ELSEVIER

Urine Periostin as a Biomarker of Renal Injury in Chronic Allograft Nephropathy

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ABSTRACT

Background. Chronic allograft nephropathy (CAN) represents the main cause of renal allograft failure after transplantation. Noninvasive CAN testing is required. Periostin promotes the expression of a mesenchymal phenotype in renal tubules and is a promising urine biomarker for progressive renal injury. Information regarding periostin expression in the setting of CAN remains scarce.

Methods. Subjects were recruited from our outpatient transplantation clinic. Random urine samples were collected from CAN patients (n = 24) and renal transplant patients with normal renal function (transplant controls, n = 18). Control samples were collected from healthy volunteers (n = 18) who had normal renal function. Urine periostin was measured by enzyme-linked immunosorbent assay.

Results. The median urine periostin in CAN patients was significantly higher than in transplant and healthy controls (1.74 vs 0.00 vs 0.14 ng/mg creatinine, respectively; $P < .001$). Urine periostin enzyme-linked immunosorbent assay at a cutoff value of 0.152 ng/mg creatinine demonstrated the sensitivity, specificity, and accuracy for distinguishing CAN patients from transplant patients with normal renal function (91.7%, 77.8%, and 85.7%, respectively). In addition, urine periostin levels correlated directly with urine protein creatinine ratio ($R = 0.566$, $P < .001$) and serum creatinine ($R = 0.522$; $P < .001$), whereas inverse significant correlations were evidenced with estimated glomerular filtration rate ($R = -0.431$; $P < .001$).

Conclusion. The appearance of urine periostin in CAN patients but not in healthy and transplant controls underscores its value as a potential biomarker for chronic progressive renal injury in transplant recipients.

CHRONIC ALLOGRAFT NEPHROPATHY (CAN) is the slow, progressive deterioration in renal dysfunction characterized clinically by an increase in serum creatinine, increasing proteinuria, and progressive hypertension, and histologically by tubular atrophy, interstitial fibrosis, and fibrous neointimal thickening of arterial walls is an almost universal finding in renal transplant recipients [1]. Accurately assessing and monitoring renal function is critically important in CAN patients. Blood urea nitrogen, serum creatinine, formulae to estimate glomerular filtration rate (GFR), and albuminuria are measures currently used to assess the presence and progress of kidney injury [2]. However, these measures are imprecise, are not direct measures of renal tissue injury, and are relatively insensitive to small changes in renal function. Ideally, novel CAN biomarkers should reflect mechanisms and activity of continuing renal injury and predict disease progression and response to treatment.

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The interest of pathway involved in development of fibrosis and tissue remodeling in transplanted kidneys is epithelial–mesenchymal transition (EMT) [3]. This describes the process of phenotypic change that cells of a variety of origins—including mesenchymal cells, resident fibroblasts, and epithelial cells—undergo, leading to fibrosis. Periostin, a member of the matricellular protein family, acts as an adhesion molecule during bone formation, supports osteoblastic cell line attachment, and is involved in cell survival and differentiation [4–7]. Evidence in kidney tissues suggests that periostin reflects the adoption of a mesenchymal phenotype by distal renal tubular cells in response to diverse renal injuries across species [8]. Its renal histopathologic expression patterns and coordinated effect on the induction of a mesenchymal phenotype suggest that periostin may be a biomarker that also participates in the pathogenesis of CAN. Information regarding periostin expression in progressive kidney injury after kidney transplant remains scarce. This study demonstrates urinary and tissue periostin expression in CAN patients.

METHODS

The study protocol was approved by the human subjects institutional review board of the Royal Thai Army Medical Department. Informed consent was obtained from all patients who participated in the study. Random blood and urine samples were collected from CAN patients (n = 24) and renal transplant patients with normal renal function (transplant controls; n = 18). A group of 18 normal age-matched individuals with normal renal function were used as healthy control subjects and stored at −80°C with protease inhibitors until assayed. Individuals with evidence of acute rejection, acute infection, or acute intercurrent illnesses were excluded. Medical history, systolic and diastolic blood pressure, body weight, body mass index, routine laboratory data including blood urea nitrogen, serum creatinine, urine protein creatinine ratio, and estimated GFR were recorded.

Immunohistochemical Renal Periostin Expression

Kidney tissues from CAN patients were randomly collected for periostin immunostaining. Four-micron sections of formalin-fixed, paraffin-embedded tissue were deparaffinized and rehydrated. Endogenous peroxidase activity was quenched by incubation in

Table 1. Clinical and Biochemical Parameters in Transplant Controls, Healthy Controls, and Patients With Chronic Allograft Nephropathy (CAN)

	CAN Subjects (n = 24)	Transplant Controls (n = 18)	Healthy Controls (n = 18)
Male (n, %)	18 (75)*,†	7 (38.9)	3 (16.7)
Age (y)	45.33 ± 9.6	48.78 ± 13.13	50.22 ± 4.77
BMI (kg/m^2)	22.20 ± 2.93	24.28 ± 5.18	24.34 ± 3.16
Systolic blood pressure (mm Hg)	125.37 ± 13.50	123.56 ± 14.85	119.17 ± 9.41
Diastolic blood pressure (mm Hg)	71.38 ± 9.41	67.72 ± 8.50	74.39 ± 8.35
Duration of transplant (y)	9.00 ± 7.00	7.73 ± 5.79	-
Duration of dialysis (y)	4.08 ± 3.27	3.92 ± 4.35	-
Type of transplant (n, %)			
Living-related kidney transplant	11 (45.8)	10 (55.6)	
Cadaveric kidney transplant	13 (51.2)	8 (44.4)	-
History of rejection			
Antibody-mediated rejection	7 (29.17)	0 (0)	
Acute cellular rejection	12 (50)*	2 (11.1)	-
Comorbid diseases (n, %)			
Diabetes mellitus	3 (12.5)	1 (5.6)	1 (5.6)
Hypertension	20 (83.3)†	16 (88.9)	0 (0)
Dyslipidemia	22 (91.7)†	16 (88.9)	3 (16.7)
Cerebrovascular disease	1 (4.2)	1 (5.6)	0 (0)
Ischemic heart disease	0 (0)	1 (5.6)	0 (0)
Immunosuppressive agents			
Tacrolimus	19 (79.2)*	8 (44.4)	
Cyclosporine	2 (8.3)*	10 (55.6)	
Sirolimus	3 (12.5)	1 (5.6)	
Mycophenolate mofetil	14 (58.3)	6 (33.3)	
Myfortic	10 (41.7)	9 (50)	
Azathioprine	0 (0)	2 (11.1)	
Prednisolone	24 (100)	18 (100)	-
Serum 25(OH) vitamin D level (ng/mL)	28.05 ± 16.75	26.20 ± 6.38	23.20 ± 4.13
Intact PTH (pg/mL)	93.52 ± 82.92	81.69 ± 41.69	-
Serum creatinine (mg/dL)	2.01 ± 1.18*,†	0.97 ± 0.11	0.74 ± 0.15
Estimated GFR (mL/min/1.73 m^2)	57.44 ± 20.49*,†	68.91 ± 10.21	90.03 ± 12.71
Urine protein/creatinine ratio	1.49 ± 2.67*	0.14 ± 0.09	-

BMI, body mass index; GFR, glomerular filtration rate; PTH, parathyroid hormone.
All data expressed in mean ± SD.
*$P < .05$ versus transplant controls.
†$P < .05$ versus healthy controls.