Retinopathy

Metabolic memory: The long-term results of early glycaemic control in type 1 diabetes

Deborah Broadbent
Honorary Senior Lecturer, University of Liverpool, Liverpool

The DCCT (Diabetes Control and Complications Trial), a randomised controlled trial conducted between 1983 and 1993, was arguably the most important study in people with type 1 diabetes, highlighting the crucial importance of intensive therapy aiming to achieve near normal glucose levels (as safely as possible), compared with conventional management, in reducing the development and progression of microvascular complications in this population. The study showed that intensive therapy for a mean of 6.5 years reduced the risk of diabetic retinopathy (DR) development and progression by 76% compared with conventional therapy.

In the observational follow-up study, EDIC (Epidemiology of Diabetes Interventions and Complications), it was shown that, 4 years after DCCT ended, the risk of further progression of DR was greatly reduced in the intensive treatment group, despite the fact that HbA_{1c} levels were now nearly equivalent in the two groups. The term "metabolic memory" was coined to describe the long-term benefit of a period of excellent control. At 10 years, EDIC showed the further persistence of this metabolic memory. In the article summarised alongside, the DCCT/EDIC investigators describe the progression of DR over a total of 18 years of EDIC follow-up. In a companion article (DCCT/EDIC Research Group, 2014), they describe the progression of nephropathy.

At the end of DCCT, participants in the conventional treatment arm were transferred to receive intensive diabetes therapy. In 1994, 1375 of the 1428 surviving subjects (96%) were enrolled in EDIC. In EDIC years 15–18, outcome data were available for 1214 participants (84% of the original DCCT cohort and 88% of those enrolled in EDIC), demonstrating remarkably high study compliance! In this article, the authors report the risk of further progression of DR, progression to proliferative DR (PDR), development of clinically significant macular oedema (CSMO) and the need for intervention (laser photocoagulation or intravitreal vascular endothelial growth factor inhibitors).

Long-term follow-up showed a persistent beneficial effect of the initial 6.5 years of intensive therapy on further DR progression, development of PDR, development of CSMO and treatment rates for both DR and maculopathy. Complication rates increased in parallel; however, the difference in risk of progression narrowed between the two groups. This was explained by a decline in incidence in the conventional treatment group rather than an increase in the intensive treatment group – a further demonstration of metabolic memory, as the HbA_{1c} in the intensive treatment group rose from around 7% (53 mmol/mol) at the end of DCCT to 8% (64 mmol/mol) at the 15–18-year EDIC follow-up, whereas in the conventional group it fell from about 9% (75 mmol/mol) to 8%.

This is yet another demonstration of the vital importance of achieving and maintaining good early glycaemic control in our patients! ■

DCCT/EDIC Research Group (2014) 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* **2**: 793–800

Diabetes

DCCT/EDIC trials: Retinopathy risk at 18-year follow-up

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓✓

1 In this study, the authors report the outcomes in terms of diabetic retinopathy (DR) development and progression 18 years into the EDIC (Epidemiology of Diabetes Interventions and Complications) study, the long-term follow-up of the DCCT (Diabetes Control and Complications Trial).

2 Outcome data were available for 1214 EDIC participants (606 and 608 from the original intensive and conventional treatment groups, respectively). Following the switch in the conventional treatment arm to intensive treatment at the end of DCCT, the mean HbA_{1c} at the final follow-up had equalised in the two groups.

3 Despite this, fewer people in the intensive treatment group had a ≥3-step progression of DR than those in the conventional group (39% vs 56%; adjusted risk reduction, 46%).

4 Similarly, the risk of severe non-proliferative DR, proliferative DR and need for photocoagulation therapy was significantly lower in the intensive group (risk reduction, 42%, 43% and 33%, respectively); the risk of clinically significant macular oedema was also reduced by 23% (P=0.09).

5 Although the between-groups difference in retinopathy risk has reduced in more recent years, the authors point out that the change was not explained by an increase in risk in the former intensive treatment group but by a decline in risk in the conventional group, following initiation of intensive treatment at the end of the DCCT.

Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group (2015) 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* **64**: 631–42

Acta Ophthalmol

Adaptive optics in diabetic retinopathy imaging

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓✓

1 Adaptive optics (AO) imaging is a new technique to investigate retinal structures at greater resolutions than in fundus photography or optical coherence tomography (OCT).

2 In this qualitative study, the authors described the structure of diabetic retinopathy (DR) lesions as observed by AO compared with fundus and OCT imaging in 19 people (38 eyes) with diabetes.

3 All lesions that appeared red on fundus photography appeared as dark, hyporeflective elements on AO imaging, although the latter method could not distinguish haemorrhages from microaneurysms.

4 AO imaging also revealed dark elements that were smaller than could be resolved with fundus imaging; the smallest of these lesions were the size of white and red blood cells (approximately 20 µm and 7 µm, respectively) and were circular.

5 All hard exudates observable on fundus and OCT imaging were observable on AO imaging, but the lesions had heterogeneous patterns comprising interchanging areas of white and dark. In high resolution, the exudates had irregular surfaces with numerous buddings of different sizes.

6 AO images were blurred in areas of retinal oedema, but cystoid spaces observable on OCT were also observable on AO and had a sharp delimitation with a darker hyporeflective rim at the inner side of the cyst wall.

7 The authors conclude that AO may improve our understanding of DR and may help with its earlier detection.

Bek T (2014) Fine structure in diabetic retinopathy lesions as observed by adaptive optics imaging. A qualitative study. *Acta Ophthalmol* **92**: 753–8

Acta Ophthalmol

Automated image analysis in diabetic retinopathy screening

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓

1 In this study, the authors assessed the accuracy of an automated system to detect signs of diabetic retinopathy (DR) within a systematic screening programme.

2 The iGrading® software (Medalytix, Manchester) comprises an algorithm that first assesses image quality in digital retinal photographs and then diagnoses DR based on the presence of microaneurysms.

3 The iGrading system was run in a cohort of DR screening participants in Spain, and the results compared with the assessments of a single specialist masked to the results.

4 Among 5278 people with diabetes screened, the estimated prevalence of DR was 15.6%. The software diagnosed DR in 29.9% of the cohort and rated 26.2% of the images as ungradable (compared with 2.0% according to the specialist).

5 Of the 44% of people assessed as having no DR by the software (n=2309), there were 31 false negatives. Overall, the system had a sensitivity of 94.5%, a specificity of 68.8%, a positive predictive value of 34.1% and a negative predictive value of 98.7%.

6 One limitation of the system is that it only detects microaneurysms, not exudates, cotton-wool spots or isolated retinal thickening; nonetheless, the authors conclude that it is accurate in ruling out DR and could thus reduce ophthalmologists' workloads.

7 Further studies to assess the cost-effectiveness of this system in other cohorts are warranted.

Soto-Pedre E, Navea A, Millan S et al (2014) Evaluation of automated image analysis software for the detection of diabetic retinopathy to reduce the ophthalmologists' workload. *Acta Ophthalmol* **93**: e52–6

Acta Ophthalmol

Relationship between pulse pressure and CMT variation in DMO

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓

1 Pulse pressure (PP), the difference between systolic (SBP) and diastolic blood pressure (DBP), has been correlated with exacerbation of diabetic retinopathy; however, its effects on diabetic macular oedema (DMO), and particularly central macular thickness (CMT) variation, are less well studied.

2 In this prospective study, 23 people with DMO and a CMT of >260 µm underwent CMT and BP measurement every 2 weeks for 3 months.

3 Over the six visits, mean CMT varied by 88 µm, and 11 participants (48%) had at least one >11% change in CMT compared with their median value. There was no difference in baseline CMT between those who had significnant CMT changes and those who did not.

4 The mean CMT varied by 32 µm over 24 hours, decreasing throughout the day and increasing at night, although the changes were not significant.

5 PP (measured at the same time as CMT) was associated with CMT first thing in the morning (r=0.29; P<0.001) and over 24 hours (r=0.48; P=0.02); however, SBP and DBP were not.

6 The authors posit that increased shear stress, brought about by increased retinal blood flow from elevated PP, could be the mechanism linking PP and CMT; however, they warn against inferring causation from correlation in this study.

7 Nonetheless, this variation in CMT and PP should be borne in mind when evaluating DMO therapies.

Dupas B, Feldman-Billard S, Bui Quoc E et al (2014) Influence of pulse pressure and spontaneous variations of macular thickness in patients with diabetic macular oedema. *Acta Ophthalmol* **92**: e372–6

"The authors conclude that adaptive optics may improve our understanding of diabetic retinopathy and may help with its earlier detection."