Nephropathy

Glycaemic control in established nephropathy – every little helps

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Although the rates of end-stage renal disease (ESRD) in people with type 1 diabetes are declining, most notably in Scandinavia, the number requiring renal replacement therapy (RRT) remains high (Finne et al, 2005). The role of tight glycaemic control in preventing the development of microalbuminuria has been established by the Diabetes Control and Complications Trial/ Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC Research Group, 2011); however, these researchers failed to demonstrate an effect of intensive control on rates of ESRD even after 22 years of study, partly because of the remarkably low numbers of individuals who required RRT (8 vs 16, intensive vs conventional control [P=0.10]; DCCT/EDIC Research Group [2011]). Moreover, intensive glycaemic control did not appear to reverse established microalbuminuria in the small cohort of patients who had it at baseline (DCCT Research Group, 1995).

Thus, the following important clinical question remains unanswered: does improved glycaemic control slow down, or even reverse, progressive loss of renal function in individuals with type 1 diabetes who have established nephropathy?

Several studies have demonstrated an association between poor glycaemic control and ESRD, and some small intervention trials have been performed showing no consistent benefit, mostly because they were seriously underpowered (Skupien et al, 2014). The recent paper from the Joslin Clinic, USA (summarised alongside) attempts to answer the question by studying a large cohort of 279 individuals with type 1 diabetes with established nephropathy, and in whom they had comprehensive data on glycaemia for 5 years before and after enrolment into a dedicated renal clinic. They showed that for the 92 patients who were able to improve their glycaemia by a reduction in HbA_{1c} of 11 mmol/mol (1%) or more, the rate of loss of estimated glomerular filtration rate (eGFR) was reduced by 0.17 mL/min/1.73 m^2/year (P<0.001). This may not sound much, but when compounded over time, it resulted in a 24% reduced hazard risk (HR) for ESRD per 11 mol/mol (1%) decrease, and a 10-year cumulative risk of ESRD of 19%, compared to 32% for those whose control remained poor or worsened.

It is worth noting that the patients were generally poorly controlled at the beginning of the observation period (HbA_{1c} 78 mmol/mol [9.3%]), and the average improvement was only a modest 7 mmol/mol (0.6%). There was also a cohort of 30 heavily albuminuric patients who reached ESRD within 5 years of observation and, therefore, were not included in the analysis. Their rate of loss of eGFR of up to 30 mL/min/1.73m^2/year was catastrophic and they had notably worse glycaemia than the rest of the cohort. The poor outlook for people with nephrotic-range albuminuria has been well described but is unexplained and needs further study.

Like all clinical cohort observational studies using a post-hoc design, there are inherent and unquantifiable biases in the analysis. Thus, caution must be exercised in interpretation. However, as the authors point out, there is unlikely to be any repeat of a DCCT-like study in individuals with established complications, neither is it likely that funding agencies will support long-term (>10 years) prospective randomised studies, so what we have is probably as good as it is going to get.

As the apparent benefit of improving glycaemia was independent of baseline HbA_{1c}, we should be working hard with our patients who have established nephropathy to improve their blood glucose control, and this is probably best delivered in a specialised clinic. We need to tell our patients and their carers that every little improvement helps, and it is never too late. ■

DCCT/EDIC Research Group (2011) Intensive diabetes therapy and glomerular filtration rate in type 1 diabetes. *N Engl J Med* **365**: 2366–76

DCCT Research Group (1995) Effect of intensive therapy on the development and progression of diabetic nephropathy in the Diabetic Control and Complications Trial. *Kidney Int* **47**: 1703–20

Finne P, Reunanen A, Stenman S et al (2005) Incidence of end-stage renal disease in patients with type 1 diabetes. *JAMA* **294**: 1782–7

J Am Soc Nephrol

Long-term improvement of HbA_{1c} and ESRD risk for people with T1D

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

1 There is a high risk of end-stage renal disease (ESRD) among people with T1D and proteinuria, but it is unknown whether long-term improvement of glycaemic control can reduce the risk of ESRD.

2 In total, 349 adults with chronic kidney disease stages 1–3 and T1D from the Joslin Proteinuria Cohort were involved in this analysis. All participants had developed proteinuria between 1990 and 2004 and were followed until 2011 as part of a larger, prospective 7- to 15-year follow-up observational study to determine ESRD onset and deaths unrelated to ESRD.

3 From 5 years pre-baseline to follow-up of 5 years post-baseline, the average HbA_{1c} decreased from 78 mmol/mol (9.3%) to 72 mmol/mol (8.7%).

4 Cumulative risk of ESRD after 15 years was significantly lower for people whose HbA_{1c} decreased compared to those whose HbA_{1c} increased or remained poor (29% vs 42%; P<0.001).

5 The difference in ESRD only became apparent at 10 and 15 years follow-up – at 5 years of follow-up there was no visible difference.

6 Long-term sustained improvement of HbA_{1c} decelerates estimated glomerular filtration rate and delays onset of ESRD in people with T1D and proteinuria.

Skupien J, Warram JH, Smiles A et al (2014) Improved glycemic control and risk of ESRD in patients with type 1 diabetes and proteinuria. *J Am Soc Nephrol* **25**: 2916–25

Clin Endocrinol

Allopurinol: Improving renal function

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

1 The authors investigated the effect of long-term effective control of serum uric acid on renal function in people with T2D and asymptomatic hyperuricaemia currently receiving allopurinol treatment.

2 In total, 176 people were split into two groups: allopurinol treatment or conventional treatment. Clinical measures of people before and after 3 years of treatment were taken.

3 After 3 years, the allopurinol treatment was more effective in reducing serum uric acid, urinary albumin excretion rate, serum creatinine ($P<0.01$ for all) and increasing glomerular filtration rate ($P<0.01$) than conventional treatment.

Liu P, Chen Y, Wang B et al (2014) Allopurinol treatment improves renal function in patients with type 2 diabetes and asymptomatic hyperuricemia: 3-year randomized parallel-controlled study. *Clin Endocrinol* 17 Nov [Epub ahead of print]

Diabetic Medicine

Metformin use for renal failure

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

1 Guidelines for the use of metformin suggest that it should be avoided in people with impaired renal function (i.e. an estimated glomerular filtration rate <30 mL/min/1.73 m^2, and used with caution <40 mL/min/1.73 m^2).

2 The authors believe that metformin has come under unfair scrutiny (mainly due to the potential association with lactic acidosis) and that it is reasonable to reduce the restrictions of metformin use among people with renal failure.

3 Their suggested dose schedule for metformin aims to maintain a mean plasma metformin of <10 mg/L (or a more conservative <5 mg/L). They emphasise that these suggestions are for individuals with stable renal function, or with a predictable and slow enough loss of renal function that would allow continuing timely dose modification.

4 The suggested dose schedule for people on dialysis is less certain.

Adam WR, O'Brien RC (2014) A justification for less restrictive guidelines on the use of metformin in stable chronic renal failure. *Diabet Med* **31**: 1032–8

Diabetic Medicine

NSAIDs: Increased risk of CKD in T2D?

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

1 The authors investigated whether there is a temporal relationship between non-steroidal anti-inflammatory drugs (NSAIDs) and the development of chronic kidney disease (CKD) in people with T2D.

2 A retrospective cohort study was carried out among people with T2D and who were CKD-free ($n=48\,715$) using national health insurance claims data in Taiwan.

3 A total of 6406 people with incident CKD were identified from 2008 to 2011.

4 Compared with people not taking any NSAID in 2007, those who were taking such drugs for at least 90 days in 2007 had a higher risk of CKD development (adjusted hazard ratio 1.37, 95% confidence interval 1.26–1.49). NSAIDs should be prescribed with caution to those with T2D.

Tsai HJ, Hsu YH, Huang YW et al (2015) Use of non-steroidal anti-inflammatory drugs and risk of chronic kidney disease in people with type 2 diabetes mellitus, a nationwide longitudinal cohort study. *Diabet Med* **32**: 382–90

Diabetes Obes Metab

Linagliptin: Use in people with mild-to-moderate renal impairment

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

1 The aim of this analysis was to evaluate the efficacy and safety of the dipeptidyl peptidase-4 inhibitor linagliptin (5 mg/day) in mono, dual or triple oral glucose-lowering regimens in people with T2D and mild or moderate renal impairment.

2 There was a pooled analysis of three 24-week, placebo-controlled, phase III trials. Mild renal impairment (estimated glomerular filtration rate 60–<90 mL/min/1.73 m^2) and moderate renal impairment (30–<60 mL/min/1.73 m^2) were compared to people with normal renal function (≥90 mL/min/1.73 m^2).

3 In total, there were 838 people with mild renal impairment, 93 people with moderate renal impairment and 1212 people with normal renal function.

4 After the 24-week study period, linagliptin achieved consistent placebo-corrected mean HbA_{1c} changes across the three renal function categories, with no significant inter-group difference.

5 Across all groups, renal function remained stable throughout the study, and the placebo- and linagliptin-treated groups experienced similar rates of overall and serious adverse events. However, there was a slight trend for higher rates of any adverse events, serious and drug-related, in people with renal impairment.

6 Mild or moderate renal impairment has no clinically meaningful impact on the efficacy and safety of linagliptin in people with T2D.

Groop et al (2014) Linagliptin treatment in subjects with type 2 diabetes with and without mild-to-moderate renal impairment. *Diabetes Obes Metab* **16**: 560–8

"Albuminuria status is a good predictor of mortality and cardiovascular and renal outcomes in people with high cardiovascular risk."