Nephropathy

Time to address hyperkalaemia in diabetic nephropathy?

Colin Close, Consultant Physician, Division of Medicine, Taunton and Somerset Hospital, Taunton

Blockade of the renin–angiotensin–aldosterone system (RAAS) with an angiotensin-convertying enzyme inhibitor (ACEi) or angiotensin-receptor blocker (ARB) is at the core of most antihypertensive treatment regimens in people with diabetic nephropathy. Both these drug classes have a propensity to elevate serum potassium concentration, which can be severe enough to warrant their discontinuation – usually at levels ≥6 mmol/L, although values in the 5.0–5.9 mmol/L range are generally tolerated in clinical practice.

A *post hoc* analysis of the RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) study by Miao and colleagues (2011; summarised alongside) examined the association between serum potassium levels (≥5.0 and ≥5.5 mmol/L) and renal outcomes (doubling of serum creatinine [DSCR], development of end-stage renal disease [ESRD]). They found that even serum potassium above the lower ≥5 mmol/L threshold was associated with a higher risk of the composite renal outcome (DSCR and ESRD), and – not surprisingly – the strongest predictor of serum potassium ≥5 mmol/L was losartan therapy. The effect of losartan on serum potassium appeared to offset the agent's renoprotective effect, with hyperkalaemia increasing the incidence of the composite endpoint from 21% to 35%.

Combination therapy (ACEi plus ARB) resulted in worse renal outcomes compared with ARB therapy alone in ONTARGET (Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial; ONTARGET Investigators et al, 2008). That dual blockade of the RAAS had a deleterious effect on renal outcomes was an unexpected finding; hyperkalaemia (potassium ≥5.5 mmol/L) was more common (5.6% vs 3%) in participants treated with combination therapy (data on the prevalence hyperkalaemia ≥5 mmol/L were not presented). Could hyperkalaemia have contributed to the worse renal outcomes with combination therapy in ONTARGET?

> ***"It is tempting to speculate that management of high serum potassium levels may improve the renoprotective effects of angiotensin -receptor blocker therapy ... and this might require greater use of thiazide diuretics in particular."***

RENAAL participants with potassium <5 mmol/L were more likely to have been treated with a thiazide (17% vs 11%) or loop diuretic (46% vs 43%) at baseline than those with potassium ≥5 mmol/L. Perhaps targeted amelioration of ARB-induced hyperkalaemia will mitigate against the apparent reduced renoprotection associated with hyperkalaemia.

It is tempting to speculate that management of high serum potassium levels may improve the renoprotective effects of ARB therapy – either alone or in combination with an ACEi – and this might require greater use of thiazide diuretics in particular. Further prospective randomised controlled trials are needed to confirm this.

ONTARGET Investigators, Yusuf S, Teo KK et al (2008) Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* **358**: 1547–59

DIABETOLOGIA

Increased serum potassium affects renal outcomes

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

1 The authors aimed to assess the effect of the angiotensin receptor blocker losartan on serum potassium (SP) and the effect of a serum potassium change on renal outcomes in people with T2D and nephropathy.

2 This study was a *post hoc* analysis of the RENAAL (Reduction of Endpoints in Angiotensin II Antagonist Losartan) study, participants in which were randomised to receive losartan or placebo therapy.

3 Outcomes were defined as a composite of doubling of serum creatinine or end-stage renal disease by study end.

4 By 6 months, 259 (38.4%) and 73 (10.8%) participants in the losartan group, and 151 (22.8%) and 34 (5.1%) in the placebo group, had a SP level ≥5.0 mmol/L and ≥5.5 mmol/L (P<0.001), respectively.

5 In this analysis, losartan was found to be an independent predictor of SP ≥5.0 mmol/L at 6 months (odds ratio, 2.8; 95% confidence interval [CI], 2.0–3.9). SP at 6 months ≥5.0 mmol/L was associated with increased risk of renal events (hazard ratio, 1.22; 95% CI, 1.00–1.50).

6 The authors concluded that treatment with losartan was associated with increased SP levels, which is in turn were associated with an increased risk of renal outcomes in people with T2D and nephropathy. Whether the renal protective properties of losartan could be increased by the management of high SP is an important clinical question.

Miao Y, Dobre D, Heerspink HJ et al (2011) Increased serum potassium affects renal outcomes: a post hoc analysis of the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial. *Diabetologia* **54**: 44–50

ARCHIVES OF INTERNAL MEDICINE

Albuminuria and cognitive decline have common microvascular pathogenesis

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

1 Similarities in the microvascular pathophysiology of kidneys that excrete excessive amounts of albumin and the brains of people with cognitive impairment have been noted.

2 In the present study, 28 384 participants with vascular disease or diabetes were included to determine whether an association between albumin excretion and Mini-Mental State Examination (MMSE) scores could be seen.

3 Urine testing for albumin excretion and MMSEs were undertaken at baseline and at 5 years. The role of angiotensin-converting enzyme inhibitor and/or angiotensin receptor blocker therapy or placebo in modifying the association between the results was also assessed.

4 Compared with participants with normoalbuminuria, those with micro- and macroalbuminuria were more likely to have a reduced MMSE score. On follow-up, participants with baseline albuminuria had increased odds of cognitive decline (decrease in MMSE score ≥3 points) compared with those with normoalbuminuria.

5 Participants with baseline macroalbuminuria treated with an angiotensin-converting enzyme inhibitor and/or angiotensin receptor blocker had lower odds of MMSE score decline than participants treated with placebo.

6 The authors concluded that factors that contribute to albuminuria may contribute to cognitive decline.

Barzilay JI, Gao P, O'Donnell M et al (2011) Albuminuria and decline in cognitive function: the ONTARGET/TRANSCEND studies. *Arch Intern Med* **171**: 142–50

CLINICAL ENDOCRINOLOGY (OXFORD)

Pioglitazone reduces urinary albumin excretion

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

1 The authors aimed to observe the effects of pioglitazone on urinary cytokine excretion in T2D and to explore a possible renoprotective mechanism.

2 Ninety-eight people with T2D (HbA_{1c} ≥7.0% [≥53 mmol/mol]) were randomised to receive either the pioglitazone or a sulphonylurea; 49 healthy individuals made up a control group.

3 At baseline and after 12 weeks of treatment, urinary cytokines were measured. Urinary albumin:creatinine ratio and HbA_{1c} level were determined at the same time.

4 At study end, urinary cytokines were reduced in both therapy groups, but the effect of pioglitazone was statistically greater than with sulphonylureas. Blood pressure was also decreased significantly by pioglitazone ($P<0.05$) but not sulphonylurea therapy, while there was no significant difference in HbA_{1c} between the two treatment groups.

5 The authors concluded that pioglitazone reduces urinary albumin excretion by a mechanism that is at least partly independent of glycaemic control.

Hu YY, Ye SD, Zhao LL et al (2010) Hydrochloride pioglitazone decreases urinary cytokines excretion in type 2 diabetes. *Clin Endocrinol (Oxf)* **73**: 739–43

ARCHIVES OF INTERNAL MEDICINE

Similar outcomes for HD and PD

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

1 The authors extracted data from the US Renal Data System to assess for secular trends in survival among people receiving haemodialysis (HD; n=620 020) and peritoneal dialysis (PD; n=64 406) on day 90 of end-stage renal disease in three cohorts over 3 years (1996–1998; 1999–2001; 2002–2004), with 5-year follow-up.

2 A progressive attenuation in the historic higher risk of death seen in people treated with PD was seen; by 2002–2004 there was no significant difference in the risk of death between people treated with HD and PD through 5 years of follow-up.

3 Median life-expectancy of people receiving HD and PD was 38.4 and 36.6 months, respectively.

4 Subgroup analyses based on age (<65 and ≥65 years), diabetes status and baseline comorbidity showed greater improvement in survival among people treated with PD relative to HD for all follow-up periods.

5 The authors concluded that in the most recent cohorts people receiving HD or PD treatment had similar outcomes.

Mehrotra R, Chiu YW, Kalantar-Zadeh K et al (2011) Similar outcomes with hemodialysis and peritoneal dialysis in patients with end-stage renal disease. *Arch Intern Med* **171**: 110–8

COCHRANE DATABASE SYSTEMATIC REVIEWS

Large fall in BP with salt restriction

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

1 Currently there is no consensus on restricting salt intake in people with diabetes. A Cochrane review was undertaken to evaluate the effect of altered salt intake on blood pressure (BP) and markers of cardiovascular disease and nephropathy.

2 An extensive article search was undertaken in January 2010.

3 The authors concluded that although the studies were not extensive, a large fall in BP with salt restriction was seen, and people with diabetes should consider reducing salt intake to <5–6 g/day.

Suckling RJ, He FJ, Macgregor GA (2010) Altered dietary salt intake for preventing and treating diabetic kidney disease. *Cochrane Database Syst Rev* (12): CD006763

"Participants with baseline macro-albuminuria treated with an angiotensin-converting enzyme inhibitor and/or angiotensin receptor blocker had lower odds of Mini-Mental State Examination score decline than participants treated with placebo."