Nephropathy

Losartan and early diabetic nephropathy

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

Despite many years of research, there is still no answer to the question "does renin–angiotensin system (RAS) blockade prevent, reverse, or merely delay the progression of diabetic nephropathy (DN)?" There is little doubt that angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) reduce albuminuria more so than other anti-hypertensive agents, and they can slow the decline in glomerular filtration rate (GFR) in advanced nephropathy (National Kidney Foundation, 2012). But, the evidence for efficacy at earlier stages is not proven, and regulatory agencies do not accept reduction of albuminuria as a valid surrogate end point for renal protection (Levey et al, 2009). This problem has led research into the impact of RAS blockade on the pathological changes of DN, reasoning that any improvement is likely to translate into long-term benefit and nephroprotection (ESPRIT Study Group, 2001; Mauer et al, 2009).

The study by Weil et al (summarised alongside) is the latest and one of the largest addressing this question. Losartan had no consistent effect on glomerular or interstitial structure except for a marginally lower mesangial volume at follow-up in those who were microalbuminuric at baseline compared to those receiving a placebo. However, those on placebo had a longer diabetes duration and a higher blood pressure at baseline. Furthermore, as there were no baseline biopsies, it is hard to be certain that this was a true benefit of losartan.

Why have these studies failed to demonstrate any effect of RAS blockade on kidney structure? One problem is the duration of follow-up; the study by Weil et al went on for 6 years, whereas others have ranged from 2–5 years (ESPRIT Study Group, 2001; White et al, 2001; Mauer et al, 2009) and this may be too short to demonstrate an effect on lesions, which could take decades to develop. Pancreas transplantation only showed conclusive evidence of reversal of glomerular lesions after 10 years of normoglycaemia (Fioretto et al, 1998). Secondly, the precision of the estimate of glomerular or interstitial damage is limited by sample size and an assumption of uniform pathological change. Each kidney has around 1 000 000 nephrons and a single biopsy will provide on average 20 or so glomeruli for analysis. Many of the structural parameters have coefficients of variation of 30–50%, which seriously affects the power to detect a change. The Renin Angiotensin System Study (RASS) study (Mauer et al, 2009) based power upon a 50% reduction in mesangial volume at 5 years, which is far in excess of that seen after 10 years in the pancreas transplant recipients. In this study, the placebo-treated group displayed an increase of 0.3% per annum, which is well below the ability of the estimate to detect a change with a sample size of 85. In addition, no power calculation was included in the current study. The study did not obtain a baseline biopsy for comparison, which severely limits the ability to detect change and places an imperative to ensure close matching from the outset (which did not happen). Finally, the study participants, which were Native American Pima, may not be completely representative of all people with T2D. Certainly, this cohort is unusual in having very high GFRs and larger glomeruli compared to their white Europid counterparts (White et al, 2001). Nonetheless, the investigators are to be congratulated on performing a very difficult protocol in a hard-to-reach population, and the data have furthered our understanding of glomerular structure and function in T2D DN.

Where does this leave us with regard to the appropriate use of RAS blocking agents in nephropathy? The latest guidance is that they should not be used for the prevention of development of microalbuminuria in normotensive, normoalbuminuric patients. For hypertensive patients, with or without albuminuria, they remain first-line therapy (National Kidney Foundation, 2012). We still do not know if they positively affect the underlying pathology of DN.

The European Study of the Prevention of Renal Disease in type 1 diabetes (ESPRIT) Study Group (2001) Effect of three years of anti-hypertensive therapy on renal structure in type 1 diabetic patients with albuminuria. *Diabetes* **50**: 843–50.

Fioretto P, Steffes MW, Sutherland DER et al (1998) Reversal of lesions of diabetic nephropathy after pancreas transplantation. *N Engl J Med* **339**: 69–75

Levey AS, Cattran D, Friedman A et al (2009) Proteinuria as a surrogate outcome in CKD: Report of a scientific workshop sponsored by the National Kidney Foundation and the US Food and Drug Administration. *Am J Kid Dis* **54**: 205–26

Mauer M, Zinman B, Gardiner R, et al (2009) Renal and retinal effects of enalapril and losartan in type 1 diabetes. *N Engl J Med* **361**: 40–51

National Kidney Foundation (2012) KDOQI clinical practice guideline for diabetes and CKD: 2012 update. *Am J Kid Dis* **60**: 850–86

White KE, Pinel D, Cordonnier DJ, Bilous RW et al (2001) Does ACE inhibition show slow progression of glomerulopathy in patients with type 2 diabetes mellitus? *Diabet Med* **18**: 933–36

DIABETES

Does losartan preserve kidney structure in early DN?

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

1 Previous research suggests that angiotensin receptor blockers (ARBs) such as losartan are effective in slowing down the progression of diabetic kidney disease. However, it is not known how effective this class of drugs is in delaying the progression of early diabetic nephropathy (DN).

2 The authors conducted a 6-year, double-blind, single-centre clinical trial to assess the efficacy of losartan in people with early diabetic kidney disease and T2D. A total of 169 normoalbuminuric participants of an American Indian descent were randomised to receive 100 mg of losartan or placebo once per day.

3 Glomerular filtration rate (GFR) was measured each year during the study period and 111 participants underwent renal biopsy. The study's primary outcome was a reduction in GFR to ≤60 mL/min or to half the baseline value (>GFR 120 mL/min).

4 Nine participants reached the primary outcome. The unadjusted hazard ratio (losartan compared to placebo) was 0.50 (95% CI, 0.12–1.99).

5 Mesangial fractional volume was reduced in microalbuminuric participants receiving losartan (18.8 versus 25.6%; P=0.02), but not in normoalbuminuric individuals (19.6 versus 17.8%; P=0.86).

6 The authors concluded that losartan treatment may convey some structural benefits in early diabetic kidney disease for individuals with microalbuminuria.

Weil EJ, Fufaa G, Jones LI et al (2013) Effect of losartan on prevention and progression of early diabetic nephropathy in American Indians with type 2 diabetes. *Diabetes* 1 Apr [Epub ahead of print]

DIABETOLOGIA

Diabetic end-stage renal disease: Increased survival rates with SPK

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

1 People with diabetes and end-stage renal disease (ESRD) can be offered simultaneous pancreatic and kidney transplantation (SPK) as treatment for their condition.

2 The authors sought to investigate if SPK transplantation is more effective in improving both patient and kidney graft survival in people with diabetic end-stage renal disease (ESRD), when compared with kidney transplantation (KTA).

3 A retrospective single-centre analysis was performed on 630 individuals with diabetic ESRD. The authors found that median patient survival was greater in those receiving SPK (14.0 years) compared to a single live donor kidney (LDK; 11.5 years) and a single deceased donor kidney (DDK; 6.7 years).

4 After adjusting for the effects of patient age, sex, time on dialysis and treatment type, a multivariate analysis revealed that mortality was lower with SPK transplantation than after LDK (P=0.02) and DDK (P=0.029).

5 Both patient survival (hazard ratio 0.40, 95% CI, 0.30–0.55; P<0.001) and pancreas graft survival (5 year survival rate; 78% versus 61% between 1988–1999) increased after the year 2000 compared to earlier years.

6 The authors concluded that SPK recipients had an increased survival rate compared to both LDK and DDK recipients, with the most notable increase after the year 2000.

Lindahl JP, Hartmann A, Horneland R (2013) Improved patient survival with simultaneous pancreas and kidney transplantation in recipients with diabetic end-stage renal disease. *Diabetologia* **56**: 1364–71

DIABETES CARE

The cost of diabetes healthcare

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

1 The authors investigated the association between HbA_{1c}, renal complications and the 5-year healthcare costs in a population of 138 662 Canadian adults with diabetes.

2 Over 5 years, the mean cost of diabetes healthcare was $26 978 per person, excluding the expense of pharmaceutical treatments. In those over 65 years of age, the mean 5-year cost was $44 511, inclusive of pharmaceuticals.

3 Deteriorating kidney function, proteinuria and inadequate glycaemic control were associated with greater costs. Other factors associated with elevated costs included older age, Aboriginal status, socioeconomic classification, length of diabetes, and the presence of comorbidities.

4 The authors concluded that the financial costs of diabetes healthcare are great, and increase with ineffective glycaemic control and kidney dysfunction.

McBrien KA, Manns BJ, Chui B et al (2013) Health care costs in people with diabetes and their association with glycemic control and kidney function. *Diabetes Care* **36**: 1172–80

DIABET MED

Common genetic determinants of eGFR

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

1 The authors aimed to identify genetic variants that have been previously shown to be associated with estimated glomerular filtration rate (eGFR) and albuminuria in people with T2D.

2 A total of 16 single nucleotide polymorphisms (SNPs) were examined in 3028 participants with T2D. rs1260326 in GCKR, rs17319721 in SHROOM3 and rs12917707 in UMOD were all found to be correlated with baseline eGFR.

3 When stratified by albuminuria status, the effect of UMOD was doubled in those with normoalbuminuria compared to people with albuminuria (P-interaction=0.002). Both SHROOM3 (P-interaction=0.003) and GCKR (P-interaction=0.08) had greater effects in individuals with albuminuria.

4 The authors concluded that albuminuria status can influence the common genetic determinants of eGFR.

Deshmukh HA, Palmer CN, Morris AD et al (2013) Investigation of known estimated glomerular filtration rate loci in patients with type 2 diabetes. *Diabet Med* 16 April [Epub ahead of print]

DIABETES CARE

Ethnicity: HbA_{1c} and risk of mortality

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

1 The authors conducted a prospective cohort analysis to evaluate the clinical value of established ethnic differences in HbA_{1c} in 2484 black and 8593 white participants without diabetes.

2 Adjusted hazard ratios (HRs) for HbA_{1c} risk of kidney disease, coronary heart disease and stroke were similar between black and white people (P for interaction >0.05).

3 White participants with a baseline HbA_{1c} ≥48 mmol/mol (6.5%) had an increased risk of all-cause mortality (HR 1.74; 95% CI, 1.38–2.18) compared to black people (HR 1.38; 95% CI, 1.05–1.81).

4 The authors concluded that HbA_{1c} is predictive of vascular disease and mortality in both black and white people.

Selvin E, Rawlings AM, Bergenstal RM (2013) No racial differences in the association of glycated hemoglobin with kidney disease and cardiovascular outcomes. *Diabetes Care* 30 May [Epub ahead of print]

"Over 5 years, the mean cost of diabetes healthcare was $26 978 per person, excluding the expense of pharmaceutical treatments."