Urinary endothelin-1 in chronic kidney disease and as a marker of disease activity in lupus nephritis

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Chronic kidney disease (CKD) is common, affecting 6–11% of the population in the developed world (23). Chronic inflammation is a major contributor to the development and progression of CKD (21). Current treatments for inflammatory CKD include immunosuppressive therapy, which is often associated with significant side effects (18). Despite this, however, some patients develop progressive renal injury resulting in end-stage renal disease. Also, those who respond to treatment remain at risk of further disease relapses. Identifying renal inflammatory disease early and assessing its response to treatment remain important clinical challenges. Measurement of renal function, using serum creatinine for example, is often inadequate because substantial renal tissue damage can occur before function is impaired to a detectable extent (15). However, serial renal biopsies are not appropriate in clinical practice. Current disease markers include serum C-reactive protein (CRP) and proteinuria. However, these lack both sensitivity and specificity for renal inflammation. There are currently no easily assessable clinical biomarkers specific to renal inflammation. Such markers would not only allow early implementation of appropriate treatments, with the hope of preventing disease progression, but also help identify future disease relapses.

Endothelin-1 (ET-1) is a 21-amino acid peptide implicated in the development and progression of CKD (10). It is produced both within the vasculature and the kidney (10). ET-1 is the most potent endogenous vasoconstrictor (39). In addition, both within the kidney and elsewhere, ET-1 has a number of other major effects including cell proliferation (32), inflammation (30), and fibrosis (17). Although plasma ET-1 levels are not a reliable measure of vascular ET-1 production, owing to its predominantly abluminal release (40), urinary ET-1 excretion is independent of plasma ET-1 concentrations (13, 31) and is well-correlated with renal ET-1 production (4, 38). A few small studies showed a rise in plasma (20) and urine (26) ET-1 in severe CKD, and our group previously demonstrated increases in plasma and urinary ET-1 concentrations in eight subjects with noninflammatory renal disease, across a range of glomerular filtration rates (GFR) (13). However, there are no data on how renal inflammation may alter these profiles and hence on the utility of urinary ET-1 as a potential biomarker of renal inflammation.

Thus, we hypothesized that, as a result of reduced clearance and increased renal production, respectively, plasma and urinary ET-1 concentrations would increase as GFR declined and that in subjects with varying degrees of inflammatory CKD, but normal renal function, urinary ET-1 would act as a surrogate measure of the underlying renal inflammation. Our main groups of interest were thin basement membrane disease (TBM), immunoglobulin A nephropathy (IgAN), and systemic lupus erythematosus (SLE) with nephritis as examples of noninflammatory, mild, and more florid inflammatory renal diseases, respectively.

METHODS

This was a prospective, cross-sectional study approved by the Multi-centre Research Ethics Committee for Scotland. It was performed between June 2005 and October 2007 in accordance with the Declaration of Helsinki, and with the written informed consent of all participants.

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Subjects. CKD subjects were recruited from the Nephrology outpatient clinic at the Royal Infirmary of Edinburgh. For study 1, the inclusion criteria were male or female CKD patients, 18–65 yr old with a blood pressure (BP) ≤160/100 mmHg. We excluded patients with a renal transplant, those requiring dialysis, and patients with a history of established cardiovascular disease, peripheral vascular disease, diabetes mellitus, respiratory disease, and neurological disease. Additionally, a systemic inflammatory disorder such as SLE or vasculitis was a specific exclusion criterion. Age- and BP-matched non-CKD subjects were recruited from the community.

For study 2, we included male and female subjects aged 18–70, with hematuria and/or proteinuria of presumed glomerular origin. All subjects had a serum creatinine and GFR in the normal range and no history of hypertension. We excluded subjects with any significant comorbidity. Rheumatoid arthritis (RA) subjects (as a control group) had no history of established cardiovascular disease, peripheral vascular disease, diabetes mellitus, respiratory disease, and neurological disease.

Estimation of GFR. GFR was calculated using the Cockcroft and Gault equation as an estimate of creatinine clearance: GFR = [(140 – age (yr)) × weight (kg) / (72 × serum creatinine) (6)]. GFR was further corrected by body surface area (BSA): BSA = [71.84 × weight (kg)0.425 × height (cm)0.725] / 10,000 as defined by Du Bois and Du Bois (11).

Plasma and urine ET-1 assessment. For plasma ET-1, 10 ml of venous blood were collected into an EDTA tube and centrifuged immediately at 2,500 g for 20 min at 4°C. For urine ET-1, a 20-ml aliquot of urine was collected into plain tubes with 2.5 ml of 50% acetic acid. Samples were stored at −80°C until analysis. After extraction (29), ET-1 was determined by radioimmunoassay (7). The mean recovery of ET-1, from extraction to assay, was >90% for both plasma and urine. The intra- and interassay variations were 6.3 and 7.2%, respectively. The cross-reactivity of the antibody was 100% with ET-1, 7% for both ET-2 and ET-3, and 10% with big ET-1.

Study protocol. Subjects refrained from alcohol for at least 24 h and caffeinated drinks, food, and smoking for at least 12 h before the study. All studies were conducted in a quiet, temperature-controlled room. Following a brief medical inquiry to confirm suitability for the study, body weight and height of the participants were recorded. After 30 min of supine rest, BP and heart rate were recorded, with an appropriate sized cuff, using a validated oscillometric sphygmomanometer, the Omron HEM-705CP (25). Following this, blood was taken for analysis and urine was collected and tested for presence of blood and/or protein.

Data and statistical analysis. Data were stored and analyzed in Microsoft Excel (version 11.3.7, Microsoft). Fractional excretion of ET-1 (FeET-1) was calculated by [(urine ET-1/plasma ET-1) × plasma creatinine/urine creatinine] × 100/%, the D’Agostino and Pearson omnibus test was used to evaluate the distribution characteristic of the data. Means were compared by one-way ANOVA, Kruskal-Wallis test, unpaired Student’s t-test, and Mann-Whitney U-test where appropriate. Correlation coefficients were calculated using the Pearson method. To measure the sensitivity and specificity for FeET-1 at different values, a conventional receiver-operator curve (ROC) curve was generated using subjects with IgAN and microhematuria as controls. The area under curve was calculated to ascertain the quality of FeET-1 as a biomarker. An area of 0.5 is no better than expected by chance, whereas a value of 1.0 signifies a perfect biomarker. A significant level was P value ≤ 0.05. Descriptive data are given as means ± SD.

RESULTS

Study 1. One hundred forty two subjects were enrolled into this study (115 CKD and 27 matched non-CKD subjects). CKD diagnoses were autosomal dominant polycystic kidney disease (n = 26), IgAN (n = 24), reflux nephropathy (n = 11), chronic glomerulonephritis (n = 10), noninflammatory glomerular disease (n = 8), obstructive nephropathy (n = 5), TBM (n = 2), cistinuria (n = 2), Alport disease (n = 1), and medullary cystic kidney disease (n = 1). Twenty-five CKD subjects had no known cause for their renal disease. GFR ranged from 8 to 154 ml·min⁻¹·1.73 m²⁻¹. Baseline characteristics of all study subjects are shown in Table 1.

Table 1. Demographic data for non-CKD and CKD subjects in study 1

<table>
<thead>
<tr>
<th></th>
<th>Non-CKD Subjects (n = 27)</th>
<th>CKD Subjects (n = 115)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>48±9 (32–64)</td>
<td>47±10 (23–65)</td>
<td>ns</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>13/14</td>
<td>77/38</td>
<td>—</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26±5 (18–46)</td>
<td>28±5 (19–41)</td>
<td>ns</td>
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<tr>
<td>SBP, mmHg</td>
<td>110±17 (83–152)</td>
<td>119±15 (85–159)</td>
<td>ns</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>70±10 (54–90)</td>
<td>74±9 (52–96)</td>
<td>ns</td>
</tr>
<tr>
<td>Creatinine*, mg/dl</td>
<td>0.88±0.15 (0.62–1.11)</td>
<td>2.20±1.86 (0.62–9.33)</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>eGFR, ml·min⁻¹·1.73 m²⁻¹</td>
<td>94±18 (68–131)</td>
<td>63±35 (8–154)</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Cholesterol*, mg/dl</td>
<td>193±31 (131–255)</td>
<td>178±35 (116–317)</td>
<td>P &lt; 0.005</td>
</tr>
<tr>
<td>CRP, mg/l</td>
<td>2±3 (0–12)</td>
<td>4±4 (0–15)</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Plasma ET-1, pg/ml</td>
<td>4.6±1.0 (2.8–7.5)</td>
<td>5.5±1.1 (3.4–9.8)</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>FeET-1, %</td>
<td>1.1±0.7 (0–3.0)</td>
<td>3.0±3.1 (0.2–14.7)</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>ACR, mg/mmol</td>
<td>0.5±0.8 (0–3.3)</td>
<td>48.6±(0–428)</td>
<td>P &lt; 0.001</td>
</tr>
</tbody>
</table>

Values are means ± SD (range). BMI, body mass index; FeET-1, fractional excretion of ET-1; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; ACR, albumin:creatinine ratio; ns, not significant. *To convert to μmol/l, multiply by 88.4. †To convert to mmol/l, multiply by 0.0259.
lupus nephritis on renal biopsy, two type V, and four both types IV and V (37). These subjects were studied before, and 6 mo after, the start of treatment. This comprised of oral prednisolone for all 10 subjects, with 6 additionally receiving mycophenolate mofetil as a steroid-sparing agent, and the remaining 4 subjects receiving cyclophosphamide. All subjects had normal renal function with GFR ranging from 61 to 153 ml·min⁻¹·1.73 m⁻². A cohort of subjects with RA was included as a control group for those with lupus nephritis as having a similar degree of systemic inflammation, as measured by serum CRP, but no evidence of renal disease as shown by a clear urinalysis and GFR >60 ml·min⁻¹·1.73 m⁻². Subject characteristics are shown in Table 3.

All groups of subjects had similar plasma ET-1 concentrations (Fig. 2A; HV: 5.3 ± 1.8, TBM: 4.4 ± 0.8, IgAN: 5.1 ± 0.7, SLE: 4.7 ± 0.9, RA: 4.6 ± 0.9 pg/ml). However, both FeET-1 and urinary ET-1:creatinine ratio were significantly higher in lupus nephritis subjects compared with HV and all other renal groups (Fig. 2, C and D; SLE:FeET-1 7.7 ± 2.7%, urinary ET-1:creatinine ratio 10.0 ± 3.0 pg/μmol, P < 0.05 vs. TBM and P < 0.001 vs. HV, IgAN, and MH, for both). Both FeET-1 and urinary ET-1:creatinine ratio were similar between HV, TBM, IgAN, and MH.

CRP concentrations followed a similar pattern (Fig. 2B; SLE: 63 ± 15 mg/l, P < 0.001 vs. HV and other renal subjects). Despite similar CRP concentrations to subjects with RA (Fig. 2B; RA: 61 ± 16 mg/l), subjects with lupus nephritis had a significantly higher FeET-1 and urinary ET-1:creatinine ratio (Fig. 2, C and D; SLE: RA: FeET-1 7.7 ± 2.7 vs. 3.7 ± 2.1%, urinary ET-1:creatinine ratio 10.0 ± 3.0 vs. 2.1 ± 1.3 pg/μmol, P < 0.01 for both). RA subjects also had higher urinary ET-1:creatinine ratio (P < 0.05) and FeET-1 (P < 0.01) than HV and subjects with MH and IgAN. There was no relationship between degree of proteinuria and FeET-1, urinary ET-1:creatinine ratio, or CRP.

For FeET-1, the area under the ROC was 1.0 (curve not shown). Table 4 lists the derived sensitivities and specificities at different cutoff values for FeET-1. A value above 2.7% in renal patients yielded good sensitivity and specificity for the detection of SLE.

For subjects with SLE and nephritis, FeET-1 fell significantly following treatment (Fig. 3; 2.7 ± 2.1% vs. 3.6 ± 1.4%, P < 0.01). Effects of treatment on other disease markers are shown in Table 5.

**DISCUSSION**

Consistent with our previous findings in a limited number of subjects (8 CKD and 8 healthy controls) (13), we now demonstrated in a large cohort of subjects that plasma ET-1 increases linearly as GFR declines, whereas FeET-1 shows an exponential rise. We also showed for the first time that urinary ET-1 concentrations are raised in patients with systemic inflammatory disease and active renal involvement (but not systemic inflammatory disease without renal involvement), even when GFR is normal, whereas there is little impact of inflammation on plasma ET-1. Finally, urinary ET-1 concentrations fall following successful disease treatment. Thus, urinary ET-1 may be a useful marker of renal inflammation in the early stages of inflammatory renal disease, before renal function is affected, and may help direct treatment in these conditions.

Previous studies showed increased plasma ET-1 concentrations in predialysis (8, 20) and dialysis-requiring (9, 20) CKD patients. Our results are in keeping with these studies. However, we also demonstrated that plasma ET-1 increases linearly as renal function declines, across a wide range of GFRs and in a relatively homogeneous, noninflammatory CKD population. This is likely to be largely due to reduced renal filtration of ET-1 and thus renal clearance from the circulation. Impor-
tantly, we also showed an exponential rise in FeET-1 as GFR declines. It is well established that a number of renal cell types are able to synthesize ET-1 (10, 19, 33) and that ET-1 is an important regulator of renal function in CKD (10, 14). It has been shown in animal models that plasma ET-1 does not account for urinary ET-1 (4) and that renal cortical interstitial ET-1 levels correlate with urinary ET-1 excretion (38). These data support the view that urinary ET-1 concentrations reflect renal ET-1 production in CKD. Our finding of an exponential increase in FeET-1 as GFR declines is consistent with this evidence. Our results also show a positive correlation between BP and FeET-1 and increasing BP, as GFR falls, may well be one of the stimuli for renal ET-1 production. Furthermore, men had a higher FeET-1 than women suggesting that gender may influence renal ET-1 production and so explain the gender bias of some renal diseases, ET-1 is proinflammatory and its up-regulation in CKD may contribute to disease progression (10). Thus, antagonizing the effects of ET-1 may offer therapeutic benefits in patients with CKD, and this is supported by pre-clinical and clinical data (1, 5, 14).

The results of our study suggest that urinary ET-1 is a useful marker of active renal inflammation in patients with lupus nephritis and normal renal function. Urinary ET-1 levels in subjects with TBM disease, a noninflammatory condition, and in those with IgAN nephropathy, associated with mild renal inflammation, were no different to those in HV. These findings are consistent with renal ET-1 production being driven by more florid inflammatory renal disease as is seen in lupus nephritis. In this study, we used spot urine samples, as are collected routinely in the clinic, rather than timed urine collections making the data more widely clinically applicable. Although a urinary biomarker of disease activity would be ideal, being noninvasive and readily available, our results show an overlap in urinary ET:creatinine ratios between different renal groups. However, our sample size is small and it will be important to see whether the same holds true in a larger cohort of subjects. Interestingly, the lack of overlap between FeET-1 levels in subjects with active lupus nephritis and levels in HV and those with other renal diagnoses does support its use as a discriminatory test in the clinical management of lupus nephritis.

Table 3. Demographic data for study 2 subjects

<table>
<thead>
<tr>
<th></th>
<th>HV (n = 29)</th>
<th>TBM (n = 8)</th>
<th>IgAN (n = 22)</th>
<th>MH (n = 35)</th>
<th>SLE (n = 10)</th>
<th>RA (n = 10)</th>
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<tr>
<td>Age, yr</td>
<td>46±10 (32–64)</td>
<td>42±11 (26–60)</td>
<td>41±11 (24–59)</td>
<td>45±13 (22–64)</td>
<td>40±14 (26–60)</td>
<td>44±8 (29–56)</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>12/17</td>
<td>3/5</td>
<td>17/5</td>
<td>14/21</td>
<td>4/6</td>
<td>3/2</td>
</tr>
<tr>
<td>SBP mmHg</td>
<td>119±9 (84–152)</td>
<td>115±10 (101–124)</td>
<td>117±9 (106–132)</td>
<td>121±14 (8–156)</td>
<td>124±17 (96–151)</td>
<td>131±13 (109–149)</td>
</tr>
<tr>
<td>DBP mmHg</td>
<td>73±10 (59–93)</td>
<td>76±5 (67–81)</td>
<td>74±8 (62–96)</td>
<td>78±11 (57–111)</td>
<td>77±11 (63–87)</td>
<td>76±8 (63–87)</td>
</tr>
<tr>
<td>Creatinine* mg/dl</td>
<td>0.87±0.14 (0.62–1.05)</td>
<td>0.83±0.11 (0.68–0.98)</td>
<td>1.04±0.26 (0.55–1.30)</td>
<td>0.92±0.18 (0.55–1.33)</td>
<td>0.94±0.24 (0.67–1.43)</td>
<td>0.92±0.10 (0.81–1.14)</td>
</tr>
<tr>
<td>eGFR ml·min⁻¹·1.73 m⁻²</td>
<td>94±16 (62–130)</td>
<td>102±13 (74–115)</td>
<td>97±26 (61–153)</td>
<td>97±25 (68–130)</td>
<td>97±27 (61–142)</td>
<td>89±19 (61–132)</td>
</tr>
<tr>
<td>Cholesterol* mg/dl</td>
<td>193±35 (147–282)</td>
<td>205±42 (127–228)</td>
<td>178±27 (139–228)</td>
<td>201±42 (124–340)</td>
<td>189±31 (143–236)</td>
<td>193±19 (166–232)</td>
</tr>
<tr>
<td>CRP mg/l</td>
<td>1±2 (0–10)</td>
<td>1±2 (0–6)</td>
<td>2±2 (0–10)</td>
<td>3±4 (0–14)</td>
<td>6±3 (15–45)</td>
<td>61±6 (18–91)</td>
</tr>
<tr>
<td>ACR mg/mmol</td>
<td>0.6±1.0 (0–3.6)</td>
<td>1.6±2.3 (0–6.6)</td>
<td>26.9±46.0 (0–173.5)</td>
<td>2.3±3.5 (0–15.2)</td>
<td>27.8±27.0 (4.3–89.3)</td>
<td>1.1±0.8 (0–2.6)</td>
</tr>
</tbody>
</table>

Values are means ± SD (range). HV, healthy volunteers; TBM, subjects with thin basement membrane disease; IgAN, immunoglobulin A nephropathy; MH, microhematuria of presumed glomerular origin; SLE, systemic lupus erythematosus with nephritis; RA, rheumatoid arthritis. For CRP, P < 0.001 for SLE vs. all renal groups. For ACR, P < 0.05 for TBM vs. SLE, P < 0.01 for HV vs. IgAN and for MH vs. SLE, P < 0.001 for HV vs. SLE, and P < 0.05 for RA vs. SLE. *To convert to μmol/l, multiply by 88.4. †To convert to mmol/l, multiply by 0.0259.

Fig. 2. Plasma ET-1 (pg/ml; A), serum C-reactive protein (CRP; mg/l; B), FeET-1 (%; C), and urinary ET-1:creatinine ratio (pg/μmol; D) in healthy volunteers (HV) and subjects with thin basement membrane disease (TBM), immunoglobulin A nephropathy (IgAN), microhematuria of presumed glomerular origin (MH), systemic lupus erythematosus with nephritis (SLE), and rheumatoid arthritis (RA). A-D: horizontal black bars show mean value. B: ***P < 0.001 for SLE vs. all groups except RA, for which P = not significant (ns). C and D: *P < 0.05 for SLE vs. TBM. ***P < 0.001 for SLE vs. all other groups. †P < 0.01 for SLE vs. RA.
Consistent with this is the area under the ROC of 1.0. Although calculation of FeET-1 requires both a blood and urine sample, it should still be feasible in most renal clinics. This would be of particular help in the assessment of renal disease activity because involvement of different organs in SLE is variable. Thus, in the group of patients who present to the renal clinic with an active urinary sediment but in the presence of normal renal function, an elevated urinary ET-1 level may help identify those who have more active inflammatory renal disease, such as lupus nephritis. It is important to note that we used the Cockcroft and Gault equation as our estimate of GFR. Although imperfect as this will not detect more subtle loss of renal function, in particular renal reserve, its use is preferable in the clinic setting where renal clearance studies are impractical.

FeET-1 and CRP were both significantly elevated in subjects with lupus nephritis compared with HV and subjects with other renal diagnoses. Thus, one may argue that it is the systemic inflammation in lupus nephritis that is driving the increase in renal ET-1 production. However, when we compared urinary ET-1 concentrations in subjects with newly diagnosed and untreated RA, with a similar degree of systemic inflammation as reflected by a similar CRP, but with no evidence of renal involvement, FeET-1 was significantly higher in those with lupus nephritis. These data suggest that the increase in urinary ET-1 in lupus nephritis is predominantly in response to the renal inflammation. As the current study had limited numbers, we are unable to comment on the relationship between histological class of lupus nephritis and renal ET-1 production, but this is an area of ongoing study. Interestingly, although subjects with RA had a lower FeET-1 than those with lupus nephritis, they had a greater FeET-1 than HV and those with other renal diagnoses suggesting that systemic inflammation may, in part, contribute to renal ET-1 production. Indeed, previous studies suggest that inflammatory mediators stimulate ET-1 production (34, 42).

The current clinical study was designed to look at a preselected group of patients: those referred to the renal clinic on the basis of an abnormal urinalysis (hematuria ± proteinuria) but in the presence of normal renal function. Our active control group ideally needed to comprise of subjects with a similar degree of systemic inflammation to those with lupus nephritis but with no evidence of renal disease. We chose patients with RA as they commonly present to the rheumatology clinic. They often have evidence of systemic inflammation but it is uncommon for the kidney to be involved (28), especially at the outset of disease. Although one may argue subjects with untreated SLE without nephritis may have been a better choice of control, these patients have variable CRP levels (2, 16) despite other evidence of systemic inflammation (12, 22), and their degree of inflammation is considerably less when not associated with nephritis. Clearly, comparing urinary ET-1:creatinine ratio and FeET-1 in those with SLE in the presence and absence of nephritis would be of some interest and an area of future study.

One problem in the management of lupus nephritis is assessing the response to immunosuppressive treatment as well as the early detection of relapse. A rising serum creatinine may be due to active disease or progressive renal scarring. However, serial renal biopsies are not without risk, making a simpler test desirable. The data from the current study show a significant fall in FeET-1 in subjects with lupus nephritis following successful treatment. At 6 mo, all subjects were in
clinical disease remission as defined by an improvement in symptoms and a fall in CRP. Importantly, all subjects showed a fall in FeET-1. By contrast, some (6 of 10), but not all, showed a resolution of their microscopic hematuria, and/or reduction in proteinuria (7 of 10). Other immunological markers of disease activity (double-strand DNA and complement levels) also showed variable changes. Thus, these data suggest that a fall in urinary ET-1 may be a useful additional marker of response to therapy. Whether monitoring urinary ET-1 levels may be useful in detecting patients who do not respond to therapy remains unclear. As a limitation, we recognize that the heterogeneity in treatment given may impact on the data and this should be studied further. Furthermore, none of the 10 patients relapsed within the 6-mo period and it remains speculative whether urinary ET-1 levels would rise before clinical relapse and this should also be the focus of larger studies.

It is important to consider whether renal impairment or significant proteinuria would affect the utility of urinary ET-1 as a biomarker of renal inflammation. The results of study 1 demonstrate that in patients with noninflammatory CKD FeET-1 only begins to increase at a GFR of ~60 ml/min. All of the subjects with lupus nephritis in study 2 had better renal function than this. It would be of great interest to see whether FeET-1 levels were higher in subjects with severe enough inflammatory renal disease to cause deterioration in GFR (<60 ml/min), such as in those with small vessel vasculitis, than in subjects with similar GFRs but noninflammatory CKD, and whether levels remained higher in those without active inflammation. With regard to proteinuria, our data show no relationship between urinary ET-1 concentrations and degree of proteinuria. This is in contrast to others who showed microalbuminuria (35) and nephrotic range proteinuria (36) associated with urinary ET-1 albeit in different cohorts of patients. Certainly, both in vitro (24) and in vivo (3) experiments showed that proteinuria may stimulate renal ET-1 production and this was associated with damage to the podocyte. All our subjects had low-grade proteinuria and whether higher degrees would relate to urinary ET-1 and whether alterations in podocyte function contribute to the development of lupus nephritis remains unclear and should be another area for further study.

Our data add to the existing and expanding literature on urinary biomarkers of inflammatory renal disease, in particular relating to lupus nephritis (41). In a recent study by Pitashny et al. (27), urinary lipocalin-2 levels were found to be higher in subjects with SLE in the presence of nephritis than in its absence. However, there was significant overlap in lipocalin-2 levels between the two groups, the population studied included a majority of Hispanics and African-Americans, and the response to disease treatment was not assessed.

In conclusion, in the current study we found that urinary ET-1 may act as a useful marker of active renal inflammation in lupus nephritis and provide additional clinically relevant information about disease activity to that given by established markers. Further study is needed to investigate whether rising urinary ET-1 concentrations are useful in identifying patients who do not respond to therapy or predicting a relapse, and whether different therapies may have variable effects on urinary ET-1. Furthermore, studying patients with other inflammatory renal diseases such as those with small vessel vasculitis would be of great interest.

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GRANTS

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REFERENCES