and a 28% higher rate of microvascular disease (HR 1.28 [95% CI 1.08, 1.53]) when compared with individuals who had a low stable HbA_{1c} trajectory [19]. These findings again demonstrated the important influence of early glycaemic control on future outcomes.

Similar results for the legacy effect were seen in a Japanese study of 1547 individuals (mean age 56 years) with diabetes (mean duration 5.9 years) followed up to 22 years [20]. Even with this long follow-up time, baseline HbA_{1c} was found to be a significant predictor of microvascular diabetes complications. The investigators used a moving mean analysis of HbA_{1c} values over the course of 22 years to determine that the duration of the legacy effect for this population appeared to be 14–19 years, with a greater effect seen at ≤10 years. The greatest effects were seen for diabetic retinopathy outcomes, followed by diabetic kidney disease, and the least effect was seen for CVD.

Systematic review evidence

One systematic review has attempted to summarise evidence for the legacy effect of glycaemic control in diabetes, specifically regarding cardiovascular outcomes [21]. In a review of seven RCTs, all of which are discussed above, data from a total of 40,346 participants were analysed. The review found that intensive glycaemic control correlated with significantly decreased risk of cardiovascular events (OR 0.86 [95% CI 0.77, 0.96]; $p = 0.007$). These findings were more pronounced in individuals with shorter duration of diabetes (<10 years) (OR 0.73 [95% CI 0.56, 0.94]; $p = 0.01$) and no pre-existing CVD (OR 0.64 [95% CI 0.48, 0.86]; $p = 0.003$), supporting the hypothesis that individuals with early diabetes are more likely to benefit from the legacy effect of intensive glycaemic control. However, when the authors of this systematic review examined post-trial observational studies, there appeared to be no evidence of a protective legacy effect on CVD (OR 0.99 [95% CI 0.92, 1.06]; $p = 0.81$). A review of observational studies carried about by the authors showed that in real-life populations there is some evidence for a legacy effect, although these studies are limited by their observational nature [21].

Other legacy effects in individuals with diabetes

While discussing the legacy effect of glycaemic control, it is important to reflect that the concept of long-term benefits conferred from early intensive treatment is not unique to glycaemic control. For example, a follow-up study of the ACCORD trial examined individuals with diabetes and

dyslipidaemia who had received fibrate therapy in addition to statin therapy during the study period [22]. Though few of the participants continued fibrate therapy after the study ended, those in the treatment group continued to display lower rates of cardiovascular outcomes (HR 0.65 [95% CI 0.45, 0.94]; $p = 0.02$) even 5 years after the end of the trial. Additionally, a retrospective study examining outcomes in individuals with type 2 diabetes who underwent bariatric surgery found that the individuals whose diabetes went into remission after surgery had improved long-term microvascular outcomes even after they experienced a relapse of diabetes [23]. This points to long-term benefits of even a brief period of glycaemic control. Lastly, an observational follow-up of an RCT found that participants with diabetes who were treated with olmesartan had a significantly decreased rate of microvascular and macrovascular complications, even 3 years after they stopped using the medication [24]. All of these examples illustrate the lasting effects that various therapies can have on long-term diabetic outcomes.

Pathophysiological mechanisms

While the pathophysiological mechanisms underlying the legacy effect are not completely understood, several reviews have well summarised the evidence to date on the extended effects of hyperglycaemia at the cellular level (see Fig. 1) [25–27]. Currently, two major hypotheses have emerged. One important factor in the cellular impact of hyperglycaemia seems to be epigenetics. Elevated blood glucose has been shown to lead to epigenetic modifications of the endothelium through histone modification, DNA methylation and non-coding RNAs. These modifications to the endothelium are believed to drive changes in the microvasculature, leading to microvascular and macrovascular diabetes-related diseases [25]. The intracellular production of superoxide anions also appears to contribute to the lasting effects of hyperglycaemia. Increased glucose levels in cells leads to overproduction of superoxide anions in the mitochondria, which results in downstream effects including the formation of AGEs, which have been associated with diabetes complications. The overproduction of superoxide anions continues even after blood glucose levels normalise, possibly explaining the lasting legacy effects seen after diabetes control is established [26]. Hyperglycaemia can also promote the formation of AGEs independently of superoxide anions. In addition, transient hyperglycaemia can induce the accumulation of senescent cells [28]. All of these mechanisms, including histone modification, DNA methylation, RNA alteration and AGE formation, converge on the activation of proinflammatory pathways, providing a rationale for the chronic low-grade inflammatory status of type 2 diabetes of long duration [29]. Moreover, some particular aspects of glycaemic control may be involved in the phenomenon of metabolic memory [30].

Evidence for the legacy effect comes from both animal and human studies. In a landmark study, hyperglycaemia was induced in dogs at various levels in order to examine its effect on retinopathy [31]. The dogs that underwent induced hyperglycaemia exhibited higher rates of retinopathy, even if they had only experienced a short period of hyperglycaemia followed by euglycaemia. This study suggested that early and even brief hyperglycaemia could have long-term effects on vascular disease progression. In human studies, AGEs, in particular, have been closely tied to diabetic complications. In a follow-up study of the DCCT, higher levels of AGEs in

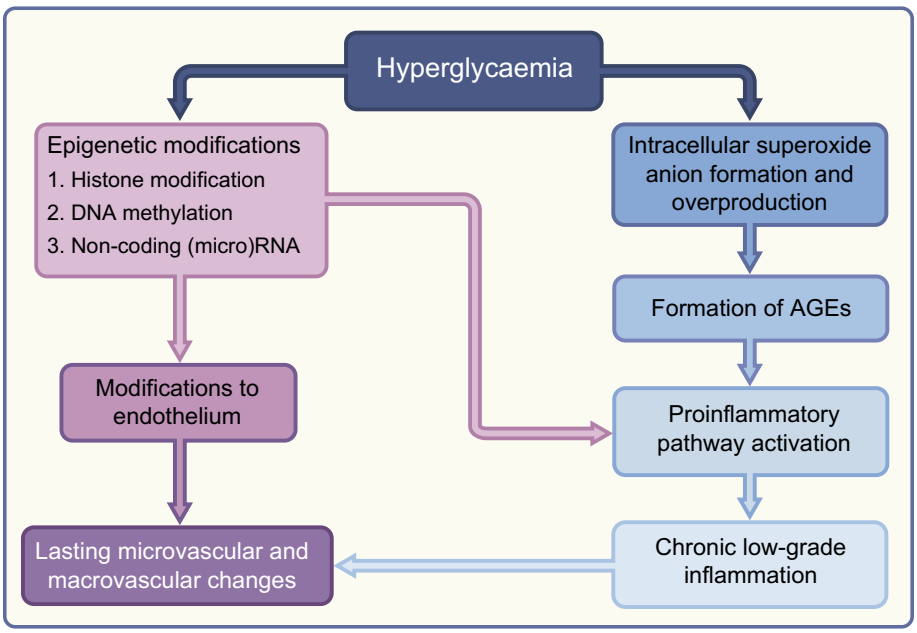

Fig. 1 Pathophysiological mechanisms underlying the legacy effect. This figure is available as a downloadable slide

skin biopsies were significantly correlated with the development of retinopathy and nephropathy [32, 33].

Conclusion

This review sought to summarise the evidence for the glycaemic legacy effect, the long-term effects of early glycaemic control in diabetes. The data seem to support more clearly the concept of a legacy effect for individuals with early diabetes. Evidence from the DCCT, UKPDS, Steno-2 and the KPNC observational cohort studies consistently demonstrate this conclusion for microvascular disease, and the DCCT, UKPDS and Steno-2 support this also for macrovascular disease. Results from trials involving individuals with established type 2 diabetes have been more mixed in regard to the legacy effect. There was consistency that there may be a glycaemic legacy effect for microvascular complications even in the ADVANCE and ACCORD long-term follow-up, but not the ADN CKD 3–4 trial. In addition, evidence for an effect on macrovascular disease was not present in ADVANCE, ACCORD or the VADT. Another complicating factor regarding the legacy effect and macrovascular complications is that glycaemic control has a small effect on macrovascular complications at best and since the time period during which DCCT and UKPDS were conducted new strategies have emerged that have a greater impact on the management of macrovascular diseases (e.g. tobacco cessation, statin therapy).

Overall, these results suggest that the glycaemic legacy effect is a long-term benefit (or risk) conferred to individuals with early diabetes that is muted over time as the individuals' vasculature changes and they develop complications from diabetes.

Supplementary Information The online version contains a slide of the figure for download available at https://doi.org/10.1007/s00125-021-05539-8.

Funding Work in NL's laboratory is supported by the National Institute on Minority Health and Health Disparities (R01 MD013420) and the National Institute of Diabetes and Digestive and Kidney Diseases (P30 DK092949). The funders had no role in the design and conduct of the review or the content and preparation of the manuscript.

Authors' relationships and activities The authors declare that there are no relationships or activities that might bias, or be perceived to bias, their work.

Contribution statement Both authors were responsible for drafting the article and revising it critically for important intellectual content. Both authors approved the version to be published.

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