Nephropathy

Diabetes and acute kidney injury

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People with diabetes are more susceptible to chronic kidney disease (CKD) and end-stage renal disease than age- and gender-matched people without the condition (Saran et al, 2015). Hitherto, reports of studies of the association between acute kidney injury (AKI) and diabetes have been inconsistent, but the paper by James et al (summarised alongside) provides conclusive evidence of a strong link.

The authors compared individual data from nearly 80 000 people with established CKD and over 1.2 million people recruited from the general population. Overall, 12% of the general population cohort and 85% of the CKD group had diabetes. AKI was more common in those with diabetes in both cohorts.

In the general population cohort, the adjusted hazard ratio (HR) for AKI in people with diabetes and an estimated glomerular filtration rate (eGFR) of 60 mL/min/1.73 m^2 was around 3 compared to people without diabetes and an eGFR of 80 mL/min/1.73 m^2. In the established CKD cohort, those with an eGFR of 30 mL/min/1.73 m^2 (irrespective of diabetes status) had an HR of around 2 compared to those without diabetes and an eGFR of 50 mL/min/1.73 m^2. Generally, the risk of AKI tended to be greater for people with diabetes compared to those without the condition at all levels of eGFR. Albuminuria did not appear to add to the risk.

Why is this important? The South Tees Mortality Study showed that 29% of 3288 people with diabetes in 1993 had an eGFR <60 mL/min/1.73 m^2 (Nag et al, 2007). In the UKPDS (UK Prospective Diabetes Study), 29% of 5032 people with newly diagnosed diabetes developed an estimated creatinine clearance rate ≤60 mL/min/1.73 m^2 over 15 years (Retnakaran et al, 2006). As the UK general population (and that of people with diabetes) ages, these proportions are only likely to increase. In the US, the overall prevalence of CKD in 2007–2012 was around 14%, with 6% of the cohort and nearly 20% of those with self-reported diabetes having an eGFR <60 mL/min/1.73 m^2. For those over 60 years of age, the odds ratio for an eGFR <60 mL/min/1.73 m^2 was over 100 (Saran et al, 2015).

What does this mean for clinical care? Firstly, we should counsel our patients with a reduced eGFR about the risk of AKI during intercurrent illness, notably diarrhoea or vomiting. Secondly, many of our patients are on routine therapies, such as diuretics and angiotensin-converting enzyme inhibitors, that can amplify the risk of AKI with dehydration. Thirdly, some hypoglycaemic medications, notably metformin and glucagon-like peptide-1 receptor agonists, are contraindicated when eGFR drops below 30 mL/min/1.73 m^2, and others, such as dipeptidyl peptidase-4 inhibitors, should have dose adjustments (*British National Formulary*, section 6.1). Insulin doses may also need reducing. We should stress to our patients the importance of seeking advice about adjusting their medications during intercurrent illness, as well as educating healthcare professionals about the need for changes in medication when people with diabetes are unwell. The hospital scenario of patients receiving intravenous saline whilst still receiving diuretics is all too familiar.

Nationally, NHS England has developed an AKI warning score based upon changes in baseline serum creatinine concentrations (NHS England, 2014). Stage 1 is a 1.5–2-fold increase in serum creatinine level, stage 2 is a 2–3-fold increase and stage 3 is a ≥3-fold increase. In our Trust, this staging is colour-coded yellow, orange and red, respectively, and needs to be electronically acknowledged by the person reviewing the result. In addition, we provide a link to advice for AKI management.

AKI has an appreciable morbidity and mortality. Hopefully the featured paper and the national initiative will raise awareness, provide timely detection and improve outcomes for our patients with diabetes, who are particularly vulnerable to to AKI. ■

References on next page

Am J Kidney Dis

Risk factors for AKI in people with and without diabetes

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

1 The authors of this meta-analysis evaluated the associations of estimated glomerular filtration rate (eGFR) and albuminuria with the risk of acute kidney injury (AKI) in people with and without diabetes and/or hypertension.

2 A total of 1 285 045 participants from eight general population cohorts and 79 519 from five chronic kidney disease (CKD) cohorts were analysed. Over a mean follow-up of 4 years, there were 18 567 episodes of AKI in these cohorts.

3 Lower eGFR and greater albuminuria were independently associated with an increased risk of AKI both in people with diabetes and in those without the condition.

4 People with diabetes generally had a higher risk of AKI at all levels of eGFR; however, the difference was smaller at lower eGFRs. In contrast, there was no interaction between diabetes, level of albuminuria and risk of AKI.

5 AKI risk was increased in people with hypertension compared with those without the condition only at higher eGFR and lower albuminuria; the presence of hypertension did not significantly affect the risk at eGFR <60 mL/min/1.73 m^2 or at albumin:creatinine ratio >30 mg/g.

6 The authors conclude that, while diabetes and hypertension are clearly associated with an increased risk of AKI, strategies to identify people at risk of this complication should incorporate measures of eGFR and albuminuria, irrespective of the presence of diabetes or hypertension.

James MT, Grams ME, Woodward M et al (2015) A meta-analysis of the association of estimated GFR, albuminuria, diabetes mellitus, and hypertension with acute kidney injury. *Am J Kidney Dis* 6 May [Epub ahead of print]

Lancet

Efficacy and safety of BP-lowering agents in diabetes and kidney disease

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

1 In this network meta-analysis, the authors compared the effects of the difference classes of blood pressure (BP)-lowering therapies in adults with diabetes and kidney disease.

2 In total, 157 studies with data on 43 256 people (mean age, 52.5 years) were analysed.

3 No treatment strategy was found to be significantly better than placebo in terms of mortality risk, although the combination of an angiotensin-converting enzyme (ACE) inhibitor and a calcium channel blocker approached significance (odds ratio [OR], 0.36; 95% confidence interval [CI], 0.12–1.05).

4 ACE inhibitor and angiotensin receptor blocker (ARB) combination therapy (OR, 0.62) and ARB monotherapy (OR, 0.77) were significantly better than placebo in terms of preventing end-stage renal disease, and ACE inhibitor monotherapy and endothelin inhibitors had a near-significant effect.

5 Treatments were generally similar to placebo in terms of acute kidney injury (AKI) risk, although ACE inhibitor and ARB combination therapy showed a trend towards increased risk (OR, 2.69; 95% CI, 0.98–7.38).

6 Regarding cardiovascular outcomes, ARB monotherapy prevented myocardial infarction (OR, 0.70); however, no treatment significantly affected stroke risk or cardiovascular mortality.

7 The authors conclude that ACE inhibitors and ARBs, alone or in combination, are the most effective option, although risk of AKI must be accounted for.

Palmer SC, Mavridis D, Navarese E et al (2015) Comparative efficacy and safety of blood pressure-lowering agents in adults with diabetes and kidney disease: a network meta-analysis. *Lancet* **385**: 2047–56

J Diabetes Complications

Glycaemic variation in haemodialysis patients with end-stage renal disease

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

1 Current guidance on blood glucose management in people with end-stage diabetic nephropathy (ESDN) is based on studies in people with diabetes and normal renal function; however, the use of peripheral blood samples and HbA_{1c} may be inaccurate in people with ESDN, especially those on haemodialysis.

2 These authors used continuous glucose monitoring (CGM) over a 72-hour period to compare blood glucose variability in 36 people with ESDN and 10 people with end-stage renal disease (ESRD) without diabetes.

3 People with ESDN were found to have higher glycaemic variability than those with ESRD, as indicated by higher mean, standard deviation (SD) and maximal fasting blood glucose levels, mean amplitude glycaemic excursion (MAGE) and the ratio of glucose readings ≥14 mmol/L.

4 In the ESDN group, mean blood glucose was significantly higher, and SD and MAGE significantly lower, on the haemodialysis day compared with off-dialysis days, whereas this trend was not observed in the ESRD group.

5 In both groups, blood glucose levels calculated from HbA_{1c} were significantly lower than actual levels.

6 These results, coupled with previous findings linking glycaemic variation to diabetes complications, suggest the need for close (and continuous) monitoring of blood glucose levels in people with ESDN undergoing haemodialysis. HbA_{1c} appears to be an inaccurate marker of glycaemic control in these patients.

Jin YP, Su XF, Yin GP et al (2015) Blood glucose fluctuations in hemodialysis patients with end stage diabetic nephropathy. *J Diabetes Complications* **29**: 395–9

Diabetic Medicine

SNPs that contribute to mitochondrial dysfunction linked to kidney disease in T1D

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

1 Mitochondria are susceptible to oxidative damage from cellular stress secondary to hyperglycaemia and chronic inflammation. Pathogenic single-nucleotide polymorphisms (SNPs) in mitochondrial DNA have been implicated in a range of disorders, including kidney disease.

2 Therefore, these authors sought to determine whether genetic variations (both in the mitochondrial genome and in nuclear genes) associated with mitochondrial dysfunction were associated with kidney disease in people with T1D.

3 In total, 823 people with diabetic kidney disease were compared to 903 with T1D but no renal disease, followed by *in silico* replication in a cohort of 5093 people with diabetic kidney disease, end-stage renal disease (ESRD) or neither condition.

4 No SNP in the mitochondrial genome was significantly associated with kidney disease; however, 38 SNPs in nuclear genes that influence mitochondrial function were associated with diabetic kidney disease, and 16 were associated with ESRD secondary to diabetic kidney disease. In the replication analysis, seven SNPs were associated with both diabetic renal disease and ESRD.

5 The authors conclude that a number of gene variants affecting mitochondrial function are associated with kidney disease in T1D. Further research into the interactions between hyperglycaemia and these SNPs is warranted.

Swan EJ, Salem RM, Sandholm N et al (2015) Genetic risk factors affecting mitochondrial function are associated with kidney disease in people with type 1 diabetes. *Diabet Med* **32**: 1104–9

> ***"These results, coupled with previous findings linking glycaemic variation to diabetes complications, suggest the need for close (and continuous) monitoring of blood glucose levels in people with end-stage diabetic nephropathy undergoing haemodialysis."***

References from commentary

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NHS England (2014) *Algorithm for Detecting Acute Repeat Kidney Injury (AKI) Based on Serum Creatinine Changes with Time*. NHS England, London. Available at: http://bit.ly/1pcal8P (accessed 04.08.15)

Retnakaran R, Cull CA, Thorne KI et al (2006) Risk factors for renal dysfunction in type 2 diabetes: U.K. Prospective Diabetes Study 74. *Diabetes* **55**: 1832–9

Saran et al (2015) US Renal Data System 2014 annual data report: epidemiology of kidney disease in the United States. *Am J Kidney Dis* **66**(Suppl 1): 1–306