

# Journal of Nephrothology



## Relationship of CD147 kidney expression with various pathologic lesions, biochemical and demographic data in patients with classes III and IV of lupus nephritis

Masoud Amiri<sup>1,2</sup>, Farima Abedini<sup>3</sup>, Azar Baradaran<sup>4\*</sup>

<sup>1</sup>Department of Epidemiology and Biostatistics, Shahrekord University of Medical Sciences, Shahrekord, Iran

<sup>2</sup>Department of Epidemiology, Erasmus Medical Center, Rotterdam, Netherlands

<sup>3</sup>Department of Internal Medicine, Shahrekord University of Medical Sciences, Shahrekord, Iran

<sup>4</sup>Department of Pathology, Isfahan University of Medical Sciences, Isfahan, Iran

### ARTICLE INFO

*Article type:*  
Original Article

*Article history:*  
Received: 10 January 2018  
Accepted: 4 April 2018  
Published online: 28 April 2018

*Keywords:*  
Inflammation  
Lupus nephritis  
Glomeruli

### ABSTRACT

**Background:** Systemic lupus erythematosus (SLE) is a chronic inflammatory disorder that affects the kidney in around 50% of patients

**Objectives:** The aim of this study was to assess CD147 expression with various pathologic lesions, biochemical and demographic data in patients with classes III and IV lupus nephritis.

**Patients and Methods:** These patients with lupus nephritis classes II and IV by renal biopsy and pathology were enrolled in this study. The strength of CD147 staining on tubules, Bowman's capsules, vessels and tuft of glomeruli was expressed as proportion of involvement.

**Results:** In this study, 23 renal biopsies for lupus nephritis of classes III and IV (documented by immunofluorescence and light microscopic studies) were included. No significant difference of CD147 staining between classes was detected ( $P > 0.05$ ). In addition, proportion of proteinuria was not related to CD147 staining in tubules, Bowman's capsules, vessels and tuft of glomeruli in classes III and IV lupus nephritis ( $P > 0.05$ ). There was no significant association of CD147 staining in tubules, Bowman's capsules and vessels with serum creatinine ( $P > 0.05$ ). However, an association between CD147 staining in tuft of glomeruli with serum creatinine was detected ( $r = 0.623$ ,  $P = 0.002$ ). None of chronicity or activity percent of glomerular involvement in two classes of III or IV had a significant association with CD147 staining ( $P > 0.05$ ).

**Conclusions:** The significant association between CD147 staining in glomeruli with serum creatinine in lupus nephritis of classes III and IV revealed that inflammation at this area may have prognostic implication.

### *Implication for health policy/practice/research/medical education:*

In a study on 23 renal biopsies for lupus nephritis of classes III and IV, we found an association between CD147 staining in tuft of glomeruli with serum creatinine ( $r = 0.623$ ,  $P = 0.002$ ).

**Please cite this paper as:** Amiri M, Abedini F, Baradaran A. Relationship of CD147 kidney expression with various pathologic lesions, biochemical and demographic data in patients with classes III and IV of lupus nephritis. J Nephrothol. 2018;7(3):101-105. doi: 10.15171/jnp.2018.24.

### 1. Background

Systemic lupus erythematosus (SLE) is considered by deficit of self-tolerance and expansion of autoantibodies to nuclear self-antigens (1). SLE is a chronic inflammatory

disorder that disturbs the kidneys in around 50% of patients. SLE is more predominant in females than males through all age groups and populaces. Lupus nephritis is a noteworthy contributor to mortality and morbidity in

\*Corresponding author: Prof. Azar Baradaran, Email; [azarbaradaran@med.mui.ac.ir](mailto:azarbaradaran@med.mui.ac.ir)

individuals with SLE. The clinical presentations of lupus nephritis are often delicate (1,2).

SLE gives many confronts for clinicians. The beginning of disorder may be insidious, with various dissimilar symptoms and signs, constructing early and accurate diagnosis problematic (1,2). Hence, all patients with SLE should be considered for renal engagement at early diagnosis. The occurrence of SLE and the chances of emerging lupus nephritis vary significantly among various areas of the world and diverse races and civilizations (2-4). However, varying degrees of kidney engagement are seen in around 60% of patients with SLE with lupus nephritis (1,2). In 10% to 30% of patients, this condition extended to end-stage renal disease in about 15 years after diagnosis. The identification of SLE is clinically reinforced by serology and histopathology. Despite the existence of clinical criteria, Lupus nephritis persists a histopathological identification. The renal biopsy provides a suggestion for disease prognosis, activity, chronicity and arranging of therapy (2-4). The glomerular lesions that commonly convoy SLE have been the topic of interest. Morphologic lesions of lupus nephritis consisted of mesangial proliferation lonely (class II), endocapillary and extracapillary proliferation; additionally, fibrinoid necrosis, wire loops and hyaline thrombi or podocytopathy may be seen. In glomeruli, involvement may be focal (class III) or diffuse (class IV), global or segmental (3,4). In addition, lesions in tubulointerstitial area are connected with glomerular lesions, however, they have also been detected to be prognostic of kidney outcome in lupus nephritis irrespective of glomerular lesions. Thus, interstitial inflammation, atrophy of the tubules and fibrosis must report in the pathology reports of lupus nephritis and graded as mild, moderate, or severe (4,5). Recently much interest has been paid towards other parameters having prognostic implication for disease progression or patients' survival. CD147, which is a transmembrane glycoprotein belongs to the immunoglobulin superfamily (2-4). CD147 has been detected to have a role in some physiological and pathological consequences by interacting with various binding partners like cyclophilins or caveolin-1 (2-4). Recent studies have shown that CD147 has participated in the control of metastatic cancers and lymphocyte responsiveness. In normal conditions, high expression of CD147 is detected only in the basolateral side of tubular epithelial cells (TECs) in the kidney (5,6). The role of CD147 in the kidneys are different, extending from its role in acute renal failure which is usually associated with inflammation and ischemia. However, the correlation of CD147 expression with tubulointerstitial injury

and glomerular damage in lupus nephritis is not fully understood while studies in this regard are scarce. It is possible that expression of CD147 in glomeruli or in interstitial area encountered as a marker for progression of lupus nephritis (5,6).

## 2. Objectives

In this study we sought to measure CD147 intensity staining in tubules, Bowman's capsules, vessels and tuft of glomeruli with some demographic data among lupus nephritis patients.

## 3. Patients and Methods

### 3.1. Patients and specimens

This study consisted of patients with lupus nephritis classes II and IV by renal biopsy. The study was conducted in renal pathology division of Baradaran laboratory in Isfahan (Iran). Renal biopsies with fewer than ten glomeruli were excluded from the study. The SLE patients also achieved the revised American College of Rheumatology (ACR) criteria for systemic lupus nephritis (7) as explained by their physicians. Various data consisted of age, gender, proportion of 24 hours proteinuria and serum creatinine was also obtained from patients' records.

### 3.2. Definition of lupus nephritis

The diagnosis of lupus nephritis is based on clinical and laboratory findings and lastly by immunofluorescence study by considerable positive C1q (more than 2+ intensity) accompanied by IgG, IgA, IgM and C3 deposits (full-house configuration), which were semi-quantitatively classified from zero to 3+. Renal biopsies were presented conferring to the 2003 ISN/RPS classification for LN (4,5).

### 3.3. Immunohistochemical analysis for CD147

To conduct immunohistochemical staining, the 4- $\mu$ m-thick sections were stained with mouse monoclonal anti-human CD147 antibody [rabbit polyclonal to CD147; anti-CD147 antibody (ab64616; abcam)]. The strength of CD147 staining on tubules, Bowman's capsules, vessels and tuft of glomeruli was expressed as proportion of involvement.

### 3.4. Ethical issues

This investigation was in accordance with the Declaration of Helsinki. This study was conducted on paraffin embedded blocks of renal biopsies to find CD147 intensity. The ethical board committee of national institute for medical research development approved this

study (NIMAD; <http://nimad.ac.ir>; Grant#943670).

### 3.5. Statistical analysis

Categorical variables were stated as percentages and evaluated with chi-square ( $\chi^2$ ) test. Continuous variables were expressed as mean  $\pm$  standard deviation (SD). The differences between groups were evaluated by student *t* test. The reported *P* value was two-sided with a value of less than 0.05 as statistically significant criteria. Pearson correlation coefficients were used for finding the correlation between factors. All analysis had done by SPSS software version 22.0 (SPSS Inc, Chicago, Ill, USA).

## 4. Results

The study consisted of 33 cases of renal biopsy with detection of lupus nephritis, which their CD147 staining were obtained. Around 23 patients who were in classes III and IV were enrolled in the study. According to the similar nature of classes III and IV regarding morphologic lesions and clinical presentation, thus this study was only conducted on patients with classes III and IV. All biopsies documented for lupus nephritis classes III and IV by IF and light microscopic studies. Mean age of patients was  $31.56 \pm 9.72$  years (minimum age; 11 years maximum age; 50 years). About 18 (78.3%) patients were female. The average of proteinuria and serum creatinine were  $2294.35 \pm 1338.92$  mg/d and  $1.65 \pm 0.82$  mg/dL, respectively. Serum creatinine in classes of III and IV was  $1.21 \pm 0.30$  mg/dl and  $1.98 \pm 0.93$  mg/dL, respectively ( $P=0.020$ ). Moreover, the average of proteinuria in classes of III and IV was  $1704.00 \pm 766.80$  mg/d and  $2748.46 \pm 1527.03$  mg/d, respectively

( $P=0.062$ ). Accordingly, the proportion of activity in of classes III and class IV was  $22.80 \pm 25.38$  versus  $69.92 \pm 28.12$  percent ( $P<0.001$ ). Likewise, the proportion of chronicity in classes III and IV was  $12.00 \pm 9.77$  versus  $11.46 \pm 21.94$  percent but not significant ( $P=0.943$ ). Furthermore, 13 cases had global lesions of glomeruli of two classes. In addition, 10 cases had focal lesions of glomeruli in classes of III and IV.

Table 1 shows the frequency distribution of CD147 intensity staining in areas of tubules, Bowman's capsules, vessels and tuft of glomeruli. As the table shows, most of the staining was related to CD147 staining of renal tubules.

Table 2 shows the distribution of CD147 in classes III and IV, with no significant difference of CD147 staining between classes ( $P>0.05$ ).

Similarly, no significant differences of CD147 staining in all four regions of interstitium, tubules, vessels or glomeruli in global versus segmental lesions of the glomeruli were detected ( $P>0.05$ ) (Table 3).

The same as Table 3, there were no significant differences of CD147 staining in all four regions of interstitium, tubules, vessels or glomeruli in focal versus diffuse lesions of the glomeruli were detected ( $P>0.05$ ) (Table 4).

The results of this study showed that the proportion of proteinuria was not related to CD147 staining in tubules, Bowman's capsules, vessels and tuft of glomeruli in classes III and IV lupus nephritis ( $P>0.05$ ). There was no significant association of CD147 staining in tubules, Bowman's capsules and vessels with serum creatinine ( $P>0.05$ ). None of chronicity or activity percent of glomerular involvement had an association with CD147 staining ( $P>0.05$ ). Additionally, there was no association

**Table 1.** Frequency distribution of CD147 intensity staining in tubules, Bowman's capsules, vessels and tuft of glomeruli

Factor	Minimum	Maximum	Mean	Standard deviation
Interstitial area	0	30	11.96	9.62
Vessels	0	10	0.87	2.46
Glomeruli	0	70	14.78	16.13
Tubules	0	50	17.04	14.65

**Table 2.** Frequency distribution of CD147 intensity staining in tubules, Bowman's capsules, vessels and tuft of glomeruli in classes III and IV

Factor	Class		Total	<i>P</i> value
	3	4		
Interstitial area	$11.50 \pm 8.83$	$12.31 \pm 10.53$	$11.96 \pm 9.62$	0.847
Vessel	$1.00 \pm 3.16$	$0.77 \pm 1.88$	$0.87 \pm 2.46$	0.829
Glomeruli	$9.00 \pm 9.37$	$19.23 \pm 19.02$	$14.78 \pm 16.13$	0.135
Tubules	$17.00 \pm 15.67$	$17.08 \pm 14.47$	$17.04 \pm 14.65$	0.990

**Table 3.** CD147 intensity staining in global versus segmental lesions of the glomeruli

Factor	Global versus segmental		Total	P value
	Segmental	Global		
Interstitial area	11.00 ± 9.37	12.69 ± 10.13	11.96 ± 9.62	0.686
Vessel	1.00 ± 3.16	0.77 ± 1.88	0.87 ± 2.46	0.829
Glomeruli	8.50 ± 9.73	19.61 ± 18.65	14.78 ± 16.13	0.102
Tubules	15.70 ± 16.38	18.08 ± 13.77	17.04 ± 14.65	0.709

**Table 4.** CD147 intensity staining in focal versus diffuse lesions of the glomeruli

Factor	Focal versus diffuse		Total	P value
	Focal	Diffuse		
Interstitial area	11.50 ± 8.83	12.31 ± 10.53	11.96 ± 9.62	0.847
Vessel	1.00 ± 3.16	0.77 ± 1.88	0.87 ± 2.46	0.829
Glomeruli	9.00 ± 9.37	19.23 ± 19.02	14.78 ± 16.13	0.135
Tubules	15.70 ± 16.38	18.08 ± 13.77	17.04 ± 14.65	0.709

between ages of patients with CD147 staining ( $P > 0.05$ ). We found an association between CD147 staining in tuft of glomeruli with serum creatinine ( $r = 0.623$ ,  $P = 0.002$ ).

## 5. Discussion

This study showed more proportion of proteinuria, serum creatinine and activity percent in class IV versus class III. We found, most of the CD147 staining was related to renal tubules. Furthermore, we found no significant difference of CD147 staining between classes. Similarly no significant difference of CD147 staining in global versus segmental lesions of the glomeruli was detected. Besides, proportion of proteinuria was not related to CD147 staining. Likewise, none of chronicity or activity percent of glomeruli had an association with CD147 staining. In this study we found an association between CD147 staining in tuft of glomeruli with serum creatinine.

In a study on a total of 218 lupus patients Wilson et al, detected class IV had worse renal survival. They also found, interstitial infiltration and tubular atrophy/ interstitial fibrosis (IFTA) individually affect kidney survival (3).

In a study on 64 lupus nephritis patients, Maeda-Hori et al detected, in lupus nephritis tissues, CD147 presentation was remarkable in damaged glomeruli; however, not in injured tubules representing atrophy. In addition, plasma CD147 levels precisely reflected the histological activity of the disease. They concluded that plasma CD147 might provide admirable diagnostic capabilities to find the best choice of lupus nephritis therapy, while plasma CD147 levels provided suitable perceptions into disease activity (6).

Very few studies conducted on CD147 staining in lupus nephropathy. However, a similar study by Sun et al, on 86 kidney biopsies in IgA nephropathy, CD147 presentation was detected in the basolateral membrane of renal tubular cells. They detected a significant indirect relationship of CD147 staining of kidney tubules with proportion of glomerular filtration. They also found a significant direct relationship of CD147 staining of kidney tubular cells with serum creatinine levels and also with lesions of tubulointerstitial area (8).

Interestingly, they found that elevated CD147 expression was correlated with reduced kidney survival. Their study revealed a raised CD147 immunostaining intensity is an independent predictor of renal outcome in IgA nephropathy. They concluded that CD147 presentation may predict renal prognosis in IgA nephropathy.

More recently, Mori et al evaluated the clinical efficacy of CD147 in biopsy-proven kidney diseases which resulted in chronic renal failure (9). Their patients included 538 patients with various renal disease. They detected the CD147 presentation in disturbed regions of kidney.

## 6. Conclusions

The observed significant association between CD147 staining in glomeruli with serum creatinine in lupus nephritis of classes III and IV revealed that inflammation at this area may have a prognostic implication, while most of the staining was related to CD147 staining of renal tubules.

## Limitations of the study

The relatively small sample of kidney biopsies is a limitation of our investigation. We suggest further

studies on this aspect of lupus nephritis patients.

#### Authors' contribution

AB and FA conducted the investigation. MA conducted the statistical analysis. AB prepared the draft. MA edited the manuscript. AB and MA prepared the final manuscript. All authors read and signed the final paper.

#### Conflicts of interest

The authors declare no conflict of interest.

#### Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

#### Funding/Support

This research project was conducted by a grant from national institute for medical research development (NIMAD) (<http://nimad.ac.ir>) from Iran (Grant#9 Grant#943670).

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