Original Article

Potential of Periostin as a Urinary Biomarker Correlated with Renal Function in Lupus Nephritis and IgA Nephropathy Patients

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Background: Lupus nephritis and IgA nephropathy are the most common causes of secondary and primary of glomerulonephritis. Periostin is a novel biomarker related to kidney disease progression. Previous studies demonstrated the expression of periostin in both animal and human with different types of kidney disease.

Objective: The present cohort study was to examine the level of urine periostin in patients with lupus nephritis and IgA nephropathy and to identify the correlation between urine periostin level and other variables. The urine periostin measurement and response to therapy after six months of treatment was also evaluated.

Materials and Methods: Fifty patients diagnosed with lupus nephritis and IgA nephropathy were included in the present study. Urine sample were collected at the biopsy date. Urine periostin measurement were performed. After six months of treatment, response to therapy was assessed and urine samples were collected.

Results: Urine periostin was detected in 23 patients and 11 healthy controls with significant higher level in patients than in controls (33.27 ng/mg versus 2.38 ng/mg, $p<0.001$). Serum creatinine was significant higher in patients with urine periostin detection (0.9 mg/dl versus 0.7 mg/dl, $p<0.05$). There was also a correlation between urine periostin level and renal function. In addition, urine periostin level was significant lower after six months of treatment in patients with response to therapy (35.70 ng/mg versus 4.35 ng/mg, $p<0.05$).

Conclusion: The present study's results supported the potential of periostin as a urinary biomarker of kidney disease progression in patients with lupus nephritis and IgA nephropathy.

Keywords: Periostin, Urinary biomarker, Lupus nephritis, IgA nephropathy, Renal function

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Lupus nephritis and IgA nephropathy are the most common causes of primary and secondary glomerulonephritis[1]. Even though the pathogenesis of kidney diseases is variable, there is a common pathway of kidney disease progression regardless of the etiology. Tubulointerstitial injury and fibrosis are the final outcomes of chronic glomerulonephritis. These processes involve inflammatory cell activation, key signaling mediators, and extracellular matrix protein accumulation. The process eventually leads to renal dysfunction from glomerulosclerosis and tubulointerstitial fibrosis in kidney tissue and finally end-stage renal failure[2]. In clinical practice, abnormal urinalysis, and impairment of renal function are generally observed by nephrologists before a definite diagnosis with kidney biopsy[3,4]. Serum creatinine, proteinuria, and estimated glomerular filtration rate [eGFR] are the most common measurements for kidney disease progression[5]. However, there are many factors that affect the serum creatinine levels and the insensitivity of serum creatinine as a measurement of GFR has been noted[6,7]. Moreover, it is not a specific marker for kidney damage and cannot be directly related to the pathogenesis of chronic glomerulonephritis[8]. Based on these limitations, the study of novel biomarkers that provide more details

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about the pathogenesis of kidney disease progression and that can be used in routine testing should be investigated.

Periostin is an extracellular matrix protein that was first found to be expressed in bone and involved in bone formation[9]. At present, periostin also appears to play a role in kidney injury. In animal studies, an increase in periostin expression at both the mRNA and protein levels has been found in several types of kidney injury. Periostin mRNA expression has been shown to increase over time, consistent with more diffusion and intensity of periostin staining in kidney tissue[10,11]. Moreover, periostin is also involved in renal inflammation and fibrosis. Genetic deletion of periostin in animal models impairs macrophage infiltration and reduces the fibrotic area in kidney tissues[12]. Supporting these results, co-expression of periostin with markers of epithelial-mesenchymal transition, a process involved in fibrosis, has also been observed in both animal and human studies[10,11]. In addition, there is a significant correlation between periostin expression and renal function[11,13]. In human studies, periostin mRNA expression has been detected in several types of kidney disease. The localization of periostin was also found in both glomerular and interstitial areas[13]. Surprisingly, periostin is not only detected in kidney tissue but also in urine. The median urine periostin level has been found to be significantly higher in proteinuric, non-proteinuric, and chronic allograft nephropathy patients than in controls[10,14]. At present, there have been few studies about the role of periostin as a biomarker in human disease, including lupus nephritis and IgA nephropathy. The objectives of the present study was to examine the urine periostin level in patients with lupus nephritis and IgA nephropathy compared with healthy controls, and to identify the correlation between urine periostin level and other variables. The urine periostin measurement and response to therapy after six months of treatment was also evaluated.

Materials and Methods

Study subjects

The present study was approved by the Institutional Review Boards and Ethics Review Committees of the Royal Thai Army Medical Department, Phramongkutklao Hospital and College of Medicine, Bangkok, Thailand (No. 1168/2556). It was also registered at the ClinicalTrials.gov (Clinical Trial Registration number NCT02493101). The present study was performed between April 2013 and February 2015 at the Department of Medicine, Phramongkutklao Hospital, Bangkok, Thailand. Informed consent was obtained from all patients who participated in the present study. Lupus nephritis or IgA nephropathy patients 18 years or older with at least three glomeruli obtained at biopsy were included in the present study. Patients with urinary tract obstruction, urinary tract infection, kidney transplant, cancer diseases, asthma, advanced heart disease, pregnancy, and lactation were excluded. Demographic data and renal parameters including serum creatinine, blood urea nitrogen, urine protein to creatinine ratio, and eGFR were collected from all patients.

Measurement of urine periostin level

Random urine samples were collected at the day of renal biopsy from 50 patients and 50 controls with normal renal function and stored at -80°C until assayed. The 96-well microplates were coated overnight with 1 µg/mL (0.1 µg/well) of antiperiostin antibody (R&D Systems, Minneapolis, MN). Plates were washed with 0.05% Tween 20 in phosphate buffered saline and then blocked with reagent diluent. A total of 100 µL of all periostin standards and samples were added and incubated for two hours. After one-hour incubation with rabbit polyclonal anti-periostin antibody (Abcam, Cambridge, UK; 1:1,000), a horseradish peroxidase conjugated antibody was added and incubated for 20 minutes. After 20 minutes of incubation with the substrate solution, stop solution was added and the absorbance was measured at 450 nm. A log-transformed standard curve was generated and the urine periostin concentration was calculated. The urine periostin level (ng/mg creatinine) was further calculated by correction with urine creatinine.

Clinical response to therapy after 6 months of treatment

After six months of treatment, patients were classified as patients with response and non-response to therapy. Urine samples were also collected from patients for urine periostin measurement. Patients with complete response or partial response were classified as "patients with response to therapy". Patients with deterioration were classified as "patients with non-response to therapy." Definitions of response to therapy were described as followed (adapted from KDIGO guideline)[15]:

1) *Complete response:* Return of serum creatinine to previous baseline, plus a decline in the urine protein to creatinine ratio to less than 500 mg/g (less than 50 mg/mmol).

2) *Partial response:* Stabilization (±25%), or

improvement of serum creatinine, but not to normal, plus a 50% or greater decrease in urine protein to creatinine ratio. If there was nephrotic-range proteinuria [urine protein to creatinine ratio of 3,000 mg/g or more (300 mg/mmol or more)], improvement requires a 50% or more reduction in urine protein to creatinine ratio, and a urine protein to creatinine ratio of less than 3,000 mg/g (less than 300 mg/mmol).

3) *Deterioration:* A sustained 25% increase in serum creatinine is widely used. Other responses that do not meet the complete or partial response definitions are also included in this type of response.

Statistical analysis

Statistical analysis was performed using SPSS, version 18.0. Experimental data were given as mean ± SD or median with interquartile ranges. The Mann-Whitney rank-sum test was used for comparing two-independent samples. The Wilcoxon signed ranks test was used for comparing two-related samples. Spearman correlation coefficients were used to test correlations. The *p*-values smaller than 0.05 were considered statistically significant.

Results

Patient data

Fifty patients were included in the present study. There were 37 patients and 13 patients diagnosed with lupus nephritis and IgA nephropathy, respectively. Most of the patients were female with average age of 32 years. Systemic lupus erythematosus was the most common comorbid disease found in lupus nephritis patients. Half of IgA nephropathy patients also had hypertension. Renal parameters including serum creatinine, blood urea nitrogen, serum albumin, urine protein to creatinine ratio, and eGFR were also reported. Renal function reduction was observed in patients compared with controls. Overall patient characteristic data is shown in Table 1.

Urine periostin levels in patients and healthy controls

Urine periostin was measured in 50 patients and 50 healthy controls by enzyme-linked immunosorbent assay and corrected for urine creatinine. Urine periostin levels were detected in 23 patients and 11 healthy controls with median values of 33.27 ng/mg and 2.38 ng/mg, respectively. Urine periostin levels in patients were significantly higher than in healthy controls ($p<0.001$). Subgroup analysis in 17 lupus nephritis patients and 6 IgA nephropathy patients with urine periostin detection reported the same, with significant difference compared with controls. The results are shown in Table 2.

Detection of urine periostin in patients with impaired renal function

A subgroup analysis between patients with urine periostin detection and without urine periostin detection was performed. In patients with urine periostin detection, a significant increase in serum creatinine was observed with median values of 0.9 mg/dl. The tendency of lowering eGFR in patients with urine periostin detection was also observed. The data is shown in Table 3.

Urine periostin levels correlated with renal parameters

The authors also assessed the correlation of urine periostin levels and other variables. The results showed a positive correlation between the urine periostin level and serum creatinine ($r = 0.410$, $p = 0.003$) as well as blood urea nitrogen ($r = 0.355$, $p = 0.011$). In contrast, a negative correlation was observed between urine periostin level and eGFR ($r = -0.399$, $p = 0.004$). The results are shown in Table 4.

Clinical response to therapy after 6 months of treatment

After six months of treatment, 16 out of 23 patients with urine periostin detection at baseline could be followed up. Seven patients were classified as patients with response to therapy, and nine patients were classified as patients with non-response to therapy. The results showed urine periostin level was significant lower after six months of treatment in patients with response to therapy with median value of 4.35 ng/mg, compared with 35.70 ng/mg at baseline. The results are shown in Table 5.

Discussion

Periostin, also known as an osteoblast-specific factor 2, was initially found in bone with some expression in the lung, but not in the kidney[9]. Nowadays, this concept has changed. Moreover, both animal and human studies have suggested the role of periostin in kidney injury. In the present study, we evaluated urine periostin level in patients with lupus nephritis and IgA nephropathy. Urine periostin was detected in 23 patients and 11 healthy controls with significant higher level in patients than in controls. The same results have been shown in both animal and human studies. In animal study, urine periostin was undetectable before nephrectomy. However, urine periostin level significantly increased over time after

Table 1. Clinical characteristics data

Characteristics	Healthy controls (n = 50)	Patients (n = 50)	LN (n = 37)	IgAN (n = 13)
Gender, n (%)				
Female	17 (34)	41 (82)	34 (92)	7 (54)
Male	33 (66)	9 (18)	3 (8)	6 (46)
Age (years)	30±10	32±12	30±10	38±14
Body weight (kg), mean ± SD	71±13	57±13	55±13	63±12
Height (cm), mean ± SD	168±8	159±10	157±10	162±9
Body mass index (kg/m^2), mean ± SD	25.0±3.6	22.6±4.5	22.1±4.8	23.9±3.3
Renal diseases, n (%)				
Lupus nephritis	-	37 (74)	37 (100)	-
IgA nephropathy	-	13 (26)	-	13 (100)
ISN/RPS classification, n (%)	-	-		-
I			0 (0)	
II			1 (3)	
III			12 (32)	
IV			12 (32)	
V			1 (3)	
VI			0 (0)	
Mix classification, n (%)	-	-		-
III + V			5 (14)	
IV + V			6 (16)	
Oxford classification, n (%)	-	-	-	
Mesangial hypercellularity				
• M0				8 (62)
• M1				5 (38)
Segmental glomerulosclerosis				
• S0				5 (38)
• S1				8 (62)
Endocapillary hypercellularity				
• E0				2 (15)
• E1				11 (85)
Tubular atrophy/interstitial fibrosis				
• T0				8 (62)
• T1				2 (15)
• T2				3 (23)
Comorbid diseases, n (%)				
Systemic lupus erythematosus	-	32 (64)	32 (86)	0 (0)
Hypertension	-	20 (40)	13 (35)	7 (54)
Dyslipidemia	-	9 (18)	5 (14)	4 (31)
Systolic blood pressure (mmHg), mean ± SD	124±17	135±20	136±21	133±16
Diastolic blood pressure (mmHg), mean ± SD	76±11	83±16	85±16	79±17
Renal parameters, mean ± SD				
Serum creatinine (mg/dl)†	0.8 (0.7, 0.9)	0.8 (0.7, 1.3)	0.8 (0.7, 0.9)	1.5 (0.8, 2.3)
Blood urea nitrogen (mg/dl)†	11.6 (9.1, 12.5)	17.5 (12.8, 25.7)	19.2 (12.8, 25.7)	16.9 (13.1, 24.4)
Serum albumin (g/dl)	-	3.2±0.7	3.1±0.6	3.7±0.7
Urine protein to creatinine ratio†	-	2.19 (0.89, 4.48)	2.58 (0.78, 4.55)	1.37 (1.16, 2.30)
eGFR (ml/minute/1.73 m^2)	119.69±10.14	87.67±36.02	96.42±33.64	62.78±31.55

LN = lupus nephritis; IgAN = IgA nephropathy; eGFR = estimated glomerular filtration rate

† Data was reported as median (Q1, Q3)

kidney injury. Consistently, urine periostin was also significantly higher in patients with proteinuric and non-proteinuric chronic kidney disease and chronic allograft nephropathy than in healthy controls[10,14]. These results demonstrated that urine periostin distinguished healthy controls from kidney disease patients. From the initial results, the urine periostin could not be detected in all patients. The authors further analyzed the variables related to urine periostin detection. Interestingly, the serum creatinine level was significantly higher in patients with urine periostin detection than those without, indicating that patients with worsening renal function were characterized by urine periostin. To support this result, the correlation

Table 2. Urine periostin level in patients and healthy controls with urine periostin detection

Subjects with urine periostin detection	Urine periostin level (ng/mg†), median (Q1, Q3)	*p*-value
Patients (n = 23)	33.27 (9.89, 158.60)	<0.001*
LN patients (n = 17)	33.27 (11.74, 124.44)	<0.001*
IgAN patients (n = 6)	27.23 (9.89, 159.32)	0.005*
Healthy controls (n = 11)	2.38 (1.34, 6.54)	-

LN = lupus nephritis; IgAN = IgA nephropathy

† mg of urine creatinine, * *p*-value <0.05 versus healthy controls

Table 3. Comparison of variables between patients with urine periostin detection and patients without urine periostin detection

Variables	Patients with urine periostin detection (n = 23) Median (Q1, Q3)	Patients without urine periostin detection (n = 27) Median (Q1, Q3)	*p*-value
Age (years)	26 (21, 34)	30 (22, 42)	0.360
Body weight (kg)	60 (49, 70)	51 (46, 63)	0.255
Height (cm)	160 (156, 165)	158 (152, 165)	0.206
Body mass index (kg/m2)	22.2 (19.5, 26.1)	21.1 (19.1, 24.6)	0.271
Systolic blood pressure (mmHg)	133 (124, 155)	128 (115, 150)	0.430
Diastolic blood pressure (mmHg)	81 (77, 97)	82 (71, 91)	0.915
Renal parameters			
Serum creatinine (mg/dl)	0.9 (0.7, 1.8)	0.7 (0.6, 1.0)	0.023*
Blood urea nitrogen (mg/dl)	23.0 (13.8, 37.8)	16.8 (12.3, 23.7)	0.094
Serum albumin (g/dl)	3.1 (2.7, 3.7)	3.4 (2.8, 3.9)	0.306
Urine protein to creatinine ratio	2.56 (1.38, 4.48)	1.61 (0.69, 4.55)	0.271
eGFR (ml/minute/1.73 m^2)	74.79 (41.03, 120.81)	97.18 (70.71, 123.38)	0.059
Pathological findings			
Interstitial fibrosis (%)	10 (0, 20)	10 (0, 15)	0.626
Interstitial fibrosis (score)	1 (0, 1)	1 (0, 1)	0.761
Tubular atrophy (%)	10 (0, 20)	10 (0, 15)	0.626
Tubular atrophy (score)	1 (0, 1)	1 (0, 1)	0.761

eGFR = estimated glomerular filtration rate

* *p*-value <0.05

Table 4. Correlation between urine periostin level and other variables

Variables	Correlation	*p*-value
Age (years)	-0.130	0.369
Body weight (kg)	0.222	0.121
Height (cm)	0.221	0.123
Body mass index (kg/m^2)	0.221	0.123
Systolic blood pressure (mmHg)	0.118	0.415
Diastolic blood pressure (mmHg)	0.005	0.973
Renal parameters		
Serum creatinine (mg/dl)	0.410	0.003*
Blood urea nitrogen (mg/dl)	0.355	0.011*
Serum albumin (g/dl)	-0.148	0.304
Urine protein to creatinine ratio	0.218	0.129
eGFR (ml/minute/1.73 m^2)	-0.399	0.004*

eGFR = estimated glomerular filtration rate

* *p*-value <0.05

between the urine periostin level and other variables were assessed. The results showed the urine periostin level was significantly correlated with renal function, including serum creatinine, blood urea nitrogen, and eGFR. In agreement with these findings, there was a significant correlation between urine periostin and renal functions in patients with chronic allograft nephropathy and diabetic nephropathy[14,16]. These results suggested a role of periostin for the prognosis of kidney disease progression.

Epithelial-mesenchymal transition is considered to be a common pathway in the progression of renal fibrosis. Loss of epithelial marker and de novo expression of mesenchymal marker are observed[17]. Some studies have reported the involvement of periostin in epithelial-mesenchymal transition, as genetic deletion of periostin preserved epithelial marker expression and decreased mesenchymal markers. Moreover, less renal fibrosis was observed in kidney tissues from these animals[12]. Serial sections of kidney tissues demonstrated the co-localization of periostin with mesenchymal markers at all time points after kidney injury[10]. The same result was also observed in human studies[11]. From the previous study, positive periostin staining was found in fibrotic areas in

Table 5. Comparison of urine periostin level at baseline and after treatment in patients with response and non-response to therapy

Response to therapy	Urine periostin level (ng/mg†), median (Q1, Q3)		*p*-value
	Baseline	After 6 months of treatment	
Patients with response to therapy (n = 7)	35.70 (33.27, 158.60)	4.35 (0.47, 21.17)	0.028*
Patients with non-response to therapy (n = 9)	11.74 (6.53, 69.96)	7.45 (5.64, 20.66)	0.173

† mg of urine creatinine, * *p*-value <0.05

both glomerular and interstitial regions of kidney tissue samples from lupus nephritis patients. The correlation between periostin staining and chronic of kidney injury was also observed. In addition, periostin staining was significantly correlated with renal functions[18]. These results suggested that periostin may be involved in the progression of kidney disease. Moreover, the results from a previous study in lupus nephritis patients showed that periostin mainly located in tubular regions including tubular epithelial cells, tubular atrophy, and tubular cell casts[18]. This result suggested the possible source of urinary periostin from the affected tubular epithelial cells, tubular atrophy, and tubular casts. In animal study, positive periostin staining was also detected in tubular cells with more intensity and diffusion in line with chronic of disease. Moreover, the increment of urine periostin after kidney injury was observed[10].

Based on the authors knowledge, this is the first prospective study to evaluate the possibility of urine periostin measurement for monitoring response to therapy. The results showed the urine periostin level was significantly lower after six months of treatment compared with the baseline urine periostin level in patients with response to therapy. To support these results, there was an association of periostin and the progression/regression of the disease reported in animals with hypertensive nephropathy. The results showed the periostin mRNA expression was significant lower after four weeks of treatment in animals with regression of disease compared with the baseline level. Moreover, a significant higher of periostin mRNA expression was found in animals with progression of disease than in those with regression. Immunohistochemistry for periostin within kidney tissue samples from animals with both progression and regression of disease also reported the same[11]. These results demonstrated the relevance of periostin and progression/regression of kidney disease after treatment. However, there is a limitation in the present study. It is due to small sample size for evaluation of the potential of the urine periostin measurement and the response to therapy after six months of treatment. The relevance of urinary periostin and kidney disease progression should be further studied in larger sample size to determine the possibility of using the urine periostin measurements in routine clinical examination.

Conclusion

The present study demonstrated the urine periostin level in lupus nephritis and IgA nephropathy patients. Urine periostin detection was found in patients with worsening renal function and also correlated with renal function. The reduction of urine periostin was found after six months in patients that responded to treatment. These results supported the potential of using periostin as a urinary biomarker of kidney disease progression in patients with lupus nephritis and IgA nephropathy. A possibility of using urine periostin measurement for monitoring response to treatment after six months was also observed.

What is already known on this topic?

Periostin is a novel biomarker related to kidney disease progression. The expression of periostin is in both animal and human with different types of kidney disease.

What this study adds?

Urine periostin was at a significantly higher level in lupus nephritis and IgA nephropathy patients than in controls. There was also a correlation between urine periostin level and renal function. These results supported the potential of using periostin as a urinary biomarker of kidney disease progression in patients with lupus nephritis and IgA nephropathy.

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Potential conflicts of interest

The authors declare no conflict of interest.

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