Nephropathy

Better research is needed into disease biomarkers

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

Historically, the number of people with serum albuminuria levels >300 mg/dL (clinical nephropathy) has been quoted as 20% at 20 years' known duration for both type 1 and type 2 diabetes (Gall et al, 1997). Although studies of recent cohorts have reported albuminuria levels approximately half of this, these individuals remain at high risk of cardiovascular disease. In the UK Prospective Diabetes Study, this population had an annual mortality rate of 4.6%, which is over twice that of people with normal albuminuria levels. With this in mind, early identification of patients who are developing nephropathy is an important clinical priority (Bilous, 2008).

The systematic review by Hellemons et al (2012; summarised alongside) describes reported data on the usefulness or otherwise of a range of serum and urinary markers in the prediction of nephropathy onset or the progression from early to established nephropathy. The authors defined a biomarker as an "indicator of normal biological processes, pathogenic processes or pharmacological responses to therapy without necessarily being causally related to the clinical end-point."

Some biomarkers may be considered eligible to substitute as a clinical end-point and thus become a "surrogate marker". Surrogate markers can only be deemed valid if there is strong evidence linking them causally to an important clinical outcome. However, they may still be useful in identifying individuals at risk of a particular end-point, and in helping to guide treatment interventions.

Hellemons et al defined the following criteria that should be satisfied when establishing a biomarker:

- Markers should be tested in longitudinal, well-designed and adequately powered studies reproduced in different cohorts to validate and generalise the results.
- The association between the marker and disease should be independent of potential confounders, and add to existing known risk factors.

These criteria are exacting but necessary and it is rather depressing to learn that very few if any of the biomarkers in the current review met them.

The paper had a number of limitations. Only 15 studies were selected for analysis and the maximum study duration was 9 years. This duration of follow-up is far too short considering that, as reported by the recent DCCT (Diabetes Control and Complications) paper, only 24 of 1441 people with T1D developed end-stage renal disease after 22 years (DCCT/EDIC Research Group, 2012). Secondly, the onset of nephropathy was defined by albuminuria, itself a surrogate marker that has not been fully validated (Levey et al, 2009). There was also no agreement on what defined progression of nephropathy but most studies used the change from micro- to overt albuminuria (30–299 mg/dL to >300 mg/dL) with the same problems when defining nephropathy onset. The authors highlighted that the difficulty with this type of categorical transition is that an increase from 29 to 31 mg/dL is nephropathy "progression" but that an increase from 31 to 299 mg/dL is not. Finally, most of the studies analysed used statistical methods such as odds ratios or relative risks, which do not accurately predict individual risk and cannot discriminate between future health and disease. True and false positives and negatives were rarely reported.

We have to do better than this. Too many studies have been conducted in inadequately powered and poorly selected populations with inappropriate analysis. The diabetes community needs to come together to agree what defines nephropathy onset and what constitutes progression of nephropathy, and only then can we proceed to test some of the potentially promising markers listed in this review and select those that show most utility. Meanwhile, despite its shortcomings, we must continue to use albuminuria as a biomarker of nephropathy as it remains the most powerful predictor of renal impairment and the strongest marker of cardiovascular risk in people with diabetes.

Bilous R (2008) Microvascular disease: what does the UKPDS tell us about diabetic nephropathy? *Diabet Med* **25** (Suppl 2): 25–9

DCCT/EDIC Research Group, de Boer IH, Sun W et al (2012) Intensive diabetes therapy and glomerular filtration rate in type 1 diabetes. *N Engl J Med* **365**: 2366–76

Gall MA, Hougaard P, Borch-Johnsen K et al (1997) Risk factors for development of incipient and overt diabetic nephropathy in patients with non insulin dependent diabetes mellitus : prospective observational study. *BMJ* **314**: 783–7

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 Kidney Dis* **54**: 25–6

DIABETIC MEDICINE

Nephropathy biomarkers in T2D: Further validation is needed

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

1 The authors set out to assess the validity of candidate biomarkers in predicting the onset and progression of nephropathy in people wth T2D.

2 Database searches (MEDLINE, EMBASE and the Cochrane Library database) and associated citation searches yielded 15 longitudinal studies and RCTs reporting on 27 urine, plasma and serum biomarkers.

3 Biomarkers were assessed against pre-defined nephropathy onset and progression, predicting either early or late nephropathy.

4 The methodological quality of the studies was scored against STARD (Standards for Reporting of Diagnostic Accuracy) criteria whilst adjustment scores were determined from the additional predicted value the biomarkers yielded on top of conventional risk markers – the two scores were combined to provide a biomarker validity score.

5 Of the 15 studies included in the analysis, six achieved a sufficient score of methological quality, identifying a total of 13 biomarkers of nephropathy that were valid and significant. The authors, however, highlighted study limitations, including statistical methods, a lack of validation in other populations and study end-point heterogeneity.

6 The authors concluded that further research and well-designed longitudinal studies are needed to discover new, and validate published, biomarkers of diabetic nephropathy.

Hellemons ME, Kerschbaum J, Bakker SJ et al (2012) Validity of biomarkers predicting onset ot progression of nephropathy in patients with type 2 diabetes: a systematic review. *Diabet Med* **29**: 567–77

J AM SOC NEPHROL

TNFR1 levels highly correlated with ESRD risk in T2D

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

1 The authors of this 8- to 12-year follow-up study examined the effect of nine inflammatory plasma markers on predicting end-stage renal disease (ESRD) in people with T2D.

2 Between 1991 and 1995, study entry plasma marker concentrations were recorded in individuals with T2D (n=410), who were then followed up until the end of 2004.

3 At the end of follow-up, 65.1% of the cohort were alive (n=267), 14.4% had developed ESRD (n=59; of whom 51 had died), and the remaining 20.5% of people (n=84) had died without ESRD.

4 Baseline levels of endothelial dysfunction and systemic inflammation markers were similar across the three outcome groups.

5 Only TNFR1 and TNFR2 determined ESRD. Following Cox proportional analysis and adjustment for proteinuria status, estimated GFR, and albumin excretion rate this was independent of all relevant clinical variables.

6 TNFR1 and TNFR2 were highly correlated (Spearman correlation coefficient r=0.9) but ESRD was more highly correlated with TNFR1 – the cumulative incidence of ESRD was significantly greater in the fourth TNFR1 quartile compared with other quartiles (54% versus 3%, P<0.001).

7 Death not related to ESRD had a moderate relationship to baseline plasma TNRF1.

8 The authors concluded that 12-year ESRD risk can be estimated from a single TNFR1 measurement and that this could have important in-practice diagnostic implications.

Niewczas MA, Gohda T, Skupien J et al (2012) Circulating TNF receptors 1 and 2 predict ESRD in type 2 diabetes. *J Am Soc Nephrol* **23**: 507–15

SCAND J CLIN LAB INVEST

Irbesartan reduces urinary tubular markers in T2D

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

1 In this randomised crossover trial, the authors aimed to determine the effect of the RAAS-blockade on markers of tubular damage in people with T2D, hypertension and miroalbuminuria.

2 Individuals (n=52) took irbesartan (300 mg, 600 mg and 900 mg) randomly over three 2-week treatment periods. Urinary neutrophil gelatinase-associated lipocalin (u-NGAL), liver-fatty-acid-binding protein (u-LFABP) and kidney injury molecule 1 (u-KIMI) were measured at baseline and 8 weeks.

3 Irbesartan dose increase correlated with reduced levels of u-KIMI. High baseline u-KIMI was associated with a 32% reduction at 8 weeks (P<0.01). There was no significant change in u-NGAL, and u-LFABP levels increased.

4 The authors concluded that further investigation is needed into the role of tubular markers as determinants of diabetic retinopathy and treatment effect.

Nielsen SE, Rossing K, Hess G et al (2012) The effect of RAAS blockade on markers of renal tubular damage in diabetic nephropathy: u-NGAL, u-KIM1 and u-LFABP. *Scand J Clin Lab Invest* **72**: 137–42

EUR J ENDOCRINOL

Immigrant status is a risk factor for microalbumineria in children with T1D

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

1 The authors set out to identify risk factors for untreated persistent microalbumineria development and progression in children and adolescents recruited from the prospective nationwide German and Austrian diabetes survey (DPV) up until March 2010.

2 Young people (n=683) were followed continuously for 5 years, during which a miminum of two annual urine analyses for microalbuminuria were performed. Multivariate logistic regression analysis was used to analyse 10 independent risk factors, including immigration status.

3 Immigration status and diabetes duration were significantly associated with microalbuminuria development and progression (P=0.009 and P=0.009). The authors concluded that further multicentre studies are needed to confirm these study findings.

Galler A, Haberland H, Näke A et al (2012) Natural course of untreated microalbuminuria in children and adolescents with type 1 diabetes and the importance of diabetes duration and immigrant status: longitudinal analysis from the prospective nationwide German and Austrian diabetes survey DPV. *Eur J Endocrinol* **166**: 493–501

DIABETOLOGIA

Albuminuria stage and CVD risk in T2D

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

1 The authors examined the relationship between chronic kidney disease (CKD) stage and cardiovascular disease (CVD) onset in Japanese people with T2D at low risk of CVD.

2 Baseline and follow-up albumin–creatine ratio (ACR) and estimated GFR (eGFR) were recorded. Individuals (n=2954) were followed for 4 years or until the first occurence of CVD. The incidence rates and risk of CVD were stratified by CKD stage.

3 CVD risk increased with progression of albuminuria stage but not eGFR stage. An ACR ≤35 mg/mmol with an eGFR <60 or 60–89 mL/min was associated with increased risk of CVD onset (P<0.05). The authors concluded that the findings highlight the importance of reducing albuminuria in T2D.

Yokoyama H, Araki S, Haneda M et al (2012) Chronic kidney disease categories and renal-cardiovascular outcomes in type 2 diabetes without prevalent cardiovascular disease *Diabetologia* **55**: 1911–8

> *"Immigration status and diabetes duration were significantly associated with microalbumineria development and progression."*