Kidney International, Vol. 68 (2005), pp. 1825–1833

Plasma, urine, and renal expression of adiponectin in human systemic lupus erythematosus

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Background. Adiponectin is an adipocyte-derived cytokine that has anti-inflammatory properties. A preliminary proteomic evaluation of urine for biomarkers of systemic lupus erythematosus (SLE) nephritis demonstrated high levels of adiponectin in SLE urine. This prompted investigation of adiponectin expression in human SLE.

Methods. Adiponectin was measured by enzyme-linked immunosorbent assay (ELISA) in the urine and plasma of a clinically well-characterized SLE cohort, with renal and nonrenal SLE being followed in a prospective longitudinal study to identify risk factors for SLE flare. Renal adiponectin expression was assessed by immunohistochemical analysis of kidney biopsies from SLE nephritis patients.

Results. Cross-sectional testing showed that plasma adiponectin levels were higher in patients with renal SLE flare than normal controls or patients with nonrenal SLE flare, after accounting for race and body mass index. Urine adiponectin levels increased significantly with renal flare, but not nonrenal SLE flare. Longitudinal testing revealed that the urine adiponectin increase began in the 2 months prior to renal flare. Urine adiponectin correlated with plasma levels and magnitude of proteinuria, and to a lesser extent serum creatinine. Plasma adiponectin levels were independent of renal function and proteinuria. In kidney biopsies, adiponectin was found on endothelial surfaces in normal and SLE kidneys, and on podocytes and in the tubules of SLE kidneys.

Conclusion. Plasma adiponectin levels are increased in patients with renal SLE compared to healthy controls and patients with nonrenal SLE. During renal but not nonrenal SLE flare, urine adiponectin levels increase significantly. Urine adiponectin may be a biomarker of renal SLE flare.

Key words: adiponectin, SLE, inflammation, proteinuria, glomerulonephritis.

Received for publication March 12, 2005
and in revised form May 1, 2005
Accepted for publication May 23, 2005

To better understand the risk factors for kidney involvement in human systemic lupus erythematosus (SLE), we have been engaged in biomarker discovery in patients enrolled in the Ohio SLE Study (OSS), a prospective longitudinal investigation of risk factors for SLE flare in recurrently active patients with renal or nonrenal SLE. One of the key goals of the study is to identify biomarkers that distinguish renal from nonrenal SLE activity. Such biomarkers could be useful to predict impending renal flare or response to therapy, or identify novel mechanisms of kidney injury that may lead to new therapies. Our approach to biomarker discovery included analysis of urine samples with an immobilized antibody array designed to reveal the presence of cytokines in biologic fluids. Using this approach, we found that one of the most highly expressed urinary proteins was adiponectin. Adiponectin is emerging as an important immunomodulatory adipocyte-derived cytokine (adipokine). The present study examined its expression in the OSS cohort.

Adiponectin is a 30 kD protein that is made almost exclusively by adipose tissue [1], although in culture other cell types such as hepatocytes can be induced to produce it [2]. Adiponectin can bind to collagens [3], and is structurally similar to complement component C1q [4]. It circulates in high (μg/mL) concentrations in plasma, appears to be involved in metabolic disorders such as obesity and diabetes mellitus, and may enhance insulin sensitivity [4–6]. Additionally, adiponectin has anti-inflammatory and vasoprotective properties [4]. For example, adiponectin blocked tumor necrosis factor α (TNFα)-induced adherence of monocytes to endothelial cells by attenuating surface expression of the adhesion molecules vascular cellular adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and E-selectin [7, 8]. Furthermore, adiponectin increased the production of tissue inhibitor of metalloproteinase-1 by human macrophages through an interleukin-10–dependent mechanism [9]. Adiponectin acts directly on endothelial

cells to enhance nitric oxide production and, thus, may function as a vasodilator [10]. Individuals with lower levels of adiponectin showed impaired endothelium-dependent vasodilation [11]. Adiponectin was found in blood vessel walls after experimental endothelial injury [12], and was strongly expressed around infarcted but not normal myocardium [3], supporting a role in vascular and endothelial remodeling.

A small number of studies have examined adiponectin in patients with kidney disease. Plasma levels are significantly increased in end-stage kidney disease [13], and levels declined but did not normalize after successful kidney transplantation [14]. In a small cohort of end-stage kidney disease patients who underwent abdominal subcutaneous fat biopsy, adiponectin gene expression was lower than in normal controls [15]. Interestingly, plasma adiponectin was found to be markedly elevated in patients with nephrotic syndrome, and this was independent of glomerular filtration rate [16]. Finally, patients with overt diabetic nephropathy were observed to have higher plasma and urine levels of adiponectin than healthy individuals or diabetics with microalbuminuria [14].

The anti-inflammatory effects of adiponectin, along with its altered metabolism in patients with kidney disease, and our finding of apparently high urine levels by antibody array in patients with active SLE nephritis, provided the rationale to study adiponectin expression in SLE.

METHODS

Patients

The subjects of this investigation were enrolled in the OSS, a prospective, longitudinal study of active patients with 4 or more American College of Rheumatology criteria for SLE, and have been described previously [17]. Each patient was evaluated clinically and with laboratory tests every 2 months, and provided plasma and a freshly voided urine specimen at each visit. The fresh urine samples were centrifuged to remove sediment and supernatants frozen in small aliquots without further manipulation at −80°C for later analysis. Plasma samples were also stored in aliquots at −80°C.

Adiponectin was measured in plasma and urine from patients at renal flare. When available, additional urine specimens collected 4 and 2 months before the renal flare, and 2 and 4 months after the renal flare were analyzed from the same patients. For comparison, adiponectin was also measured in the plasma and urine of healthy volunteers, patients with nonrenal flare, and SLE patients with physician-defined stable renal and nonrenal disease activity (disease controls). For disease controls, urine was obtained from patients who did not have a flare during the observation period and patients who flared more than 4 months before or after the specimen was collected. Maintenance immunosuppression for disease controls was similar to the flare group.

Adjudication and classification of SLE activity status

After all clinical results were compiled from each 2-month study visit, the patient's study physician determined whether an SLE flare occurred, whether it was renal, nonrenal, or both, and whether the flare was mild, moderate, or severe. Confirmation of the flare was required by independent review of the data by another study physician. Identification of flares and determination of flare severity was based on prespecified criteria [18–20], as reported previously [17]. Briefly, a mild renal relapse was defined as an increase in glomerular hematuria from <5 to >15 RBC/hpf on urinalysis, with at least 2 acanthocytes/hpf, or recurrence of 1 or more red blood cell casts or leukocyte casts (in the absence of infection) or both. A moderate renal relapse was defined as an increase in serum creatinine and/or proteinuria that was attributable to SLE as follows: if baseline serum creatinine was <2 mg/dL, an increase of 0.2 to 1.0 mg/dL; if baseline creatinine was ≥2, an increase in serum creatinine of 0.4 to 1.5 mg/dL. Daily urine protein excretion rate was estimated by measuring the ratio of protein to creatinine (Pr/Cr ratio) in a 24-hour urine collection [21]. The proteinuria criteria for moderate relapse were an increase from a baseline Pr/Cr ratio <0.5 to ≥1; an increase from a baseline Pr/Cr ratio of 0.5 to 1.0 to ≥2; a doubling of Pr/Cr ratio from a baseline >1.0, with the absolute ratio <5.0. A severe renal relapse was defined as an increase in serum creatinine >1.0 mg/dL if baseline creatinine was <2.0 mg/dL, or an increase in serum creatinine >1.5 mg/dL if baseline creatinine was ≥2.0 mg/dL, and/or an absolute increase in urine Pr/Cr ratio >5.

A nonrenal flare was declared if the patient developed symptoms or signs of nonrenal SLE and they were of sufficient severity that the managing study physician increased therapy. The severity of nonrenal relapse was based on the British Isle Lupus Assessment Group (BILAG) severity categories [20]. A mild nonrenal relapse was defined as 1 or more of the following attributable to SLE: typical rash, symmetric mild to moderate arthralgias, fever, thrombocytopenia 50,000 to 100,000/mm^3, significant fatigue, oral ulcers, and mild-moderate hair loss. A moderate nonrenal relapse was defined as 1 or more of the following: serositis, hemoglobin 9 to 11, thrombocytopenia 25,000 to 50,000/mm^3, neutrophil count ≤1500/mm^3, severe migraine headache, seizures in the absence of neurologic deficit, uveitis, retinal cytoid bodies, severe alopecia, or extensive mucosal ulceration. A severe nonrenal relapse was defined as 1 or more of the following: pulmonary hemorrhage, vasculitis involving abdominal viscera or brain, severe myositis, thrombocytopenia <25,000/mm^3, hemolytic anemia with

hemoglobin <9, severe rash involving >2/9th body surface area, aseptic meningitis, transverse myelitis, cerebritis, myocarditis, or pericarditis with tamponade.

Immobilized antibody array

Human cytokine antibody array VII was purchased from RayBiotech (Norcross, GA, USA). Urine samples (1 mL) were added directly to individual arrays and incubated at room temperature for 2 hours. The arrays were washed and developed using chemiluminescence per manufacturer's directions.

Adiponectin measurement

Plasma and urine adiponectin were measured by specific enzyme-linked immunosorbent assay (ELISA) according to manufacturer's directions (R&D Systems, Minneapolis, MN, USA). The lower range of the assay was 3.9 ng/mL of adiponectin. Urine and plasma values below this were considered undetectable and assigned a value of zero. Urine adiponectin levels were standardized to urine creatinine measured in the same spot urine and expressed as ng/mg creatinine (ng/mg Cr).

Immunoblotting

Proteins from 15 μL of human urine were directly separated by polyacrylamide gel electrophoresis under reducing conditions and immunoblotted for adiponectin. The primary antibody was goat antihuman adiponectin (AF1065; R&D Systems) used at a concentration of 0.2 μg/mL. To ensure specificity, nonimmune goat IgG was used in place of the primary antibody for some blots (not shown). Furthermore, in other experiments 2 μg/mL recombinant human adiponectin (R&D Systems) was added to the incubation as a competitor. Blots were developed using a horseradish peroxidase conjugated-rabbit anti-goat secondary antibody (Zymed, South San Francisco, CA, USA) and an enhanced chemiluminescence system (Amersham, Arlington Heights, IL, USA).

Immunohistochemistry

Paraffin embedded renal biopsies from normal kidneys (renal allograft donors), class IV and class V SLE nephritis patients, or patients with idiopathic membranous glomerulopathy were cut at 2 microns, deparaffinized, and subjected to antigen retrieval by heating the slides to 94°C in a citric acid solution (pH 6.1) for 25 minutes. Endogenous peroxidase and biotin were quenched and slides were immunostained using a Dako Autostainer System (Dako, Carpinteria, CA, USA). The primary antibody was goat antihuman adiponectin (R&D Systems), followed by rabbit antigoat IgG (Vector Laboratories, Burlingame, CA, USA). The reaction was visualized by the Vectastain Elite detection system (Vector Laboratories) using diamino benzidine as the chromogen. Slides were counterstained with hematoxylin I (Richard-Allen Scientific, Kalamazoo, MI, USA). Specificity of staining was verified by replacing the primary antibody with a nonimmune goat primary antibody (not shown, R&D Systems, #AB-108-C).

Statistics

Data are shown as mean ± SEM. Comparisons between two groups were done by Student t test. Multiple comparisons were done using multiple regression, repeated measures analysis of variance (ANOVA), or Kruskal-Wallace ANOVA as appropriate. Logarithmic transformation was used when necessary and diagnostics were carried out for model validation. Specific groups were compared with post-hoc Tukey HSD or Dunn's multiple comparisons test. Associations were tested by simple and multiple linear regression. $P < 0.05$ was considered significant. The statistics program used was SAS JMP version 5 (Cary, NC, USA).

RESULTS

In preliminary experiments, urine samples from patients with renal SLE were screened using an immobilized antibody array for human cytokines. Adiponectin was consistently found to be present in these urines, and although this assay is not quantitative, the intensity of the adiponectin spots generally appeared higher in urine from patients than healthy individuals (Fig. 1A). To verify the presence of adiponectin in urine from patients with SLE, urine samples were directly immunoblotted with an antibody to human adiponectin (Fig. 1B). This demonstrated a band around 30 kD, the expected molecular mass of monomeric adiponectin [22]. This band was attenuated in the presence of excess human recombinant adiponectin, suggesting specificity for adiponectin (Fig. 1B). Finally, samples of normal kidney tissue ($N = 3$), class IV SLE nephritis ($N = 3$), and class V SLE nephritis ($N = 4$) were immunostained for adiponectin. Adiponectin was found on the endothelium and smooth muscle cells of intrarenal arteries/arterioles, and the endothelium of glomerular and peritubular capillaries in normal kidneys (Fig. 2). In idiopathic membranous nephropathy, adiponectin staining was comparable to normal kidneys, except for more adiponectin-positive resorption droplets in proximal tubular epithelial cells (not shown). SLE renal tissue also showed a similar staining pattern as normal tissue, except in areas of glomerular hypercellularity or sclerosis and interstitial inflammation. In these areas endothelial staining was markedly decreased or absent (Fig. 2). Additionally, podocytes were focally stained in SLE kidneys (class IV > class V),

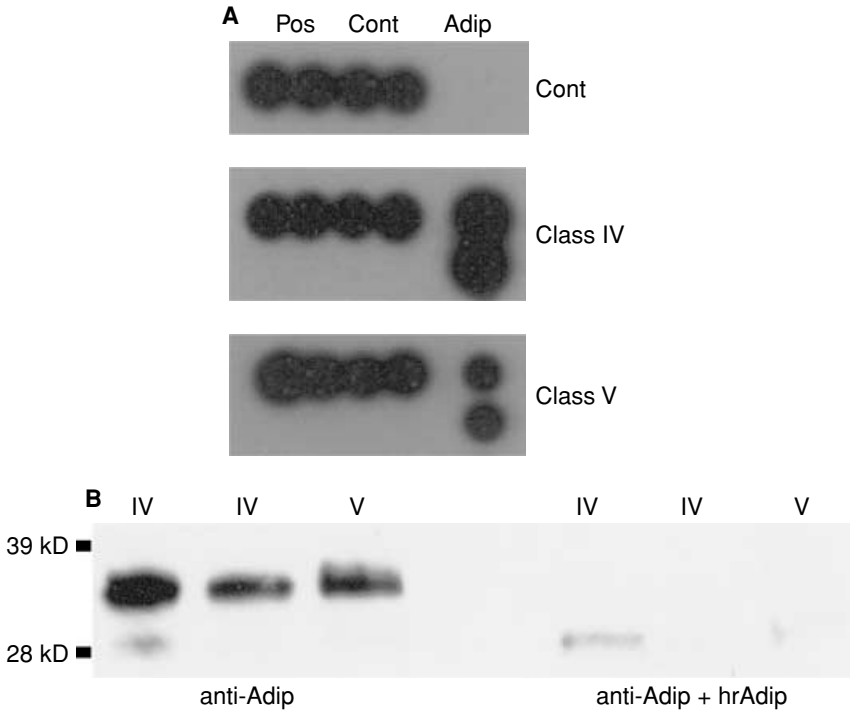

Fig. 1. Identification of adiponectin in urine. (*A*) Urine from a healthy individual (Cont), a patient with active class IV SLE nephritis, and a patient with active class V SLE nephritis were incubated on immobilized antibody arrays. The developed arrays demonstrated the presence of adiponectin (Adip) in the urine from SLE patients. The blots contained a series of control wells (Pos Cont) to normalize spot intensity between individual arrays. (*B*) Urine proteins from three SLE patients with nephritis (class IV or V as indicated) were separated by electrophoresis and immunoblotted for adiponectin in the presence or absence of human recombinant adiponectin (hrAdip). A specific band was detected around 30 kD.

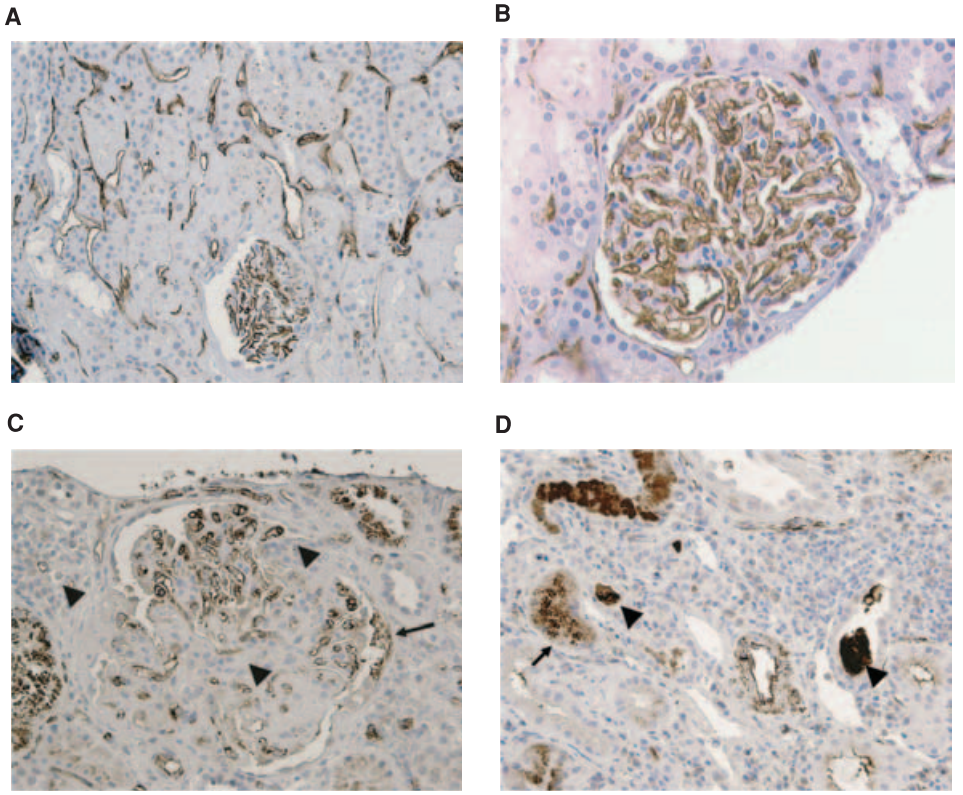

Fig. 2. Adiponectin in human kidneys. Immunohistochemical staining of human kidney tissue for adiponectin was performed as described in **Methods** and representative sections are shown. (*A*) Normal kidney demonstrates extensive endothelial staining in the glomerular and peritubular capillaries. (*B*) A normal glomerulus at higher magnification. (*C*) An SLE class IV kidney shows similar glomerular and interstitial endothelial staining except in areas of proliferation or leukocyte infiltration (arrowheads). Adiponectin was also present in podocytes (arrow). (*D*) An SLE class IV kidney demonstrates adiponectin in tubular epithelial cells (arrow), and tubular casts (arrowhead).

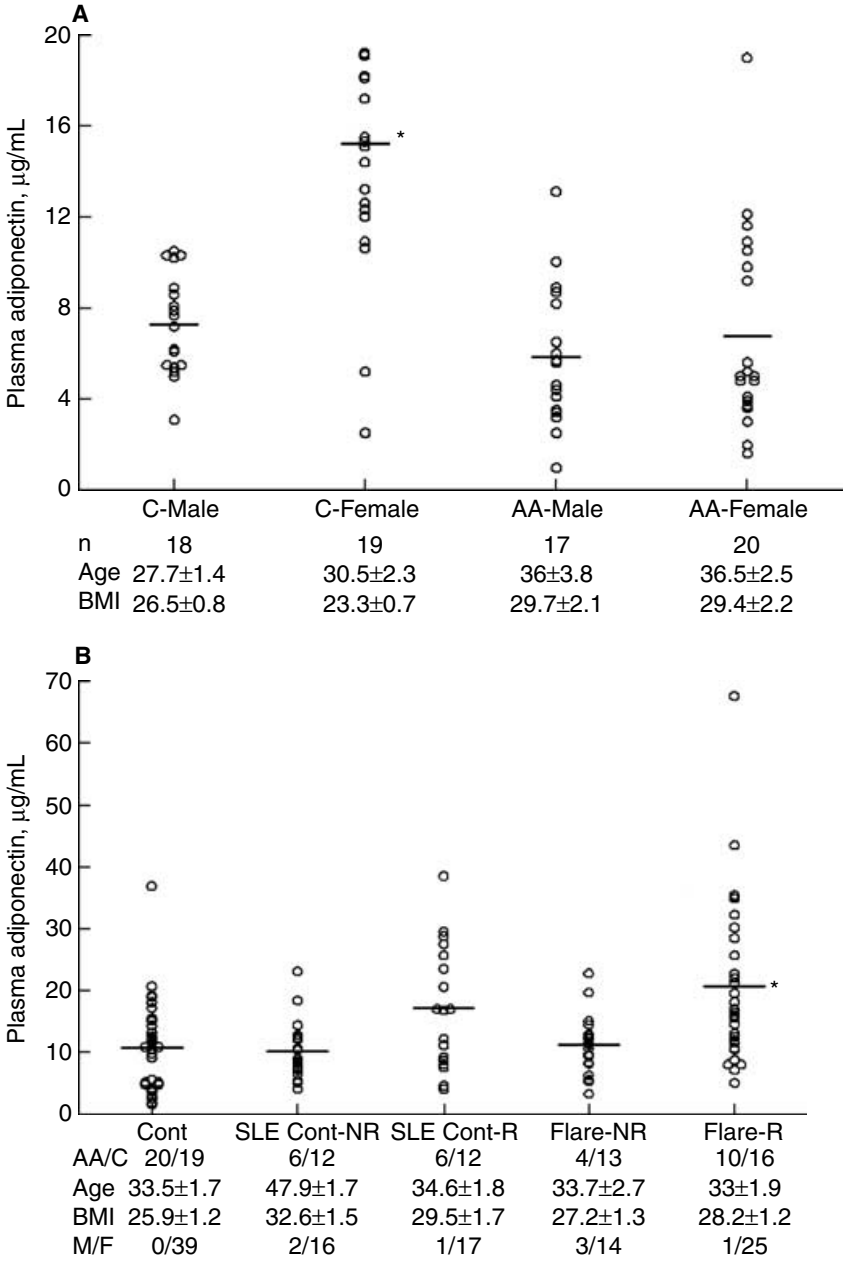

Fig. 3. Cohort demographics and plasma adiponectin levels in healthy individuals and patients with SLE. (*A*) Adiponectin was measured in the plasma of Caucasian (C) and African American (AA) men and women. Each symbol represents a single individual and the bars indicate mean values. The number of subjects in each group, average age, and BMI are indicated. $^*P < 0.05$ vs. Caucasian and African American males. (*B*) Plasma adiponectin was measured in SLE patients at renal (R) or nonrenal (NR) flare, and compared to healthy individuals (Cont), and renal (Cont-R) and nonrenal (Cont-NR) disease controls. For each group the mean age, BMI, number of African Americans and Caucasians (AA/C), and the number of males and females (M/F) is indicated. $^*P < 0.05$ vs. normal controls and patients at nonrenal flare.

and adiponectin was found in tubular casts and tubular epithelial cell protein droplets (Fig. 2).

Further investigation of the association of adiponectin with human SLE was undertaken by measuring plasma and urine adiponectin in control and patient cohorts. Figure 3 shows the demographics of the study groups in this report. Plasma adiponectin levels in healthy individuals are demonstrated in Figure 3A. After accounting for body mass index (BMI), a known determinant of adiponectin [4], race and gender were found to have significant effects on plasma levels ($P < 0.003$ for race and gender each, using a multiple regression model). Caucasian females had the highest levels of plasma adiponectin and were significantly different than Caucasian and African American males. There was no statistical difference between Caucasian and African American females.

Plasma adiponectin levels and demographics for the SLE cohort are shown in Figure 3B. Patients with renal SLE flare had a significantly higher mean plasma adiponectin level than healthy controls and patients with nonrenal SLE, but not renal disease controls. These comparisons take into account BMI and race; because there were so few males in the patient cohort they were not analyzed separately, and the control group was composed of healthy African American and Caucasian

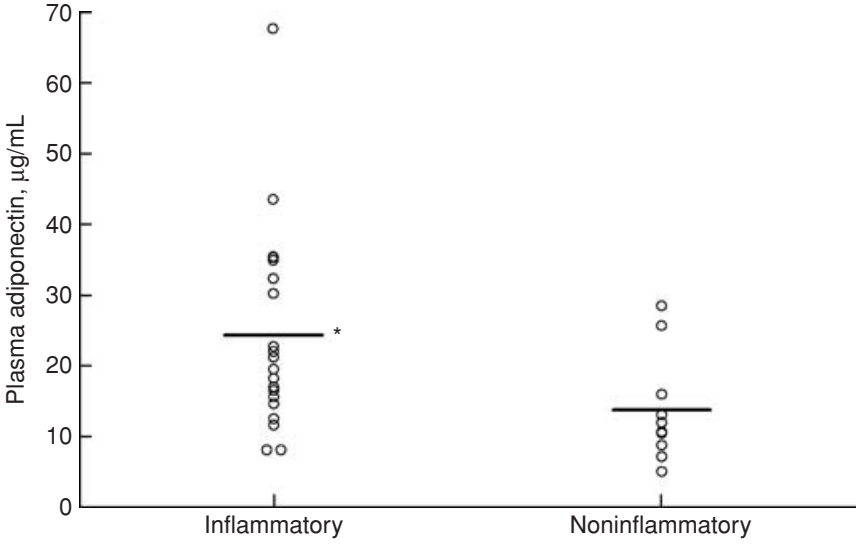

Fig. 4. Plasma adiponectin levels in patients with inflammatory and non-inflammatory SLE nephritis. Adiponectin was measured in the plasma of patients at renal flare, and the data were segregated on the basis of WHO biopsy classification at the time of diagnosis. $^*P < 0.02$ vs. the noninflammatory group.

females. Interestingly, the mean plasma adiponectin of the renal flare group combined with the renal disease control group (19.5 ± 1.8) was significantly higher than the mean plasma adiponectin from the nonrenal and healthy control groups combined (10.51 ± 0.7, $P < 0.0005$).

Multiple regression analysis found no relationship between plasma adiponectin and serum creatinine or proteinuria at renal flare ($P = 0.94$). The association with putative markers of systemic inflammation was also examined. C-reactive protein (CRP) was negatively correlated with plasma adiponectin at renal flare ($r = -0.52$, $P < 0.005$), whereas erythrocyte sedimentation rate showed no relationship with plasma adiponectin ($P = 0.43$).

Patients were separated into inflammatory (class III, IV) and noninflammatory (class V plus 1 class II patient) SLE nephritis based on their biopsies at initial diagnosis. As shown in Figure 4, at renal flare the mean plasma adiponectin level in the inflammatory group (24.3 ± 3.2 μg/mL, $N = 20$) was significantly higher than the mean level in the noninflammatory group (13.8 ± 2.5 μg/mL, $N = 10$, $P < 0.02$). These groups were well matched for BMI (28.3 ± 1.9 vs. 28.4 ± 1.5) and race (40% vs. 50% African American). Although not statistically significant, the urine protein to creatinine ratio tended to be higher in the noninflammatory group (5.5 ± 1.6 vs. 2.7 ± 0.4, $P = 0.12$), while serum creatinine tended to be higher in the inflammatory group (1.49 ± 0.28 vs. 1.01 ± 0.22 mg/dL, $P = 0.09$).

Urine adiponectin was below the limit of detection in all of the healthy controls tested ($N = 28$, 18 females, 23 Caucasians, 5 African Americans). In contrast, adiponectin was present in the urine of patients at renal flare, and the mean value was significantly greater than that of patients with nonrenal SLE flare, and renal and nonrenal disease controls (Fig. 5). Race and BMI did not affect urine adiponectin.

The relationship of urine adiponectin to urine protein, serum creatinine, and plasma adiponectin was determined at renal flare. Individual pairwise correlations demonstrated a significant association between urine adiponectin and: urine protein ($r = 0.45$, $P < 0.04$), serum creatinine ($r = 0.44$, $P < 0.03$), and plasma adiponectin ($r = 0.53$, $P < 0.006$). These 3 variables were used to construct a predictive model for urine adiponectin by multiple regression analysis. Taken together, proteinuria, serum creatinine, and plasma adiponectin were significant predictors of urine adiponectin ($P < 0.002$), and accounted for 56.4% of the variation in urine adiponectin. Plasma adiponectin and serum creatinine were the strongest predictors of urine adiponectin, while proteinuria contributed only 8% to the model. The renal disease control cohort showed no significant correlations between urine and plasma adiponectin, serum creatinine, or proteinuria.

Serial measurements of plasma and urine adiponectin were made in 10 patients over the course of 11 renal flares (Fig. 6). Plasma adiponectin did not change significantly before, during, or after flare, whereas urine adiponectin increased markedly at flare, and declined to preflare levels within 4 months of treatment.

The influence of immunosuppressive therapy on urine and plasma adiponectin was examined. At the time of renal flare most patients had been taking prednisone, mycophenolate mofetil, or both. There was no relationship between urine or plasma adiponectin levels at flare and the cumulative amount of therapy received in the 30 days preceding flare (data not shown).

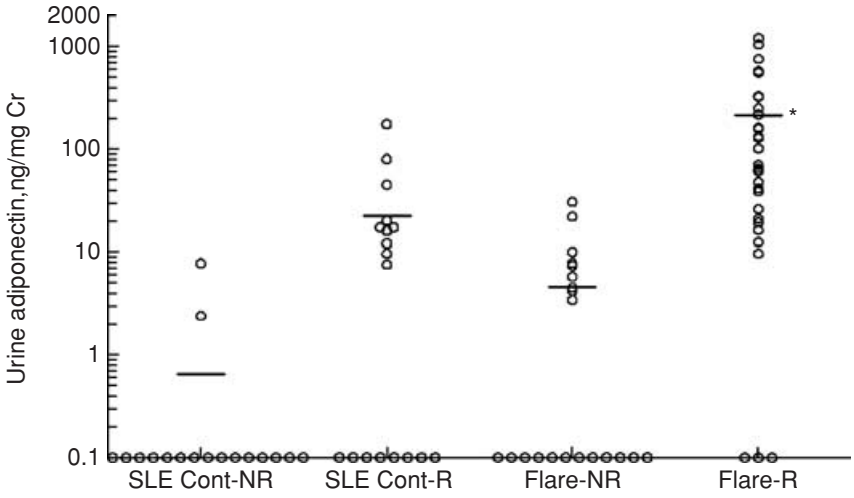

Fig. 5. Urine adiponectin at renal and nonrenal SLE flare. Adiponectin was measured in the urine of patients at renal and nonrenal flare, and in urine from renal and nonrenal disease controls. $^*P < 0.001$ vs. nonrenal flare; $^*P < 0.01$ vs. disease controls.

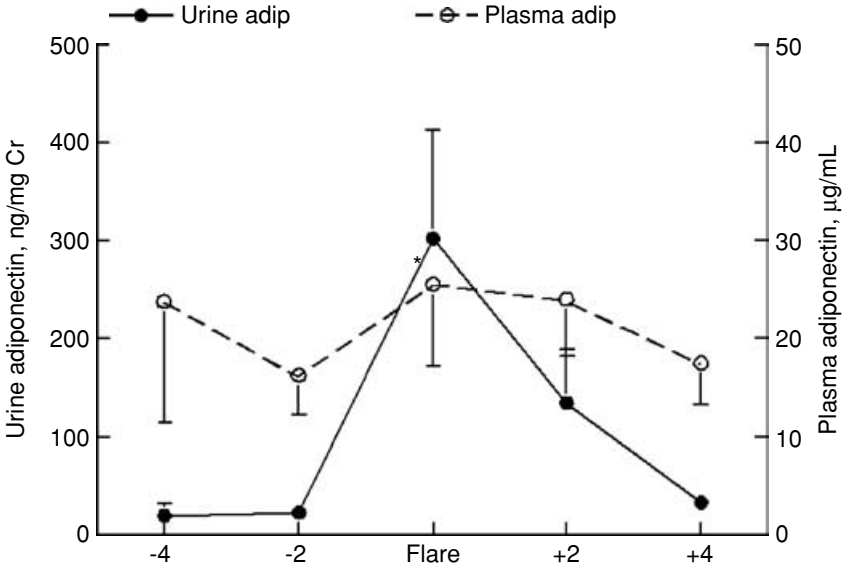

Fig. 6. Time course of plasma and urine adiponectin levels in relation to SLE renal flare. In 11 renal flares plasma and urine adiponectin were measured in specimens obtained 4 and 2 months before flare and 2 and 4 months after flare. Plasma adiponectin levels did not change during the flare cycle. Urine adiponectin at renal flare was significantly greater ($^*P < 0.05$) than either time point before flare, or at 4 months' postflare.

DISCUSSION

This work is the first to characterize the expression of adiponectin in human SLE. While surveying SLE urine for potential disease biomarkers, a highly abundant cytokine was tentatively identified as adiponectin. Immunoblotting verified that adiponectin was present in the urine of those with kidney involvement. Plasma and urine adiponectin were then measured quantitatively. After accounting for BMI, sex, and race, variables known to influence adiponectin levels [4, 23], we found that plasma adiponectin was higher in those with renal SLE compared to healthy controls, nonrenal SLE disease controls, or those with nonrenal SLE flare. Although increased in renal SLE flare, plasma adiponectin did not change significantly before, during, or after treatment of renal SLE flare. In contrast, urine adiponectin increased dramatically within 2 months of renal flare, but not nonrenal flare, and declined to preflare levels by the fourth month postflare. High plasma adiponectin levels and increased urine adiponectin occurred in renal SLE patients despite chronic immunosuppression with corticosteroids and, in many cases, mycophenolate mofetil. Although corticosteroids were shown to block adiponectin secretion by cultured adipocytes [24], this was not observed in vivo [14], and we found no relationship between the amount of immunosuppression given and the level of adiponectin expression. These findings suggest adiponectin expression is not altered in response to generalized systemic SLE activity or its therapy, but may specifically reflect kidney injury during SLE.

The mechanism for the increase in circulating adiponectin in renal SLE is presently unclear. Previous studies have shown high plasma adiponectin in patients with end-stage kidney disease [13, 14]. These data

were interpreted as evidence for renal clearance or catabolism of adiponectin under normal circumstances. However, decreased renal function does not appear to explain high plasma levels in renal SLE because plasma adiponectin did not correlate with serum creatinine in patients with SLE renal flare. Other investigations also did not find a strong independent effect of GFR on circulating adiponectin levels in patients with only mild-moderate renal impairment [25, 26]. Alternatively, proteinuria or its metabolic consequences have been postulated to increase adiponectin expression. Although a positive association between proteinuria and circulating adiponectin was observed in nephrotic patients and proteinuric diabetics [16, 27], there was no correlation between plasma adiponectin and proteinuria at SLE renal flare. Finally, the increase in circulating adiponectin in SLE does not seem to be a response to systemic inflammation because there was no relationship between adiponectin and erythrocyte sedimentation rate, a negative correlation with CRP, and no increase in levels during nonrenal flare. However, renal inflammation may influence plasma adiponectin, as suggested by the finding of higher levels in those with inflammatory nephritis compared to noninflammatory nephritis. This raises the possibility of communication between the kidney and adipose tissue.

The increase in urine adiponectin at renal flare appears to be due, at least in part, to glomerular capillary leak. This interpretation is supported by the correlation of urine adiponectin levels with plasma levels and the magnitude of proteinuria. Additionally, the appearance of adiponectin in podocytes, tubular cells, and tubular casts during active nephritis is consistent with this interpretation. The only other report on urine adiponectin showed that in patients with overt diabetic nephropathy intact urine adiponectin levels also correlated with proteinuria [27].

Presently it is not clear whether increased urinary excretion of adiponectin has a functional effect on the kidney in SLE renal flare, or is simply a biomarker of SLE activity. Interestingly, in vitro studies have described several anti-inflammatory activities of adiponectin [3, 4, 7–9, 28, 29], and mice genetically deficient in adiponectin showed a more severe glomerulonephritis after injection with antiglomerular basement membrane serum than wild-type mice [abstract; Li P et al, *J Am Soc Nephrol* 15:9A, 2004]. It is thus conceivable that adiponectin may modulate renal inflammation in SLE.

The presence of adiponectin lining glomerular capillaries and other endothelial surfaces in the kidney was an unexpected finding. In rodents, larger blood vessels did not stain for adiponectin unless the endothelial layer was disrupted by trauma, after which adiponectin bound to exposed collagens in the intima [12]. Furthermore, in normal human myocardium adiponectin was found in the perivascular interstitium, but was not described in blood vessels [3]. These observations suggest that kidney endothelium may have unique adiponectin binding properties, the function of which remains to be explored. It is also curious that adiponectin staining was absent from inflamed capillaries. It is possible that the inflammatory milieu promotes shedding of adiponectin from endothelial surfaces. It is interesting to speculate that this aggravates the local inflammatory cell influx and may account for the focal nature of tubulointerstitial injury.

CONCLUSION

Urine adiponectin appears to be a fairly sensitive marker of renal SLE flare. It will be important to pursue longitudinal testing of urine adiponectin at more frequent intervals than every 2 months to determine if it increases early enough in the flare cycle to predict impending clinical relapse. In contrast, elevated plasma adiponectin is present in patients who have had renal manifestations of SLE, is not restricted to flare, and appears to be independent of renal function and proteinuria. The significance of high levels of circulating adiponectin in patients with SLE and kidney involvement remains to be determined. Testing is currently underway to see if measuring plasma adiponectin adds to the clinical information of kidney status obtained from the standard renal biomarkers of serum creatinine and proteinuria.

ACKNOWLEDGMENTS

This work was supported in part by USPHS grants DK 55546, DK064085, and MO1 RR 00034, and the Lupus Clinical Trials Consortium.

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