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 (*n*; range)	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 (mmHg)	138.6 ± 24.7	153.8 ± 21.7	0.23
Diastolic blood pressure (mmHg)	73.6 ± 15.0	81.3 ± 8.5	0.32
Antihypertensive drugs (*n*)	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%)	–	
Intertitial 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.

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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 inulin 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

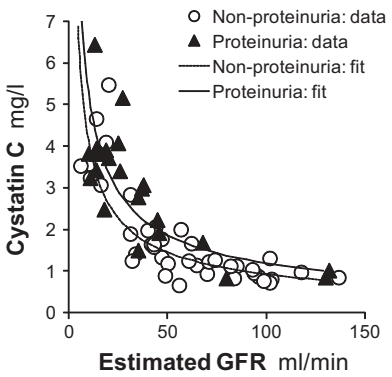

Fig. 1. Cystatin C versus GFR, with best-fit lines (see key) converted from a log–log fit derived by grouped linear regression.

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-proteinuria 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 [2]Clinical Biochemistry and Metabolic Medicine, Royal Liverpool and Broadgreen University Hospital NHS Trust [3]Division of Cellular and Metabolic Medicine, University of Liverpool Liverpool, UK

Thomas Ledson[1]
Matthew L. P. Howse[1]
Norman B. Roberts[2]
Graham J. Kemp[3]
Peter S. Williams[1]

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

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