Urinary albumin to protein ratio: more of the same or making a difference?

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In this issue, Smith et al. [1] consider whether the simple ratio of urine albumin to total protein (uAPR) provides a measure of low molecular weight (LMW) proteinuria that distinguishes tubular versus glomerular pathology. In a retrospectively studied cohort of 1011 proteinuric patients [protein:creatinine ratio (PCR) >30 mg/mmol], uAPR was correlated with simultaneous findings on urine protein immunofixation electrophoresis (uPEI). A single, blinded observer categorized the electrophoresis pattern as being either tubular (predominantly LMW), glomerular (a dominant albumin band), mixed or overflow (light chain monoclonal) proteinuria. The LMW protein β2-microglobulin (β2M) and the tubular enzyme N-acetyl-β-D-glucosaminidase (NAG) were also measured in a subgroup (n = 248) of outpatients and their predictive performance at uPEI classification compared to that of uAPR. Renal biopsy results were available to confirm the diagnostic utility of uAPR for only 68 patients. uAPR gave a reasonable prediction of a ‘tubular’ uPEI proteinuria pattern in ROC curve analysis (AUC 0.84), which was similar to that of β2M and NAG. It also performed better than

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Clearly, measurement of urine protein leak is central to the detection, diagnosis, prognosis and treatment of kidney disease. Most guidelines currently recommend the measurement of an early morning spot urine for either albumin:creatinine ratio or protein:creatinine ratio. In general, low-level albuminuria/proteinuria is considered reflective of vascular or tubulointerstitial renal pathology, while higher levels (>1 g/gL ≈ 1 g/24 h) are thought to reflect underlying glomerular pathology. Such interpretation is rather simplistic and frustrating in view of the ready availability of urine for more extensive analysis and interpretation. With the exception of haematology, no other specialty has easy access to a body fluid so closely related to the function of the organ for which it is responsible.

Interpretation of raised urine protein level is confounded by the various inter-related factors that influence its excretion (Table 1). These include glomerular factors affecting filtration, tubular factors controlling reabsorption of filtered proteins and vascular influences both at the glomerular and peritubular level. Consequently, the excreted urine protein is seldom the simple result of a well-defined pathology; instead, it mirrors complex glomerular, tubular and vascular interactions. Furthermore, excessively filtered/re-absorbed protein has been implicated for the last 20 years in the pathogenesis of glomerular and tubulointerstitial sclerosis, respectively [2, 3], thus potentially aggravating the very processes that contribute to its leakage.

Previous investigations of the clinical implications of urine protein profiles have categorized leaked plasma proteins as low, intermediate or high molecular weight (MW) [4]. LMW proteins (e.g. β2M and retinol-binding protein) are filtered freely at the glomerulus and reabsorbed in the proximal tubule. Increased levels of these proteins in the urine are thus considered to reflect impairment of tubular function. However, excessive glomerular filtration of other proteins may overwhelm the tubular reabsorption capacity and lead to urinary tubular protein leakage in primary glomerular pathology [5]. Albumin, an intermediate MW protein (60 kDa), may leak into the urine due to a failure of tubular reabsorption, but excretion rates >1 g/24 h usually indicate a glomerular pathology. The presence of high MW proteins (e.g. gamma globulins) in the urine reflects a glomerular pathology causing a marked increase in effective pore size. Measurements of some of these proteins and calculation of their ratios have been used extensively in attempts to better define the nature of proteinuria, its aetiology and clinical implication.

The ratio of urinary β2M to albumin was first used to differentiate between primary tubular and glomerular pathology over 40 years ago [6]. Subsequent reports have confirmed that electrophoretic urinary protein profiles differentiate tubular versus glomerular disease [7]. Since tubulointerstitial damage is a major determinant of outcome in glomerular disorders, LMW proteinuria might also be expected to predict outcome in glomerulonephritis. Greater excretion of LMW proteins has indeed been reported to predict outcome, response to therapy and histological tubulointerstitial damage in various glomerulonephritides [4, 8, 9]. Some increase in LMW proteinuria is anticipated to accompany greater glomerular protein leak due to competition for tubular reabsorption [3, 10]; nevertheless, additional prognostic information independent of total proteinuria can apparently be provided by LMW proteinuria quantification [9, 10].

The use of a selectivity index (i.e. a ratio between the urinary leaks of a high MW and an intermediate MW protein) to predict diagnosis and outcome in glomerular disease has also been advocated for many years. The ratio of urinary IgG to transferrin is the most often-used selectivity index, with a ratio <0.2 considered to reflect non-selective glomerular leak [11]. This may predict a lower likelihood of proteinuria remission, increased risk of function loss and more severe accompanying histological tubulointerstitial lesions [12].

Why have none of these refinements to total proteinuria quantification reached routine clinical practice? None has been shown to satisfy all the necessary criteria of being cost effective, straightforward to perform and able to provide sufficient diagnostic/prognostic information to improve on the current more simplistic approach. Measurement of albuminuria or total proteinuria is straightforward and cheap and provides useful diagnostic/prognostic information. Assessment of other urinary proteins by electrophoresis (and immunofixation) or specific assays is more expensive and requires analytic expertise. Basically, in acute presentations, proteinuric patients are often submitted to a kidney biopsy for diagnostic and prognostic purposes as well as to determine the treatment of choice. In chronic cases, the interpretation of proteinuria is more complex due to the interactions highlighted above between the glomerular and tubulointerstitial components of scarred kidneys and while a renal biopsy is seldom indicated, it is more doubtful that the nature of the proteinuria would affect current management approaches. The latter most often consist of inhibition of the renin–angiotensin–aldosterone system.

The finding by Smith et al. that low uAPR gave a reasonable prediction of a ‘tubular’ electrophoretic proteinuria pattern is perhaps not surprising, given that non-albuminuria proteinuria consists mainly of low and high MW proteins;
high MW proteinuria is unlikely to be a common cause of low uAPR since it is found in the setting of more severe glomerular permeability defects where the leak of albuminuria is much higher. Previous studies have shown that the relative contribution of non-albumin proteinuria to total proteinuria is (highly variable, but) generally greater at lower total proteinuria levels [13]. A striking finding here was the fact that only 5% of uEI patterns were considered ‘mixed’, the rest being classified as glomerular (69%), tubular (24%) or overflow (3%). Given the frequent co-existence of glomerular and tubular pathology as well as the competition between filtered proteins for tubular reabsorption, it might be anticipated that a mixed pattern would be common. The mixed pattern group here had the highest level of proteinuria, perhaps because the most severe glomerular pathology is more likely to be accompanied by tubulointerstitial pathology and secondary failure of tubular protein reabsorption.

Although uEI can distinguish glomerular from tubular proteinuria, it is a subjective assessment and is not itself a clinical end point. In the small biopsied cohort of Smith et al., uEI pattern performed well at differentiating tubular versus glomerular disease, but uAPR was not validated for the rest of the study population. Therefore, although the finding that lower uAPR predicts tubular uEI pattern is interesting, it is not demonstrative of clinical usefulness.

In the cohort of renal outpatients where β2M and NAG measurements were made, uAPR was non-inferior to these established tubular proteinuria markers in predicting a tubular uEI pattern. Again, performance in predicting a uEI pattern is of no clinical utility, though the similar predictive performance of uAPR, β2M and NAG is consistent with lower uAPR acting as a marker of tubular proteinuria. Surprisingly, the correlation between uAPR and the levels of β2M/NAG was not reported. This would have been useful in confirming the extent to which lower uAPR is indeed a marker of tubular proteinuria.

A uAPR of <0.4 predicted a primary tubulointerstitial pathology in the biopsied cohort with a sensitivity and specificity of 88% and 99%, respectively. Importantly, although albuminuria was heavier for glomerular diseases than tubular diseases, uAPR distinguished these categories better than albuminuria or proteinuria alone. This was nevertheless a small cohort with some atypical features; for example there was just one case of IgA nephropathy but 14 cases of necrotizing crescentic glomerulonephritis. Excluding a case of myeloma cast nephropathy with overflow proteinuria, there were only six cases of primary tubulointerstitial disease and all of these were due to tubulointerstitial nephritis. This is clearly too small and selected a tubular disease cohort on which to base firm conclusions regarding the diagnostic performance of uAPR. In support of the current finding, Ohisa et al. [14, 15] previously reported that a higher uAPR predicts glomerular disease in cohorts with microscopic haematuria. Although the comparator groups in these studies included patients with urological causes of haematuria that would not be considered a diagnostic challenge, uAPR was similarly a better differentiator than either albuminuria or proteinuria. Whether this finding reflected more LMW proteinuria in non-glomerular disease was not investigated. In paediatric cohorts, albuminuria has also been reported to constitute a greater percentage of total proteinuria in primary glomerular pathologies than tubular pathologies [16].

Consistent with previous reports linking tubular proteinuria to histological tubulointerstitial damage, biopsies in the cohort of Smith et al. with a moderate-severe tubulointerstitial damage score were accompanied by lower uAPR than those with a none-moderate score. The cohort was, however, too small to allow assessment of the prediction of tubulointerstitial damage by uAPR in particular diseases.

What are the implications of these findings? Given the previously reported utility of tubular proteinuria assessment for predicting diagnosis, prognosis and treatment response, if uAPR is confirmed to provide a cheap and simple surrogate measure of tubular proteinuria, then it could be a useful addition to the investigative armoury. A clinical use for this test will need to be found though; differentiating tubular versus glomerular pathology in a biopsied cohort is not after all a terribly helpful. Kidney biopsies are performed not simply to differentiate tubular versus glomerular pathology but rather to make a diagnosis that will support the use of (often potentially toxic) appropriate therapy. Diagnostic performance of uAPR in a biopsied cohort cannot necessarily be extrapolated to non-biopsied populations, which by definition have a different set of clinical features (including urinalysis findings). In this respect, it is noteworthy that the performance of uAPR in predicting uEI pattern was markedly worse for the overall cohort than for the biopsied patients. Whether uAPR performed similarly well across lower strata of proteinuria (e.g. PCR 30–100), where differentiation of glomerular versus tubular disease is more difficult, is not reported.

The authors speculate that uAPR might provide useful prognostic information. Since uAPR is affected by the nature of the underlying pathology, prognostic performance need to be assessed on a disease-specific basis (or at the very least for either glomerular or tubular pathologies). Absolute quantity of non-albumin proteinuria might also be important in this regard and has been shown to predict outcomes independently of albuminuria in the context of renal transplantation [17]. Among populations with chronic kidney disease, albuminuria and total proteinuria have similar prognostic significance [18], but tubular proteinuria is nevertheless a predictor of outcome in glomerulonephritides [4]. uAPR might therefore also predict outcome and response to therapy in a particular pathology such as membranous nephropathy [9].

The importance of this study may be in stimulating the further work needed to determine whether uAPR actually provides clinically useful information. It must be confirmed whether the non-albumin component of proteinuria that determines uAPR is consistently low MW and whether this is the case across all pathologies, levels of proteinuria and strata of kidney function. Demonstration of clinical utility of uAPR will require larger cohorts with clinical end points such as progression of kidney disease and response to therapies as well as correlation with biopsy findings. This should be straightforward in view of the ease and low cost of the analysis, though Smith et al. highlight the important point that different assays for proteinuria and albuminuria can give different results. Benefits of uAPR measurement may ultimately be as part of an investigative algorithm that includes other urinary biomarkers such as those that are currently being pursued through proteomic approaches.
As such novel markers are pursued, however, we should at least ensure we are making the best use of the ‘unsophisticated’ measures that we have already available.

Ultimately, a new diagnostic test has to fulfil a number of criteria including a high predictive value for a given pathology, reproducibility, ease and cost effectiveness against currently available methods and most importantly impact on patients’ management. Urine albumin:protein ratio while undoubtedly of interest warrants further validation before its full potential is appreciated.

Conflict of interest statement. None declared.

(See related article by Smith et al. The value of simultaneous measurements of urinary albumin and total protein in proteinuric patients. *Nephrol Dial Transplant* 2012; 27: 1534–1541.)

References


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