Nephropathy

Type 2 diabetes and nephropathy – better outcomes?

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The seminal and oft-quoted data from the UKPDS (United Kingdom Prospective Diabetes Study) showed that the annual mortality rate for people with type 2 diabetes plus albuminuria >300 mg/L and a serum creatinine level >175 µmol/L (roughly equivalent to chronic kidney disease [CKD] stage 3b), or who were receiving renal replacement therapy (RRT), approached 20%, worse than for many cancers (Bilous, 2008). Moreover, people with increased albuminuria were much more likely to die from cardiovascular disease (CVD) than develop end-stage renal disease (ESRD). The UKPDS participants were newly diagnosed and were mainly white and male. In total, 5097 were recruited between 1977 and 1997, with a median follow-up of 10.4 years. This issue's featured article by Andrésdóttir et al (summarised alongside) comes from the Steno Diabetes Center in Copenhagen, Denmark, and reports better outcomes for people with nephropathy followed between 2000 and 2010 compared with historical data from the same clinic. Is this really so, and what might be the reasons for this apparent improvement?

The authors report a cumulative mortality rate of 37% after a median follow-up of 5.7 years in the current cohort, compared to 53% after 6 years in the participants studied between 1983 and 2002 (Rossing et al, 2004). The adjusted hazard ratio for death was 0.50 (95% confidence interval, 0.36–0.71; $P<0.001$). The proportions of people developing ESRD or entering RRT were very similar in both cohorts: 7% versus 6% for the earlier and later groups, respectively. The rates of decline in glomerular filtration rate (GFR) were 5.2 and 4.4 mL/min/1.73 m^2/year, respectively – a significant but relatively modest improvement. The authors ascribe these apparent improvements to the adoption of a more intensive CVD risk factor management protocol based upon the Steno-2 study (Gaede et al, 2008), a landmark trial in people with type 2 diabetes and CKD (microalbuminuria), which demonstrated a 50% reduction in a combined endpoint of micro- and macrovascular complications including ESRD, fatal and non-fatal myocardial infarction and stroke, and amputations after 13 years of a regimen comprising renin–angiotensin system blockade, low-dose aspirin, lipid-lowering therapy, lifestyle advice (weight loss, exercise, stopping smoking) and intensified glycaemic control.

However, there is always a risk of bias when using historical controls. It is not possible to control for factors such as dietary change, clinic staffing and structure, and population changes in morbidity, etc. The latter is a particular problem, as the first cohort was recruited and studied over 20 years compared to 10 years for the current group, and CVD mortality rates for type 2 diabetes have declined in recent decades (Gregg et al, 2014). A total of 182 patients were included in both study cohorts, and whilst the authors found no difference in rate of change of GFR in these individuals during the first and later observation periods, there is a possible survivor bias in terms of CVD.

How do these results compare with the UKPDS data? Disappointingly, mortality rates and the proportions developing ESRD at the different stages of nephropathy were very similar; in particular, annual mortality for those with ESRD and CVD was 20%, an almost identical result to that in the UKPDS. So the message is that the outlook for people with nephropathy is a bit better, at least in the Steno Center, but CVD remains a much greater risk than ESRD for individuals with type 2 diabetes with nephropathy, even with intensive risk factor management. Thus prevention of nephropathy by optimising glycaemic and blood pressure control must remain the long-term priority. Meanwhile, careful surveillance for, and intensive management of, CVD must be undertaken for all our patients with nephropathy. ■

Bilous R (2008) *Diabetic Med* **25** (Suppl2): 25–9
Gaede P et al (2008) *N Engl J Med* **358**: 580–91
Gregg EW et al (2014) *N Engl J Med* **370**: 1514–23
Rossing K et al (2004) *Kidney Int* **66**: 1596–605

Diabetes Care

Improved prognosis of nephropathy in people with T2D

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

1 Researchers at the Steno Diabetes Center (Copenhagen, Denmark) investigated the long-term survival, development of renal endpoints and decline in glomerular filtration rate (GFR) in people with T2D and diabetic nephropathy (DN) after renin–angiotensin system (RAS) inhibition and multifactorial treatment of cardiovascular risk factors.

2 In total, 543 people receiving RAS inhibition treatment were followed from 2000 to 2010. Their results in terms of the above outcomes were compared with historical data of people with the same criteria (T2D and DN) prior to current treatment guidelines and RAS inhibition being available.

3 The annual GFR decline (SD) was significantly lower in the RAS inhibition cohort compared with the earlier cohort: 4.4 (0.24) versus 5.2 (0.27) mL/min/1.73 m^2/year ($P=0.04$).

4 Crude mortality risk was reduced by 42% in the RAS inhibition group, and after adjustment for age, the mortality risk was reduced by 50% ($P<0.001$ for both). Renal endpoints were also improved in the new-treatment group.

5 The improvements in mortality risk can be attributed to better control of several modifiable cardiovascular risk factors since the introduction of RAS inhibition.

6 The current multifactorial treatment of DN in T2D, including long-term RAS inhibition, has improved the prognosis of DN.

Andrésdóttir G, Jensen ML, Carstensen B et al (2014) Improved survival and renal prognosis of patients with type 2 diabetes and nephropathy with improved control of risk factors. *Diabetes Care* **37**: 1660–7

Diabetes Care

Antihypertensive treatment in people with T1D based on stages of diabetic nephropathy

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

1 The aim of this analysis was to assess blood pressure (BP) control, antihypertensive treatment and prevalence of resistant hypertension (RH) in people with T1D stratified by stages of diabetic nephropathy (DN). RH was defined as failure to reach a defined BP target despite the use of three or more hypertensive drugs of different classes.

2 The study population was a nationally representative cohort of people with T1D from Finland (n=3678).

3 Of participants with a normal albumin excretion rate, 14.1% were on antihypertensive treatment; of these, 74.6% had uncontrolled BP despite treatment. As the stages of DN increased, the proportion of participants in these groups increased.

4 The prevalence of RH was 1.2% in the normoalbuminuric, 4.7% in the microalbuminuric, 28.1% in the macroalbuminuric, 36.6% in the dialysis and 26.3% in the kidney transplant groups.

5 Age, estimated glomerular filtration rate, waist-to-hip ratio, triglyceride levels, microalbuminuria and macroalbuminuria were independently associated with RH.

6 The prevalence of uncontrolled hypertension and RH increases alongside worsening DN in people with T1D.

Lithovius R, Harjutsalo V, Forsblom C et al (2014) Antihypertensive treatment and resistant hypertension in patients with type 1 diabetes by stages of diabetic nephropathy. *Diabetes Care* **37**: 709–17

J Diabetes Complications

Serum uric acid: A predictor for CKD?

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

1 The role of high-normal serum uric acid (SUA) levels in predicting the development of chronic kidney disease (CKD) in people with T2D and preserved kidney function was investigated.

2 In total, 512 people with T2D and preserved kidney function and normouricaemia were divided into four quartiles depending on their SUA level (in mg/dL: Q1 ≤3.8, Q2 3.9–4.5, Q3 4.6–5.5 and Q4 >5.5).

3 The endpoint was the development of CKD of stage 3 or greater.

4 After a mean follow-up of 3 years, 62 participants (12.1%) had progressed to CKD stage 3 or greater.

5 The group with the highest-normal range of SUA (Q4) showed a greater cumulative incidence of stage 3 or greater CKD than those in the lower quartiles.

Kim WJ, Kim SS, Bae MJ et al (2014) High-normal serum uric acid predicts the development of chronic kidney disease in patients with type 2 diabetes mellitus and preserved kidney function. *J Diabetes Complications* **28**: 130–4

Diabetologia

Cardiac autonomic neuropathy and renal function decline

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

1 The authors analysed the impact of cardiac autonomic neuropathy (CAN) on the development of chronic kidney disease (CKD) in people with T2D.

2 A cohort study of 204 people was carried out, and at baseline the prevalence of CKD and CAN was 40% and 42%, respectively.

3 Participants with CAN had a lower estimated glomerular filtration rate (eGFR) and higher prevalence of albuminuria and CKD.

4 After 2.5 years' follow-up, eGFR declined to a greater extent in people with CAN than in those without CAN (P=0.009).

5 CAN was an independent predictor of eGFR decline over the follow-up period (P=0.03).

6 CAN is independently associated with CKD, albuminuria and eGFR in people with T2D.

Tahrani AA, Dubb K, Raymond NT et al (2014) Cardiac autonomic neuropathy predicts renal function decline in patients with type 2 diabetes: a cohort study. *Diabetologia* **57**: 1249–56

Diabetologia

New gene loci that predispose for diabetic ESRD

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

1 The authors used a new algorithm to detect novel genetic variants associated with diabetic nephropathy and end-stage renal disease (ESRD).

2 The algorithm was applied to a cohort of 3464 Finnish people with T1D, and its findings validated in a further 4263 individuals taken from three other studies or registries.

3 Five loci linked to ESRD were identified in the primary cohort.

4 Of these, rs17709344 (located between *RGMA* and *MCTP2*) was confirmed in all three replication cohorts, and rs12137135 (located between *WNT4* and *ZBTB40*) was confirmed in a single replication cohort.

5 These results support previous observations of ESRD susceptibility loci at the *RGMA*/*MCTP2* region, and suggest two novel loci; however, these will need to be replicated in larger cohorts, especially the rare recessive associations.

Sambo F, Malovini A, Sandholm N et al (2104) Novel genetic susceptibility loci for diabetic end-stage renal disease identified through robust naive Bayes classification. *Diabetologia* **57**: 1611–22

"The current multifactorial treatment of diabetic nephropathy in type 2 diabetes, including long-term renin–angiotensin system inhibition, has improved the prognosis of diabetic nephropathy."