The value of simultaneous measurements of urinary albumin and total protein in proteinuric patients

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Abstract

Background. Proteinuria is a common pathological finding in renal disease. Examining the urinary protein electrophoretic pattern gives clues to the site of origin of the protein. We hypothesized that the type of proteinuria, classified by urine protein electrophoresis and immunofixation (uPEI), may be predicted by simply examining the proportion of higher molecular weight protein (e.g. albumin) in urine total protein content.

Methods. One thousand and eleven patients, whose urine had been sent to the pathology department for uPEI, were analysed for total protein and albumin to creatinine ratio (uPCR and uACR) and the ratio reported as the albumin to total protein ratio (uAPR). In a group of renal outpatients (n = 248), we also specifically measured tubular proteins (N-acetyl-β-D-glucosaminidase, NAG, and β₂-microglobulin) and expressed these as ratios to creatinine (uNCR and uβ₂CR). To validate these findings, we correlated these measurements with 68 patients in whom we also had renal biopsy data.

Results. In receiver operating characteristic (ROC) curve analysis, the AUC for uAPR was 0.84 for predicting tubular proteinuria pattern on uPEI. In the renal outpatient subgroup, uAPR predicted a tubular pattern of urinary protein equally as well as testing for specific tubular protein markers (uNCR and uβ₂CR). In the validation cohort, a uAPR cut-off of <0.40 was 88% sensitive and 99% specific for the diagnosis of primary tubulointerstitial disorders on renal biopsy.

Conclusions. Useful information about the origins of urinary protein may be inferred by measuring uAPR, the measurement of which is both simple and inexpensive.
Keywords: renal dysfunction; tubular pathology; urine albumin to creatinine ratio; urine albumin to protein ratio; urine protein to creatinine ratio

Introduction

Normal glomerular function only permits the filtration of proteins with a molecular weight below ~60 000 Da, and much of the protein filtered is subsequently reabsorbed by proximal tubular endocytosis [1]. Urinary protein loss is thus usually <80 mg/day [2]. However, in kidney disease, higher levels of proteinuria often occur, resulting from a disruption of the glomerular filtration barrier, tubular dysfunction or both. Urine protein electrophoresis has been used as a diagnostic aid for renal diseases since the 1950s [3].

Several studies have demonstrated the utility of urine protein electrophoresis in distinguishing between glomerular and tubulointerstitial pathologies either by sodium dodecyl sulphate–polyacrylamide gel electrophoresis [4–6] or agarose gel electrophoresis [7–9]. In glomerular pathologies, e.g. steroid-responsive nephrotic syndrome, proteinuria shows a predominantly high molecular weight protein pattern, highlighted by strong staining for albumin, transferrin and immunoglobulin. In tubulointerstitial pathologies, e.g. Fanconi syndrome, there is selective low molecular weight protein loss, characterized by a stronger bands for ($\alpha_1$-)microglobulin, retinol-binding protein and in the [β₂-microglobulin region [10]. Although informative, urine protein electrophoresis and immunofixation analysis are not widely used in this clinical setting because of their cost (~£40/€45), the need for skilled interpretation and lack of standardization.

The strategy of determining the origins of urinary proteins by examining multiple protein markers is not a new concept. However, these methods suffer from lack of widely available standardized tests and the high costs of analysis [11]. Thus, based on urine protein electrophoresis and immunofixation (uPEI) analysis, we tested the hypothesis that a relatively higher albumin content as a proportion of the total urinary protein content would reflect a predominantly glomerular pattern and a lower albumin content may reflect a tubulointerstitial pattern of urinary protein loss. We examined the relationship between the urinary albumin to creatinine ratio (uACR), urinary total protein to creatinine ratio (uPCR) and the ratio (uACR/uPCR) of these (uAPR) with the uPEI patterns in a cohort of urine samples. Only a few published studies have evaluated uAPR in the diagnosis of kidney disease. In paediatric populations, significantly lower uAPR was associated with tubular rather than primary glomerular disease [12, 13]. More recently in adult cohorts, Ohisa et al. [14, 15] showed that uAPR also had excellent predicative power to distinguish the origin of haematuria.

This is the first relatively large study to our knowledge to have compared the very easy to obtain figure of uAPR, with uPEI analysis and correlated these findings with renal biopsy histology.

Materials and methods

Samples

The study samples were 1011 consecutive random urine samples received by the Department of Biochemistry and Immunology at Brighton and Sussex University Hospitals NHS Trust for uPEI between August 2010 and March 2011. Patients’ uPCR <30 mg/mmol are routinely excluded from uPEI analysis as there is an exceptionally low chance of finding pathology on uPEI. We also excluded samples from renal transplant patients. This clinical laboratory is fully CPA accredited and participates in external quality control schemes for all routine urine protein analyses. Urine samples were collected without preservative and stored at 4°C for <48 h prior to analysis. The source of referral was recorded in each case and categorized into general practice (primary care), outpatient clinics, acute inpatient units or other inpatient units.

Acute inpatient units included the emergency department, intensive care unit and acute medical units.

Measurements

Urinary total protein concentration was measured by turbidimetry after alkaline denaturation and precipitation with benzethonium chloride. Measuring range was 40–2000 mg/L. Samples with a concentration above this upper limit were automatically rerun at dilution to give an absolute value. Intermediate imprecision (based on 1 run/day for 28 days) was 3.9% at 55 mg/L and 2.5% at 260 mg/L. Urine albumin was measured by immunoturbidimetric assay using polyclonal anti-human albumin (sheep antiserum). This method includes an antigen excess check and has no high-dose hook effect up to an albumin concentration of 40 000 mg/L. Working analytical range was 12–200 mg/L. Samples with a concentration above this upper limit were automatically rerun at dilution. Intermediate imprecision was 2.0% at 20 mg/L and 2.3% at 120 mg/L. Urine creatinine concentration was determined by enzymatic (creatininase) colorimetry. Measuring range was 0.1–40.0 mmol/L. Intermediate imprecision was 1.8% at 5.8 mmol/L and 3.6% at 25.6 mmol/L.

The commonly measured and semi-quantitative estimates of urinary albumin and urinary total protein were first separately expressed as a ratio to urine creatinine concentration (uACR and uPCR, respectively). To clarify the relationship between albumin and protein excretion, the ratio of uACR to uPCR was then calculated (uAPR). All urine chemistries were performed on a Cobas Integra 800 analyzer (Roche Diagnostics, UK).

Urine protein electrophoresis was performed with unconcentrated urine by agarose gel electrophoresis and visualized with acid violet stain (SAS3 Urine Protein analysis; Helena Biosciences, UK). Samples with discrete bands on electrophoresis were then submitted for immunofixation with antisera to macro-proteins (α₁-antitrypsin, transferrin) and micro-proteins (retinol-binding protein, β₂-microglobulin and γ₂-microglobulin) and γ, α, μ, κ and λ immunoglobulin chains (Helena Biosciences). Electrophoretic patterns were assessed in conjunction with available immunofixation results by a single biochemist (E.R.S.) blinded to uPCR and uACR results. The use of uPEI to differentiate types of proteinuria is well established and offers greater specificity and more robust interpretation of urine protein contents than electrophoresis alone [8, 16].

The pattern was classified as predominantly glomerular if there was a dominant albumin band, and typically other high molecular weight proteins such as transferrin (β₅), α₁-glycoprotein and γ₂-anti-trypsin were present in a broad α₂-zone. A pattern resembling that of the serum was considered indicative of severe non-selective glomerular disease. On immunofixation, these samples showed reactivity with macro-protein antisera but relatively little micro-protein reactivity (Figure 1).

The pattern was considered predominantly tubular if there was a relatively faint albumin band, a double band in the α₂ region (due to α₂-microglobulin), a strong band in the mid-beta region (due to β₂-microglobulin) and diffuse staining in the gamma region (due to free light chains). On immunofixation, these samples showed reactivity with micro-protein antisera but relatively little macro-protein reactivity. A ‘mixed’ proteinuria type was assigned when glomerular and tubular patterns appeared superimposed: typically indicated by the presence of a strong albumin band and double bands in the α₂-globulin region. Immunofixation showed reactivity to both macro- and micro-protein
Subsequently, the term ‘tubular proteinuria’ refers to a predominantly tubular pattern and ‘non-tubular proteinuria’ if predominantly glomerular, mixed or overflow pattern was observed. 

Urine N-acetyl-b-D-glucosaminidase (uNAG) and b2-microglobulin (uB2M) were measured in all 248 samples from the renal outpatient clinics. uNAG activity was determined spectrophotometrically using commercially available reagents (Roche Applied Science, UK). This assay is based on the hydrolysis of 3-cresolsulfonphthaleinyl-N-acetyl-b-D-glucosaminide, releasing 3-cresolsulfonaphthalein which was detected at 580 nm. Between-batch imprecision was 5.1% at 10 U/L. uB2M concentration was measured by latex particle-enhanced immunoturbidimetry using a BN Prospec nephelometer (Siemens Healthcare Diagnostics, UK). Aliquots of urine were stabilized by alkalization (pH > 7) on receipt. Between-batch imprecision for this assay was 3.9% at 1.5 mg/mmol. Both uNAG and uB2M were expressed as a ratio to urinary creatinine (uNCR and uB2M-CR). Control ranges were established in 40 apparently healthy individuals (mean age 56.7 ± 10.2 years, 24 males) without biochemical evidence of renal dysfunction (eGFR at 10 mg/mmol, uACR < 5 mg/mmol, uB2M-CR < 5 mg/mmol). The ranges for uB2M-CR was determined as 23.4 µg/mmol [interquartile range (IQR): 17.3–23.9] and for uNCR as 0.16 U/mmol (IQR: 0.10–0.22).

Histological correlation
To correlate our findings, we retrospectively examined the histopathology reports of patients that had concurrent uPCR, uACR, uPEI and a native renal biopsy since October 2006. For comparative purposes, a clear primary glomerular pathology was defined as a biopsy showing glomerulonephritis with/without any tubulointerstitial change. A primary tubular pathology was defined as a biopsy showing tubulointerstitial necrosis, inflammation or fibrosis with minimal or absent glomerular damage. Minimal glomerular damage was defined as age-related changes that were not present throughout the biopsy sample, for example an occasional subcapsular sclerosed glomerulus. All biopsies were given a tubulointerstitial score of none, mild, moderate or severe, depending upon the severity of tubular changes or interstitial disruptions by inflammation or fibrosis. These were scored independently by a renal histopathologist (D.A.W.) and a renal physician (S.G.H.) and without a reference to the urinary findings. Where scores differed, the reports were discussed and a score agreed upon. These diagnoses were then compared to findings on electrophoresis and immunofixation.

Statistical analyses
uPCR, uACR, uAPR, uNCR and uB2M-CR were analysed as continuous variables. The appropriate summary statistics were used after assessment for normality. Spearman’s rank correlation test (p) was used to assess the association between two continuous variables. Receiver operating characteristic (ROC) curves were compared using the Delong Clarke Pearson test (Analyse-it; Analyse-it Software Ltd, UK). Other data were analysed using SPSS version 18.0 for Windows (IBM, SPSS.com). An alpha value of P < 0.05 was used to determine statistical significance.

Results
One thousand and eleven urine samples sent for uPEI were analysed. Patients were referred from general practitioners (n = 397, 39%), outpatient clinics (n = 344, 34%), acute inpatient units (n = 157 16%) and other inpatient units (n = 125, 12%). The majority (n = 248, 72%) of outpatient clinic samples came from renal outpatient clinics. The median urine total protein was 501 mg/L (IQR: 232–1129) and median albumin concentration 207 mg/L (IQR: 91–536). The median uPCR was 87 mg/mmol (IQR: 48–226), uACR 39 mg/mmol (IQR: 20–103) and uAPR 0.49 (IQR 0.29–0.66). Around a fifth of patients (199/1011) had a uPCR >300 mg/mmol (nephrotic range). To investigate the potential selection bias of

![Fig. 1. Urine protein analysis by electrophoresis and immunofixation. Examples of the characteristic urine protein electrophoretic patterns are shown in the upper panel of the figure. (A) Glomerular pattern: uACR 90 mg/mmol, uPCR 110 mg/mmol, uAPR 0.82. (B) Tubular pattern: uACR 15 mg/mmol, uPCR 65 mg/mmol, uAPR 0.23. (C) Mixed pattern: uACR 84 mg/mmol, uPCR 146 mg/mmol, uAPR 0.57. (D) Overflow pattern: uACR 8 mg/mmol, uPCR 112 mg/mmol, uAPR 0.07. Proteins are separated out in the agarose gel according to charge and flow pattern: uACR, uPCR, uAPR, uNCR and uB2M-CR were analysed as continuous variables. The appropriate summary statistics were used after assessment for normality. Spearman’s rank correlation test (p) was used to assess the association between two continuous variables. Receiver operating characteristic (ROC) curves were compared using the Delong Clarke Pearson test (Analyse-it; Analyse-it Software Ltd, UK). Other data were analysed using SPSS version 18.0 for Windows (IBM, SPSS.com). An alpha value of P < 0.05 was used to determine statistical significance.](image-url)
the study, we looked at the results of all patients with uPCR measurements requested over a 3-month period submitted for analysis to our laboratory. Of the 3062 samples, 949 had an uPCR >30 mg/mmol (the lower limit of investigation used in this study). The median uPCR of this cohort was not significantly different to our study cohort [92 versus 87 mg/mmol (P = 0.215)].

Assessment of uPEI patterns

A predominantly glomerular pattern was found in 696 (69%) of samples. A tubular pattern of proteinuria was found in 240 (24%) samples. Mixed and overlap patterns were found in 49 (5%) and 29 (3%) samples, respectively. Tubular proteinuric samples had a lower uAPR than non-tubular proteinuric samples (P < 0.001, Mann–Whitney U-test). The levels of uPCR, uACR and uAPR for the different proteinuria types can be found in Table 1.

Relationship between uPCR, uACR, uAPR and uPEI patterns

The ROC curve analysis for uAPR in predicting tubular proteinuria showed an area under the curve (AUC) of 0.84 [95% confidence interval (CI) 0.82–0.87]. When patients with heavy proteinuria or albuminuria (uPCR ≥ 100 mg/mmol, uACR ≥ 70 mg/mmol) were removed from analysis, the AUC remained similar at 0.86 (95% CI 0.82–0.89). When analysis was confined to nephrotic samples (uPCR > 300 mg/mol), the AUC was 0.81 (95% CI 0.73–0.89). The AUC for uAPR was superior to both uACR (ΔAUC: −0.11, 95% CI −0.14 to −0.07, P < 0.001) and uPCR (ΔAUC: −0.30, 95% CI −0.35 to −0.26, P < 0.001) (Figure 2a). There were no significant differences in the AUC for uAPR between referral sources (indicated by overlapping 95% CI; Supplementary Table S1).

In the renal outpatient group (n = 248), the median uPCR was 102 mg/mmol (IQR: 50–325) and uACR 46 mg/mmol (IQR: 23–119). The median uNCR was 0.18 U/mmol (IQR: 0.13–0.28) and uβ2CR was 27 μg/mmol (IQR: 20–43). Sixty-five (26%) samples in this subgroup had a lower uAPR than non-tubular proteinuric samples (P < 0.001, Mann–Whitney U-test). The levels of uPCR, uACR and uAPR for the different proteinuria types can be found in Table 1. When analysis was confined to nephrotic samples (uPCR ≥ 100 mg/mmol), the AUC was 0.81 (95% CI 0.73–0.89). The AUC for uAPR was superior to both uACR (ΔAUC: −0.11, 95% CI −0.14 to −0.07, P < 0.001) and uPCR (ΔAUC: −0.30, 95% CI −0.35 to −0.26, P < 0.001) (Figure 2a). There were no significant differences in the AUC for uAPR between referral sources (indicated by overlapping 95% CI; Supplementary Table S1).

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Table 1. Levels of uPCR, uACR, uAPR according to uPEI patterns in the main cohort (n = 1011)*

<table>
<thead>
<tr>
<th></th>
<th>Predominantly glomerular (n = 696)</th>
<th>Predominantly tubular (n = 240)</th>
<th>Mixed (n = 49)</th>
<th>Overflow (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>uPCR (mg/mmol)</td>
<td>84 (46–221)</td>
<td>79 (46–189)</td>
<td>210 (118–477)</td>
<td>208 (84–840)</td>
</tr>
<tr>
<td>uACR (mg/mmol)</td>
<td>46 (23–119)</td>
<td>19 (11–44)</td>
<td>106 (51–232)</td>
<td>30 (16–175)</td>
</tr>
<tr>
<td>uAPR</td>
<td>0.57 (0.40–0.70)</td>
<td>0.22 (0.14–0.40)</td>
<td>0.53 (0.42–0.64)</td>
<td>0.17 (0.14–0.25)</td>
</tr>
</tbody>
</table>

*All levels expressed as median (IQR).

Histological correlation

Sixty-eight kidney biopsies were available for analysis, and of these, 48 (71%) biopsies had a primary glomerular disorder, 8 (12%) had a primary tubulointerstitial disorder, 12 (18%) had a mixed disorder. None of the patients with primary tubulointerstitial disease had a glomerular pattern of proteinuria on uPEI; conversely, no tubular uPEI pattern was found in those with pure glomerular pathology. A glomerular uPEI pattern was found in 86% of primary glomerular pathologies, with the remaining 14% showing a mixed pattern. The histological diagnosis, urine indices and tubulointerstitial scores are illustrated in Supplementary Table S4. This validation cohort had higher median uPCR, uACR and uAPR values when compared to the main cohort. Figure 3 illustrates the histological diagnosis with their respective uAPR and uPEI pattern. Unlike uACR and uPCR, there was a minimal overlap in uAPR between primary glomerular and primary tubulointerstitial pathologies (Supplementary Figure S1). Based on Table 2, a uAPR cut-off of 0.4 gave similar sensitivity and specificity values, we therefore tested this cut-off value in the biopsy cohort. We found a uAPR cut-off of 0.4 had sensitivity and specificity of 88 and 99%, respectively, for the diagnosis of primary tubulointerstitial disorders.

Tubulointerstitial scores

Three (4%), 22 (32%), 22 (32%) and 21 (31%) biopsies showed no, mild, moderate and severe tubulointerstitial damage, respectively. uAPR was lower in the lower grades (none/mild versus moderate/severe) of tubulointerstitial damage (P = 0.001, Mann–Whitney U-test, Figure 4). This remained significant when analysis was limited to primary glomerular disorders only (P = 0.04). There were no significant differences between uPCR, uACR and the degree of tubulointerstitial damage.

Discussion

Previous studies have used a multi-marker strategy to diagnose tubular pathology [13, 17, 18]. However, this approach is both expensive and impractical for routine use given the prevalence of abnormal protein excretion (~7% of the general population) [19]. uPCR and uACR are cheap (£0.20 and £0.40/€0.50, respectively) and are widely
available for the assessment of renal disease. Thus, we tested
the hypothesis that the relative quantities of albumin may
help differentiate the different types of proteinuria. As evi-
dent from this study and others [19–21], there is consid-
erable variability in the proportion of albumin in total protein,
evidenced by the wide distribution of uAPR. Methven et al.
[21] reported similar findings in 6842 CKD patients and
found that albuminuria did not give an accurate reflection

Fig. 2. (a) ROC curves for uAPR, uACR and uPCR demonstrating the superiority of uAPR over uACR in discriminating between tubular pattern and non-tubular proteinuria pattern on uPEI ($n = 1011$). (b) ROC curves for uAPR and the specific tubular markers uNCR and uβ2CR demonstrating non-
inferiority of the uAPR for detecting tubular proteinuria patterns on uPEI in the renal outpatient subgroup ($n = 248$).
of total proteinuria. We have utilized this inherent variability in the urine albumin content to demonstrate the usefulness of uAPR in predicting types of proteinuria, based on uPEI and biopsy data. The confounding factor in this logic is that albumin filtered at the glomerulus is taken by tubular cells, by a mechanism involving the megalin/cubulin pathway, and which may lead to tubulotoxicity [22, 23]. However, these tubulotoxic effects may be relatively late sequelae of chronic tubular loading with albumin [24].

Very heavy proteinuria >3–5 g/day is usually glomerular in origin and in this group, the diagnosis of a glomerular disease is rarely difficult, and generally these patients would go on to have a renal biopsy for histological diagnosis. However, the group of patients where diagnosis is often challenging and where extra diagnostic information may be helpful is that group who have >300 mg/day but <3 g/day. We have shown here that in this cohort of patients, a simple uAPR determination provided useful information in the interpretation of the type of proteinuria in the majority of patients. In a subgroup of patients from nephrology outpatient clinics, we also showed that uAPR performed as well as other established specific markers (uNCR and uβ2CR) of tubular dysfunction. The robustness of uAPR was shown in ROC curve comparisons. The AUC was consistently >0.8 across different referral sources and in samples with varying amount of proteinuria.

To advance beyond the laboratory correlations, the clinical relevance of this study is demonstrated by our histological validations. A uAPR of >0.40 was previously suggested as showing glomerular disease by Ohisa et al. [15]. Our data accord with this cut-off, where an uAPR of <0.40 provided high sensitivity and specificity for tubulointerstitial disorders. In such patients, uAPR may provide a valuable tool in helping to establish a diagnosis and may be useful in determining the likely source of the protein leak, especially where the risks of performing a kidney biopsy is high.

We speculate that uAPR could potentially provide prognostic value. In our study, biopsies with higher grades of tubulointerstitial damage had lower uAPR values, even when analysis was confined to glomerular disorders. The association between tubulointerstitial damage and progressive renal function decline is well established [25, 26]; nevertheless, independent prognostic value of uAPR needs to be defined in further studies.

One of the strengths of this study is that it included a large sample across various outpatient and inpatient settings. However, there were also significant limitations.

These include the fact that the proteinuria classification was determined by potentially subjective methodology and visual interpretation of uPEI patterns. This technique is well validated and widely reported, and although in our study this was reported by an experienced biochemist without reference to the urinary values, there are limitations of minor subjectivity [9]. Indeed histological interpretations are subject to the same level of subjectivity and rely on the experience of the reporting clinician. To reduce the subjectivity further, only uPEI with obvious tubular pattern were classified as tubular proteinuria,

Table 2. uAPR performance for the diagnosis of tubular proteinuria in the entire cohort (n = 1011)

<table>
<thead>
<tr>
<th>uAPR cut-off</th>
<th>Sensitivity % (95% CI)</th>
<th>Specificity % (95% CI)</th>
<th>Likelihood ratio (+)</th>
<th>Likelihood ratio (−)</th>
<th>Positive predictive value (%)</th>
<th>Negative predictive value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.20</td>
<td>42 (36–49)</td>
<td>94 (92–96)</td>
<td>7.05</td>
<td>0.62</td>
<td>68</td>
<td>84</td>
</tr>
<tr>
<td>&lt;0.30</td>
<td>68 (61–73)</td>
<td>86 (84–89)</td>
<td>4.86</td>
<td>0.38</td>
<td>60</td>
<td>89</td>
</tr>
<tr>
<td>&lt;0.40</td>
<td>75 (69–80)</td>
<td>73 (70–76)</td>
<td>2.81</td>
<td>0.34</td>
<td>47</td>
<td>90</td>
</tr>
<tr>
<td>&lt;0.50</td>
<td>85 (80–90)</td>
<td>59 (56–63)</td>
<td>2.10</td>
<td>0.25</td>
<td>40</td>
<td>93</td>
</tr>
<tr>
<td>&lt;0.60</td>
<td>95 (92–98)</td>
<td>43 (40–47)</td>
<td>1.68</td>
<td>0.11</td>
<td>35</td>
<td>97</td>
</tr>
<tr>
<td>&lt;0.70</td>
<td>99 (96–99)</td>
<td>32 (29–35)</td>
<td>1.46</td>
<td>0.04</td>
<td>29</td>
<td>98</td>
</tr>
</tbody>
</table>
ambiguous patterns were classified as mixed and hence classified as non-tubular. We also showed good correlation of the uPEI pattern with the independently obtained histological report. This suggests that these techniques are relatively robust, in that we have shown a correlation of histological structure with function (uPEI and uAPR).

It is possible that the urine samples collected were subjected to selection bias because only samples sent for electrophoresis were included for analysis. While it is the case that a proportion of the samples came from patients being investigated for haematological malignancies (which we readily acknowledge as a potential limitation of this study), a significant proportion of urine investigations were also primarily requested as part of the workup for renal dysfunction or proteinuria. We feel that all patients with significant persistent proteinuria should be tested for monoclonal gammapathies, and this is routine advice at our hospitals. Thus, we feel that most patients simply had this test as a routine part of investigation, minimizing selection bias. However, to investigate this concern further, we looked at the results of all patients with uPCR measurements requested and found that the median uPCR was not significantly different from patients being investigated for proteinuria.

Although the biopsy cohort had heavier proteinuria than the main cohort (median uPCR 341 versus 87 mg/mmol), nephrotic range proteinuria was well represented in the main cohort (median uPCR 341 versus 87 mg/mmol), and uAPR cut-off of 0.4 to distinguish between glomerular versus non-glomerular pathologies.

Based on the biopsy data from our study and others, glomerular diseases rarely resulted in a uAPR of <0.4 [12, 15]. In most cases, urinary albumin would increase in proportion to high molecular weight proteinuria, but it is theoretically possible that some patients with non-selective glomerular proteinuria might filter more higher molecular weight proteins which would be interpreted by an uAPR as a ‘non-albumin’ protein and therefore risk being misclassified as tubular proteinuria [31]. In practice, however, it is unlikely that the proportion of non-albumin protein in urine would exceed those of plasma. Thus, even in very non-selective proteinuria, high molecular weight protein is unlikely to contribute to a uAPR <0.4.

In conclusion, the use of concurrently measured uACR and uPCR is a simple and inexpensive test that may further assist in determination of the underlying renal pathology in patients with proteinuria. A low uAPR (<0.4) may usefully point to a tubulo-interstitial disease on renal biopsy. Furthermore, a high uAPR may attest to a purely glomerular pathology, e.g. minimal-change/membranous nephropathy. The uAPR may also help to indicate how much interstitial damage is present in some renal pathology. Further work is underway to see if this index may be prognostically useful.

Supplementary data

Supplementary data are available online at http://ndt.oxfordjournals.org.

Conflict of interest statement. None declared.

(Supplementary data are available online at http://ndt.oxfordjournals.org.)

Conflicts of interest. None declared.

References

Differentiating types of proteinuria


Received for publication: 21.8.11; Accepted in revised form: 9.11.11