Table 1. Basic characteristics and laboratory parameters

|                          | Controls (n = 61) | NSF patients (n = 4) | P-value |
|--------------------------|------------------|----------------------|---------|
| Age (years)              | 58.2 ± 15.6      | 50.6 ± 18.5          | 0.36    |
| Sex (m/f)                | 49/12            | 3/1                  | >0.05   |
| Patients with prior KTX  | 17 (1–4)         | 1 (3)                | >0.05   |
| Time of ESRD             | 4.5 ± 6.2        | 2.6 ± 3.3            | 0.56    |
| Kt/V                     | 1.1 ± 0.2        | 1.0 ± 0.3            | 0.36    |
| Systolic blood pressure  | 138.6 ± 24.7     | 153.8 ± 21.7         | 0.23    |
| Diastolic blood pressure | 73.6 ± 15.0      | 81.3 ± 8.5           | 0.32    |
| Antihypertensive drugs   | 2.0 ± 1.7        | 1.3 ± 1.3            | 0.41    |
| Primary renal disease    |                  |                      | >0.05   |
| Diabetic nephropathy     | 20 (32.8%)       | 2 (50%)              |         |
| Vascular nephropathy     | 7 (11.5%)        | 1 (25%)              |         |
| Glomerulonephritis       | 19 (31.1%)       | –                    |         |
| Intertstitial nephritis  | 2 (3.3%)         | –                    |         |
| Reflux nephropathy       | 3 (4.9%)         | –                    |         |
| Tumour                   | 3 (4.9%)         | 1 (25%)              |         |
| Others                   | 2 (3.3%)         | –                    |         |
| Unknown                  | 5 (8.2%)         | –                    |         |
| Haemoglobin (mg/dl)      | 12.0 ± 1.3       | 11.0 ± 1.0           | 0.15    |
| Serum iron (µg/dl)       | 66.3 ± 28.9      | 35.5 ± 12.5          | 0.04    |
| Transferrin (mg/dl)      | 184.7 ± 38.3     | 146.8 ± 20.0         | 0.06    |
| Transferrin saturation (%) | 26.4 ± 13.3   | 17.5 ± 6.9           | 0.19    |
| Ferritin (ng/ml)         | 459.6 ± 349.4    | 536.0 ± 254.2        | 0.67    |
| CRP                      | 2.0 ± 3.0        | 2.7 ± 1.9            | 0.68    |

CRP: C-reactive protein; ESRD: end-stage renal disease; KTX: kidney transplantation.

gadolinium-based contrast media in causation and the beneficial effect of intravenous sodium thiosulfate. Clin J Am Soc Nephrol 2007; 2: 258–263
5. Leung N, Swaminathan S, Ahmed I et al. Erythropoietin, gadolinium, and nephrogenic fibrosing dermopathy—author reply. Ann Intern Med 2007; 146: 230
6. Centers for Disease Control and Prevention (CDC). Nephrogenic systemic fibrosing dermopathy—St. Louis, Missouri, 2002–2006. MMWR Morb Mortal Wkly Rep 2007; 56: 137–141
7. Goveia M, Chan BP, Patel PR. Evaluating the role of recombinant erythropoietin in nephrogenic systemic fibrosis. J Am Acad Dermatol 2007; 57: 725–727
8. Marckmann P, Skov L, Rossen K et al. Case-control study of gadodiamide-related nephrogenic systemic fibrosis. Nephrol Dial Transplant 2007; 22: 3174–3178
9. Othersen JB, Maize JC, Woolson RF et al. Nephrogenic systemic fibrosis after exposure to gadolinium in patients with renal failure. Nephrol Dial Transplant 2007; 22: 3179–3185
10. Cowper SE, Su LD, Bhawan J et al. Nephrogenic fibrosing dermopathy. Am J Dermatopathol 2001; 23: 383–395
11. Perazella MA. Nephrogenic systemic fibrosis, kidney disease, and gadolinium: is there a link? Clin J Am Soc Nephrol 2007; 2: 200–202

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Cystatin C as a surrogate for glomerular filtration rate in the presence of proteinuria

Sir,

All methods for assessing glomerular filtration rate (GFR) have shortcomings. Serum creatinine has a reciprocal relationship to GFR that is related to age, race, sex and muscle mass and is affected by tubular secretion. Creatinine clearance requires a timed urine collection, and radio isotope and insulin clearance methods are expensive. Estimated GFR may only be valid in the steady state of chronic kidney disease (CKD) [1].

There has been much [2] interest in cystatin C, a serine protease inhibitor produced by all nucleated cells, freely filtered at the glomerulus and, although reabsorbed, apparently fully metabolized in tubular cells [3]. Serum cystatin C may be more sensitive to changes in GFR than serum creatinine [4,5].

Renal disease is often accompanied by proteinuria, the severity of which correlates with progression [6], possibly because protein in the tubular fluid injures tubular cells via mechanisms involving reactive oxygen species [7]. We hypothesized that proximal tubular injury by proteinuria might affect cellular handling of cystatin C, leading to an altered relationship to GFR.

We measured serum cystatin C in 65 nephrology-clinic patients, with and without proteinuria, using a latex-enhanced immunonephelometric assay based on rabbit polyclonal antibodies (Dade Behring, UK) with a ProSpec analyser (Dade Behring, UK). Urinary creatinine and protein were measured using standard chemistries on Roche Modular systems (Roche/Hitachi, Roche Diagnostics, Gmbh, Germany). GFR was estimated using the modification of diet in renal disease (MDRD) formula [8]. Patients were being treated for stable CKD secondary to primary glomerulonephritis (28%), diabetes (15%), vasculitis or lupus (8%), chronic pyelonephritis (6%), hypertensive nephrosclerosis (3%), miscellaneous conditions (16%) or unknown cause (24%). They were classified as proteinuric
if excreting >1 g protein/24 h (range 1–15 g/24 h, n = 24), otherwise non-proteinuric (n = 41).

To normalize variance, the reciprocal relationship between serum cystatin C and GFR was analysed as −log(cystatin) versus log(GFR), grouped linear regression (StatsDirect Ltd, Cheshire, UK) being used to assess the common slope and the (statistically significant, P = 0.03) vertical separation of the regression lines in the two groups, and converted back to the linear domain for presentation (Figure 1). When the regression line for the non-proteinuric group is used to predict cystatin C values for each proteinuric patient, their observed cystatin C is on average 33 ± 8% higher than expected from GFR.

Although we did not formally measure GFR, these results suggest the need for caution in using cystatin C as a marker for GFR in proteinuria. A similar warning was sounded by anomalies in four patients with sickle cell disease [11] and also by a large study of diabetic patients in which mean cystatin C was ~50% higher in patients with microalbuminuria than those without, despite no significant difference in mean serum creatinine [12]. The present study extends this by calculating the discrepancy for each proteinuric patient. Although the close reciprocal correlation between cystatin C and radioisotope GFR can be used to predict GFR from cystatin C with high accuracy and precision [9], such formulae may need modification in proteinuria. Longitudinal studies will be needed to determine whether changes in proteinuria in individual patients alter this relationship. More complex interactions between serum cystatin C, markers of tubular dysfunction and measures of diabetic control [13] also merit further investigation.

There are two possible explanations for our finding. First, proteinuria might affect the accuracy of the MDRD equation. This significantly underestimates GFR in the presence of microalbuminuria during the hyperfiltration phase of diabetic nephropathy [10], but none of our relatively few diabetic patients were hyperfiltering (GFR > 100 ml/min). Alternatively, proteinuria might raise serum cystatin C. Since proteinuria damages proximal tubular cells cultured in vitro [6,7], we speculate that damaged cells might fail to metabolize all reabsorbed cystatin C, leaving some to re-enter the circulation. If so, a rising serum cystatin C might prove useful in monitoring tubular injury.

Conflict of interest statement. None declared.

1 Departments of Nephrology and Thomas Ledson
Clinical Biochemistry and Matthew L. P.
2 Metabolic Medicine, Royal Howse
Liverpool and Broadgreen Norman B.
University Hospital NHS Trust Roberts
3 Division of Cellular and Metabolic Graham J. Kemp
Medicine, University of Liverpool Peter S. Williams
Liverpool, UK

E-mail: Matthew.Howse@rlbuht.nhs.uk

1. Lamb EJ, Stevens PE. Challenging times in renal medicine: an opportunity for clinical biochemistry. *Ann Clin Biochem* 2005; 42: 318–320
2. Simonsen O, Grubb A, Thysell H. The blood serum concentration of cystatin C (gamma-trace) as a measure of the glomerular filtration rate. *Scand J Clin Lab Invest* 1985; 45: 97–101
3. Zahrani A, El-Husseini A, Shoker A. Can cystatin C replace creatinine to estimate glomerular filtration rate? A literature review. *Am J Nephrol* 2007; 27: 197–205
4. Dharnidharka VR, Kwon C, Stevens G. Serum cystatin C is superior to serum creatinine as a marker of kidney function: a meta-analysis. *Am J Kidney Dis* 2006; 47: 221–226
5. Risch L, Blumberg A, Huber A. Rapid and accurate assessment of glomerular filtration rate in patients with renal transplants using serum cystatin. *Nephrol Dial Transplant* 1999; 14: 1991–1996
6. Williams PS, Fass G, Bone JM. Renal pathology and proteinuria determine progression in untreated mild/moderate chronic renal failure. *Q J Med* 1988; 67: 343–354
7. Shalamanova L, Mc Ardle F, Amara AB et al. Albumin overload induces adaptive responses in human proximal tubular cells through oxidative stress but not via angiotensin II type 1 receptor. *Am J Physiol Renal Physiol* 2007; 292: F1846–F1857
8. Levey AS, Bosch JP, Lewis JB et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med* 1999; 130: 461–470
9. Hock FJ, Kemperman FAW, Krediet RT. A comparison between cystatin C, plasma creatinine and the Cockcroft and Gault formula for the estimation of glomerular filtration rate. *Nephrol Dial Transplant*. 2003; 18: 2024–2031
10. Rossing P, Rossing K, Gaede P et al. Monitoring kidney function in type 2 diabetic patients with incipient and overt diabetic nephropathy. *Diabetes Care* 2006; 29: 1024–1030
11. Alvarez O, Zilleruelo G, Wright D et al. Serum cystatin C levels in children with sickle cell disease. *Pediatr Nephrol* 2006; 21: 533–537
12. Mijiminyi OA, Abdella N. Evaluation of cystatin C and beta-2 microglobulin as markers of renal function in patients with type 2 diabetes mellitus. *J Diabetes Complications* 2003; 17: 160–168
13. Ush S, Efe B, Alatas O et al. Serum cystatin C and urinary enzymes as screening markers of renal dysfunction in diabetic patients. *J Nephrol* 2005; 18: 559–567

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