Nephropathy

Establishing proteinuria thresholds for clinical practice

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Proteinuria, the hallmark of glomerular diseases, characterises diabetic nephropathy. Historically, the presence of proteinuria in excess of 0.5 g/day indicated the onset of clinical diabetic nephropathy, with rising blood pressure, ever increasing proteinuria and rapidly progressive renal failure the inevitable outcomes. However, despite blockade of the renin-angiotensin-aldosterone system (RAAS) and blood pressure reduction, many people continue to exhibit significant levels of proteinuria.

Hypertension in the context of diabetic nephropathy is salt sensitive and oedema – a consequence of salt and water retention – is a common finding. Blood pressure can be treatment resistant in people with proteinuria and loop diuretics, often at high doses (for example, up to 250 mg furosemide daily) may be needed to lower blood pressure and control the oedema. Nephrotic syndrome is a clinical diagnosis comprising heavy proteinuria (historically exceeding 3–3.5 g/day), hypoalbuminaemia, oedema and dyslipidaemia. Correcting urinary protein excretion for creatinine has proved useful in establishing the presence of microalbuminuria, typically in the 3.5–35 mg/mmol range.

The Irbesartan in Diabetic Nephropathy Trial investigators (Stoycheff et al, 2009; summarised alongside) re-examined their cohort of people with type 2 diabetes and proteinuria exceeding 0.9 g/day to define nephrotic range proteinuria and evaluate threshold levels of measures of proteinuria for the discrimination of outcomes of kidney disease, other signs and symptoms of nephrotic syndrome and subsequent disease progression.

They found that proteinuria 3.5 g/day equated to 3.5 g/g creatinine (equivalent to 310 mg/mmol creatinine), and that this approximated to urine albumin excretion 2.2 g/day (195 mg/mmol) in 24-hour collections, and identified people with the characteristics of nephrotic syndrome who subsequently experienced more rapidly progressive kidney disease and increased mortality. Interestingly, the prevalence of nephrotic-range proteinuria was quite high with over 40% people at baseline exhibiting proteinuria of this magnitude.

These threshold levels might prove useful in clinical practice to help identify and characterise people at higher risk of progressive renal failure and death, triggering an intensified effort to control blood pressure and other cardiovascular risk factors and the use of heavier loop diuretic therapy. It remains unclear whether attempts to reduce proteinuria by further inhibition of the RAAS with "high dose" angiotensin-converting enzyme inhibition or aldosterone receptor blockade, combination therapy using both drug classes, the addition of specific aldosterone blockade, or use of other antihypertensive drugs (verapamil or diltiazem) that lower proteinuria, can improve outcomes in people with nephrotic-range proteinuria.

AMERICAN JOURNAL OF KIDNEY DISEASES

Update of the definition of nephrotic syndrome

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

1 The definition of nephrotic syndrome is urine total protein excretion of ≥3.5 g/day, low serum albumin level, high serum cholesterol level and peripheral oedema.

2 The authors of this diagnostic test study aimed to evaluate these threshold levels in people with diabetic kidney disease by using the preferred method of measuring proteinuria, urine albumin excretion.

3 Participants were 1715 adults with type 2 diabetes, hypertension and urine total protein level >0.9 g/day, who had enrolled in the Irbesartan in Diabetic Nephropathy Trial.

4 In 1608 participants (for whom the correct data was available) total urine protein level of 3.5 g/day was equivalent to 2.2 g/day (95% confidence interval, 1.4 to 3.5).

5 At baseline, 641 out of 1467 (44%) participants had a urine total protein level of ≥3.5 g/day, 132 (9%) had other signs and symptoms of nephrotic syndrome at baseline, and in 385 (26%), kidney disease progressed over a mean follow-up of 2.6 years.

6 For measures of proteinuria, areas under the receiver operating curves were 0.80 to 0.83 for other signs and symptoms of nephrotic syndrome and 0.72 to 0.74 for kidney disease progression.

7 The authors concluded that the threshold levels that define nephrotic-range proteinuria in people with diabetic kidney disease appear reasonable.

Stoycheff N, Stevens LA, Schmid CH et al (2009) Nephrotic syndrome in diabetic kidney disease: an evaluation and update of the definition. *Am J Kidney Dis* **54**: 840–9

DIABETIC MEDICINE

Cardiovascular impairment not resolved after pancreas-kidney transplant

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

1 The authors of this study aimed to determine whether simultaneous pancreas-kidney (SPK) transplantation can reverse the impairment of cardiovascular and endothelial function that occurs in people with type 1 diabetes.

2 A total of 45 people underwent a number of tests: pulse wave velocity, stroke volume, heart rate and serological markers of endothelial dysfunction.

3 Ten people had type 1 diabetes and had received an SPK transplant; 10 people had type 1 diabetes and poor glycaemic control; 10 had type 1 diabetes with good control; 6 did not have diabetes but had received a kidney transplant and 9 were controls.

4 Systolic blood pressure was increased in the SPK group compared with controls ($P<0.05$). Heart rate was elevated in SPK and people with type 1 diabetes and poor glycaemic control compared with the other groups ($P<0.0003$).

5 Soluble intercellular and vascular cell-adhesion molecules were 100% and 44% higher in the SPK group compared with controls ($P<0.03$).

6 It was concluded that SPK transplantation may not completely resolve cardiovascular impairment in people with type 1 diabetes.

Stadler M, Theuer E, Anderwald C et al (2009) Persistent arterial stiffness and endothelial dysfunction following successful pancreas-kidney transplantation in type 1 diabetes. *Diabet Med* **26**: 1010–18

CLINICAL NEPHROLOGY

Rosiglitazone slows decline of renal function

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

1 This analysis aimed to establish whether treatment with a thiazolidinedione would slow the rate of renal insufficiency in people with type 2 diabetes (T2D).

2 Participants (113 men, one woman; mean age 66.8±9.4 years) had all initiated rosiglitazone from 1996 to 2003 and had at least two consecutive serum creatinine levels ≥132 µmol/L at least 4 weeks apart.

3 The rate of decline of renal function before (phase 1) and after (phase 2) initiation of a roziglitazone was calculated using slope estimates of the reciprocal of creatinine vs. time (days) from linear models.

4 The mean duration of phase 1 was 586.2 days and phase 2 was 613.2 days ($P=0.47$). The mean slope difference (phase 1 to phase 2) was 0.00005 ($P<0.0001$ [Wilcoxon signed rank test] and $P=0.0023$ [t-test]). The adjusted difference between phase 1 and phase 2 on the mean slope was 0.00007 ($P=0.0135$).

5 After initiation of rosiglitazone renal function declined at a slower rate in people with T2D and renal insufficiency.

Trivedi H, Lu N, Andresen BT, Whaley-Connell A (2009) Slower decline of renal function after initiation of rosiglitazone in diabetics – a pilot study. *Clin Nephrol* **72**: 181–5

DIABETES CARE

Aliskiren and irbesartan combined is more effective than monotherapy

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

1 This double-blind, randomised cross-over trial investigated whether aliskiren's antiproteinuric effect is comparable to that of irbesartan and the effect of combined treatment.

2 A total of 26 people with albuminurea, hypertension and type 2 diabetes were randomly assigned to receive placebo, aliskiren once-daily, irbesartan once-daily, or a combination over four 2-month treatment periods.

3 Albuminuria was reduced by 48% with aliskiren treatment ($P<0.001$ vs. placebo) and 58% with irbesartan ($P<0.001$ vs. placebo). Combined, the drugs reduced albuminuria by 71% ($P<0.001$ vs. aliskiren and $P=0.028$ vs. irbesartan).

4 Combined aliskiren and irbesartan therapy was found to be more antiproteinuric than monotherapy.

Persson F, Rossing P, Reinhard H et al (2009) Renal effects of aliskiren compared with and in combination with irbesartan in patients with type 2 diabetes, hypertension, and albuminuria. *Diabetes Care* **32**: 1873–9

DIABETES CARE

Change in distribution of albuminuria

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

1 This cross-sectional study examined trends in the distribution of albuminuria and estimated glomerular filtration rate (eGFR) in pima indians ≥15 years of age with type 2 diabetes in 1982–88 and 2001–06.

2 Between time periods, the overall standardised distribution of albumin to creatinine ratios shifted towards lower values ($P=0.001$).

3 The standardisation of eGFR did not shift between time periods ($P=0.45$).

4 Among Pima Indians, the distribution of albuminuria changed significantly along with the improvement of medicines to treat hyperglycaemia and hypertension.

Pavkov ME, Mason CC, Bennett PH et al (2009) Change in the distribution of albuminuria according to estimated glomerular filtration rate in Pima Indians with type 2 diabetes. *Diabetes Care* **32**: 1845–50

"After initiation of rosiglitazone renal function declined at a slower rate in people with type 2 diabetes and renal insufficiency."