Nephropathy

DCCT: The gift that keeps on giving

Rudy Bilous, Professor of Clinical Medicine, Newcastle University, Newcastle and Consultant Physician James Cook University Hospital, Middlesbrough

The DCCT (Diabetes Control and Complications Trial) is a gift that keeps on giving, particularly with regard to our understanding of the development of microvascular complications.

The article summarised alongside (DCCT/EDIC Research Group et al, 2012) is another such gift and concentrates on nephropathy, specifically the loss of glomerular filtration rate (GFR). This is important because hitherto we have had to rely on measures of surrogate outcomes in nephropathy intervention trials such as albuminuria, which can fluctuate from day to day, regress to the normal range spontaneously and have a poor direct correlation with GFR and pathological structure.

This latest analysis shows conclusively that participants randomised to receive intensive diabetes therapy experienced a 50% risk reduction in GFR declined to <60 mL/min/1.73m^2 when compared with conventional therapy. Moreover, there were similar reductions in those with GFR <30 mL/min/1.73m^2 and those entering end-stage renal disease (ESRD), although the numbers were small and the differences did not achieve significance.

What can we derive about the pathophysiology of nephropathy from these findings? Interestingly, a small group of participants had a direct estimate of GFR using iothalamate clearance during the DCCT and at year 1–2 follow-up in the EDIC (Epidemiology of Diabetes Interventions and Complications) study. The absolute values were similar to those derived from serum creatinine, which is reassuring, but the acute changes in the intensively treated participants in years 1–2 of DCCT, and in the conventionally treated participants in years 1–2 of EDIC, were greater using iothalamate estimates. GFR is known to be higher in people newly diagnosed with type 1 diabetes than age-matched controls – this phenomenon is termed hyperfiltration. One of the drivers of hyperfiltration is hyperglycaemia so it is perhaps no surprise that GFR falls with intensive therapy. The rates of loss of GFR did not differ after this initial fall for both the intensively and conventionally treated participant, implying that hyperfiltration may not be a major driver of progressive loss of GFR.

These data reveal several interesting points for consideration. First, that tight glycaemic control has long-term benefits in terms of preservation of renal function in those with type 1 diabetes, although the authors estimate that 29 people need to be treated for 6.5 years to prevent one of them from developing a GFR <60 mL/min/1.73m^2. Second, the numbers developing albuminuria are much lower than historical cohorts and suggest that the incidence of advanced nephropathy is declining. This is reflected in the small numbers with ESRD (eight intensive vs 16 conventional arms) after 22 years' follow-up. Third, the absolute numbers developing microalbuminuria in the intensive and conventional arms continue to increase with time such that the absolute difference was only 3.2% at 22 years. Thus, intensive control may just delay, rather than completely preventing, nephropathy – shifting the survival curve to the right. Fourth, the numbers requiring antihypertensive therapy (specifically renin–angiotensin system blockade) were equal in the two arms, implying that use of these agents alone is not enough to prevent the development of microalbuminuria. Finally, the benefit of allocation to the intensive arm was completely attenuated when corrected for time-weighted estimates of glycaemia and albuminuria, suggesting that reducing both – by whatever method – is what counts.

We should be reassured by these data and the declining rates of significant renal complications. People with diabetes should be reassured too.

NEJM

Risk of impaired GFR attenuated by intensive T1D treatment

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓

1 People with T1D are at high risk of kidney disease, characterised by impaired glomerular filtration rate (GFR) which leads to end-stage renal disease and increases the risk of cardiovascular disease and death.

2 In the DCCT (Diabetes Control and Complications Trial), 1441 people with T1D were randomised to receive either 6.5 years of intensive diabetes therapy aimed at achieving near-normal glycaemia, or to conventional diabetes therapy aimed at preventing hyperglycemic symptoms.

3 Some 1375 participants were followed-up in the EDIC (Epidemiology of Diabetes Interventions and Complications) study, during which serum creatinine levels were measured annually and GFR estimated with the use of the Chronic Kidney Disease Epidemiology Collaboration formula.

4 In the present study, the authors analysed data from the DCCT and EDIC to determine the long-term effects of intensive diabetes therapy on the risk of impairment of the GFR (defined as incident estimated GFR <60 mL/min/1.73 m^2 of body-surface area at two consecutive study visits.

5 Median follow-up was 22 years. GFR impairment developed in significantly fewer (n=24) participants assigned to intensive therapy than those (n=46) assigned to conventional therapy (P=0.006).

6 The authors concluded that risk of impaired GFR was significantly lowered by the early and intensive management of glycaemia in T1D.

DCCT/EDIC Research Group, de Boer IH, Sun W et al (2012) Intensive diabetes therapy and glomerular filtration rate in type 1 diabetes. *N Engl J Med* **365**: 2366–76

DIABETES

High and low HbA_{1c} place those on haemodialysis at increased risk of death

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓

1 The literature is inconsistent with regard to the association between glycaemic control and outcomes among people with diabetes who are receiving maintenance haemodialysis (MHD).

2 The authors examined the predictability of mortality by HbA_{1c} and random serum glucose levels.

3 Some 54 757 people with diabetes receiving MHD between July 2001 and June 2006 (age 63±13 years; 51% men) were recruited and followed up for 1 year.

4 Adjusted all-cause death hazard ratio (HR) for baseline HbA_{1c} increments of 8.0–8.9, 9.0–9.9, and ≥10% (64–74, 75–85 and ≥86 mmol/mol, respectively) were compared with a reference level of 7.0–7.9% (53–63 mmol/mol) and found to be 1.06 (95% confidence interval [CI], 1.01–1.12), 1.05 (95% CI, 0.99–1.12) and 1.19 (95% CI, 1.12–1.28), respectively.

5 A symmetric increase in mortality also occurred with time-averaged HbA_{1c} levels in the low range (6.0–6.9% [42–52 mmol/mol]; HR, 1.05 [95% CI, 1.01–1.08]; 5.0–5.9% [31–41 mmol/mol], 1.08 [95% CI, 1.04–1.11], and ≤5% [≤31 mmol/mol], 1.35 [1.29–1.42]) compared with 7.0–7.9% in fully adjusted models.

6 The authors concluded that HbA_{1c} levels ≥8% (64 mmol/mol) and very low glycaemic levels were both associated with high mortality risk in this population.

Ricks J, Molnar MZ, Kovesdy CP et al (2012) Glycemic control and cardiovascular mortality

DIABETOLOGIA

Consistent reno-protection of ACEI–ARBs over other antihypertensives

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓

1 The authors of this meta-analysis aimed to compare the renal outcomes between angiotensin converting enzyme inhibitor (ACEI)–angiotensin II receptor blocker (ARB) and other antihypertensive drugs or placebo in people with T2D.

2 Risk ratios from eligible studies (673 identified, 28 eligible) were pooled using a random- or fixed-effects models based on heterogeneity.

3 ACEI–ARB had significantly lower risk of serum creatinine doubling (pooled relative risk [PRR], 0.66), macroalbuminuria (PRR, 0.70) and albuminuria regression (PRR, 1.16) than other antihypertensive drugs, mainly calcium channel blockers.

4 The authors concluded that ACEI–ARB offer a consistent reno-protective effect over other antihypertensive drugs in T2D.

Vejakama P, Thakkinstian A, Lertrattananon D et al (2012) Reno-protective effects of renin-angiotensin system blockade in type 2 diabetic patients: a systematic review and network meta-analysis. *Diabetologia* **55**: 566–78

WORLD JOURNAL OF SURGERY

Diabetes diagnosis before or after renal transplant impairs allograft outcome

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓✓

1 The authors of this retrospective observational cohort study aimed to compare the impact of preexisting diabetes (PD), posttransplant diabetes (PTD) and diabetes-free (DF) status on the long-term outcomes of renal transplant recipients (RTRs).

2 RTRs (n=427) who underwent transplantation between 1999 and 2008 were identified and followed up for the composite primary outcome of doubling of the serum creatinine level, graft failure or death.

3 A total of 70 people had PD, 104 had PTD and 253 were DF; relative to the DF group, the PD group had a 6.36-fold increased risk (P<0.001), and the PTD group had a 2.00-fold increased risk (P=0.029) of developing the primary outcome.

4 The authors concluded that either PD or PTD significantly impaired kidney allograft outcome.

Tsai JP, Lian JD, Wu SW et al (2011) Long-term impact of pretransplant and posttransplant diabetes mellitus on kidney transplant outcomes. *World J Surg* **35**: 2818–25

AMERICAN JOURNAL OF KIDNEY DISEASE

ESRD at 3 years more likely than death in T2D nephropathy

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

1 In this retrospective analysis, rates of end-stage renal disease (ESRD), cardiovascular death and all-cause mortality in 3228 adults with T2D and nephropathy were assessed.

2 During mean follow-up of 2.8 years 19.5% of the cohort developed ESRD at approximately 2.5 times the incidence of cardiovascular death and 1.5 times that of all-cause mortality.

3 The authors concluded that people with T2D and nephropathy were more likely to reach ESRD than die during 3 years' mean follow-up and stressed the implications for future renal replacement therapy requirements given the rapidly increasing number of cases of T2D.

Packham DK, Alves TP, Dwyer JP et al (2012) Relative incidence of ESRD versus cardiovascular mortality in proteinuric type 2 diabetes and nephropathy: results from the DIAMETRIC (Diabetes Mellitus Treatment for Renal Insufficiency Consortium) database. *Am J Kidney Dis* **59**: 75–83

> *"The authors concluded that people with T2D and nephropathy are more likely to reach end-stage renal disease than die during 3 years' mean follow-up and stressed the implications for future renal replacement therapy requirements given the rapidly increasing number of cases of T2D."*