Albuminuria-proteinuria: the new modifiable major vascular risk factor

By Dr Mark Thomas,
Renal Physician, RPH.

For more than 25 years, the presence of albuminuria (and/or proteinuria) in diabetes mellitus was known to be strongly associated with the risk of subsequent kidney failure. Two important new facts have recently emerged:

- Albuminuria-proteinuria is an independent risk factor for cardiovascular death in both diabetes mellitus and non-diabetic patients.
- Regression of albuminuria-proteinuria on treatment is an independent predictor of reduced risk of renal impairment and reduced cardiovascular death in both diabetes mellitus and in non-diabetic patients.

Hence, albuminuria-proteinuria can be regarded as the "poor man's ophthalmoscope" in predicting risk.

Cardiovascular risk prediction

Numerous studies now show a strong independent correlation between the presence and degree of albuminuria-proteinuria and cardiovascular mortality risk.

This correlation applies not only in diabetic patients but also in hypertensive non-diabetic patients and elderly patients.

Some studies of Type 2 diabetes put proteinuria as a stronger predictor of cardiovascular death than hypertension.

In non-diabetic patients, the correlation extends into the normal range of albuminuria, that is, patients in the lower half of the normal range have a lower risk than patients in the upper half. This is probably because albuminuria, analogous to a "renal sphygmo", indicates leakage through pressure-damaged glomerular capillary walls.

In this way, albuminuria selects out patients with more established vascular disease who are at higher risk of a vascular event compared to others who have hypertension for many years before vascular damage occurs.

Proteinuria regression as a treatment goal

Prognosis varies markedly between patients (diabetic and non-diabetic) whose albuminuria increases, compared to those in whom levels fall.

Post-hoc analysis of the LIFE study (losartan vs atenolol in hypertensive diabetic and non-diabetics with LVH) found five-year composite cardiovascular mortality to increase from 5.5% to 8.6% in the initially low-albuminuria group whose albumin-creatinine ratio (ACR) deteriorated. In contrast, five-year CV risk fell from 13.5% to 9.4% in the initially high albumin group whose ACR fell.

Benefit of ACE-inhibitors and angiotensin II receptor blockers (ARBs)

As these agents cause relaxation of the efferent arteriole, the resultant fall in glomerular capillary pressure allows a relatively greater fall in albuminuria-proteinuria (40-50%), more than expected for the same fall in BP using other anti-hypertensive agents (10-20%). The effectiveness of either agent is augmented by the addition of diuretics, which help counteract the risk of hyperkalaemia. Combining ACEI and ARB's can achieve a remarkable 80-90% proteinuria reduction.

Take-home messages

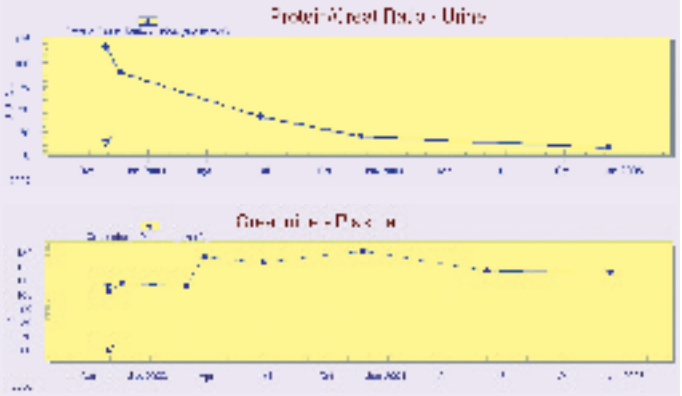
- **Assessing vascular risk:** Check early morning spot urine ACR, along with fasting lipids, glucose, BP and BMI. If heavy proteinuria, use spot urine protein: creatinine ratio.
- **Treatment:** BP reduction by any means usually reduces proteinuria. ACE-inhibitors and angiotensin receptor blockers are generally the most effective anti-proteinuric agents, particularly with a diuretic, and especially if used together.
- **Assessing response:** The greater the reduction in ACR, the greater the renoprotection and cardioprotection.

Fig 1. CASE STUDY. Suppression of proteinuria with sequential ARB / diuretic / ACEI therapy.

Male aged 60. 10 years hypertension and hypercholesterolaemia. Recently detected CKD & proteinuria.

BP: 160/90 on ARB ➔ 140/85 on ARB / diuretic ➔ 130/70 on ARB / diuretic / ACEI.

Serum K^+: 5.1 on ARB ➔ 4.6 on ARB / diuretic ➔ 4.8 on ARB / diuretic / ACEI.



ARB

ARB / diuretic ➔

ACEI ➔

Measure albuminuria or proteinuria?

Albuminuria tends to be more sensitive than proteinuria for detecting the first manifestations of glomerular damage and is thus favoured by endocrinologists tracking uncomplicated diabetic patients.

Proteinuria is a more robust test that is not liable to false-negative results in the presence of massive nephrosis (unlike the albumin radioimmunoassay), and is thus favoured by nephrologists tracking patients with advanced kidney damage. Use the dipstick urinalysis to guide which test is more appropriate.

Timed collection or spot sample?

Timed overnight or full 24-hour urine collections will reduce the daily variation in proteinuria associated with posture, exercise and dietary protein intake. Nevertheless, the procedure is inconvenient and prone to errors from missed samples or incomplete bladder emptying.

Spot samples are much more widely used, but should be collected first thing in the morning for best results. The results are expressed as an albumin: creatinine ratio (or protein: creatinine ratio), to correct for variation in urinary concentration from fluid intake or diuretic use.

Is albuminuria always bad?

Transient low-level albuminuria can be found after exercise, fever, urinary infection or high-protein meal, without necessarily indicating established renal and vascular disease. Nevertheless, it is prudent to follow-up, particularly if other risk factors are present eg. obesity, labile hypertension, dietary hypercholesterolaemia or impaired glucose tolerance.

This clinical update is supported by an independent educational grant from Amgen Australia, manufacturers of Aranesp®