

## Role of Urinary Biomarkers for Diagnosis of Lupus Nephritis

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### Abstract

Systemic lupus erythematosus (SLE) patients are having significant morbidity and mortality due to lupus nephritis (LN). To early management of lupus nephritis, these biomarkers have advantageous on the prognosis of LN. Kidney biopsy can be associated with significant morbidity, not possible carry out serially. Furthermore; renal biopsy may have sampling error because of extent number of glomeruli obtained for LN activity and chronicity. For diagnosis and observe of LN, there is always a need to find a non-invasive, easily available, and precise marker that can be followed continuously. The urinary biomarkers may be of such category. Routine clinical variable such as creatinine clearance, proteinuria, urine sediments, antids DNA, and complement levels are not sufficient for diagnosis of progressive disease activity in the LN and early regression of nephritis. Therefore, innovative biomarkers are compulsory to increase the diagnostic precision and sensitivity of lupus kidney disease, prognostic thesaurus, observing of treatment response, and identification of early kidney flares. In the index paper we reviewed recently discovered urinary biomarker in comparison to serum biomarker and kidney biopsy in LN.

**Keywords:** Lupus nephritis; Biomarkers; Sensitivity

### Introduction

#### SLE (Systemic lupus erythematosus)

Is a persistent life-threatening illness because involvement of multiple systemic organs. The most prevalent presentation of SLE is lupus nephritis (LN) that can be seen in up to 60% of all SLE patients [1]. Lupus nephritis is responsible for significant morbidity and mortality in SLE patients [2]. Despite comprehensive enhancement in observance of SLE in the past two decades, the prognostication of LN is not satisfactory [2]. Early diagnosis and treatment of lupus nephritis has a beneficial effect on the prognosis of lupus nephritis [3]. Delayed detection is related with a higher occurrence of end stage renal disease (ESRD) [4]. Renal biopsy is gold standard for detection, evaluation, and prognosis of lupus nephritis. Nonetheless, renal biopsy can be associated with significant morbidity and, therefore, is not commonly implement continuously [4]. Furthermore, renal biopsy may have sampling error because of limited number of glomeruli obtained for lupus nephritis activity and chronicity [5]. Mostly use laboratory markers, which encompass serological ascertainment of serum anti-double-stranded (ds) DNA antibodies and complement levels, for LN activity. These can be supportive clinically, but the association between those and LN is limited. Sensitivity and specificity of serological markers for active LN between all SLE patients separate according to different studies and tests used (enzyme immunoassay vs. immunofluorescence) [6]. Therefore, for diagnosis and monitoring of lupus nephritis, there is always need to find a non-invasive, easily obtainable, and accurate marker that can be followed serially. The urinary biomarkers may be of such category. In the index paper we reviewed recently discovered urinary biomarker in comparison to serum biomarker and renal biopsy. We also reviewed correlation of urinary biomarkers to activity, chronicity of lupus nephritis and clinical manifestation of patients.

### Methods

The literatures were searched up to March 2017 related to urinary biomarkers of lupus nephritis.

#### Requirement of unachievable unique urinary biomarkers in lupus nephritis

Use of laboratory parameters for LN such as creatinine clearance, anti-ds DNA, proteinuria, urine protein-to-creatinine ratio (U-PCR), and complement levels are undesirable. These markers are less sensitivity and specificity for evolve renal activity and injury in LN. They are not directly correlated with kidney damage, which can arise before kidney function is diminish and first detected by laboratory markers. Proteinuria can occur from pre-existing chronic renal disease and acute inflammation of kidney. Outbreak of nephritis may occur in any condition in absence and new rise in the level of proteinuria. Kidney biopsy is a gold standard to assess the histological category of LN and the level of activity and chronicity in glomeruli. But, it is an invasive procedure and continual biopsies are inappropriate in the observing of LN. Thus, novel urinary biomarkers, which are able to distinguish lupus kidney activity and its extremity, anticipate kidney outbreak, and observe treatment reciprocation and illness breakthrough are clearly obligatory. The biomarker defined as a biologic, biochemical, or molecular matter which can be estimated qualitatively and quantitatively by laboratory methods [7]. The ideal biomarkers should associate with illness pathogenesis or activity in divergent organ systems. A supreme biomarker for LN should have as the following characteristics: 1. They have a superior association with kidney activity which considered by the level of proteinuria and urinary sediments, 2. Biomarkers are sensitive to small change so that it can be used for consecutive observing of illness activity in the renal and determine the treatment reciprocation and clinical reprieve, 3. They capability to pretend kidney activity/recrudescence before an clear change in traditional, clinical markers appears so that prior management planning can be designed, 4. Specific for LN, and 5. Most

specific to SLE for helping in early detection of LN. The urinary biomarkers should be simple to analysis, easy to analyst, and rapidly accessible in most laboratories with a rational cost.

### Essential urinary biomarkers for lupus nephritis

**Neutrophil gelatinase-associated lipocalin (NGAL):** Lipocalin-2 was initial demonstrated in human being's neutrophil granules as neutrophil gelatinase associated lipocalin (NGAL), it is a very little glycosylated protein material in many tissues and organs system [7]. NGAL is a family member of transporter proteins which play important role for cellular iron carrier, apoptosis, tissue discern and inhibition of the growth of bacteria. NGAL is upregulated in following conditions like acute kidney lesion and different type offend such as ischemia, inflammation, and infection [8]. Urinary protein-to-creatinine (UPCR) ratios and kidney SLE debility activity scores were correlated with uNGAL levels, but not with pervasive injury or extra kidney illness activity scores [7]. Urinary NGAL levels were more greatly associated with histologic activity scores than chronicity scores on kidney biopsies. Suzuki et al. reported that patients with LN associated remarkably higher levels of NGAL in plasma and urine NGAL than healthy controls or juvenile idiopathic arthritis and were not related to body weight, age, and height [8]. Moreover, Urinary NGAL levels but not plasma NGAL levels related with kidney illness activity scores. The origin of uNGAL in LN could be damaged kidney tubular cells, neutrophils, or inflamed vessels [8]. However, the magnitude of reversal in degree of biomarkers is much higher with urine compared to plasma NGAL in this study. Both biomarkers have a merit in pretending exacerbating of kidney illness activity in childhood LN. The sensitivity and specificity of urinary NGAL levels pretending kidney explode was higher than that of in anti-ds DNA titer.

### Chemokines

**Monocyte chemo-attractant protein-1 (MCP-1):** It is a leukocyte chemotaxis element which is play important role in damage and inflammation in LN [9]. Urine levels of MCP-1 were found to be remarkably greater in patients with a renal flare [10]. Rovin et al. reported the mean uMCP-1 degree at the time of kidney flash was remarkably greater than that of patients with inactive kidney disease, healthy controls, and patients with active or inactive non-renal SLE [11]. Urinary MCP-1 was more precise for kidney activity and it amount did not corroborate with non-renal SLE activity. According to Rovin et al. uMCP-1 was also found to be a delicate sign for kidney flare, with 73% of the flare merit above the 95<sup>th</sup> percentile of illness controls [11]. Finally, uMCP-1 is a precise for kidney activity, delicate to prognosticate kidney flares and corroborate with graveness of flares and proliferative types of LN [7].

**IL-6:** IL-6 is an adjective cytokine and expressed on antigen-presenting cells such as dendritic cells, macrophages, B lymphocytes, and other cells like fibroblasts, mesangial cells, T lymphocytes, endothelial cells vessels, epithelial cells and astrocytes [12]. Tsai et al. found that IL-6 urinary elimination was remarkably greater in patients with active LN compared to inactive LN ( $p=0.034$ ) and compared to controls ( $p=0.001$ ) [13]. IL-8 too manifested a comparable fashion to IL-6 [13].

### Tumor necrosis factor-like inducer of apoptosis (TWEAK)

TWEAK is a versatile cytokine and it have place to the TNF-ligand superfamily, its main source is the macrophages [14]. TWEAK's main

functions are cellular multiplication, continuity, delimitation, vascular proliferation and emigration [14]. Kaplan et al. reported that elevated appearance of TWEAK on activated T lymphocytes has been revealed to impel macrophage apoptosis that may accord to induct of SLE nephritis through increasing load of apoptotic stuff [15]. Schwartz et al. reported that SLE patients with active nephritis were having remarkably greater levels of urine TWEAK (uTWEAK) as compared to those with inactive or no nephritis [16]. uTWEAK was reported higher in ranking to anti-dsDNA or complement amounts in discerning LN from non-renal SLE patients [7].

### Urine proteomics

Though, entire urinary protein remainder a mostly used parameter for nephritis, it is additional contemplative than prognosticative of illness activity and many prosecutor are yet curious for a suitable urine biomarker by scrutinize the different proteins in the urine of SLE patients. Some authors were utilized the surface enhanced laser desorption/ionization time-of-flight mass spectrometry (SELDI-TOF MS) mechanization to segregate a group of urinary protein trademark for pediatric patients with LN [17]. As another method for urine proteomics, liquid chromatography-tandem mass spectrometry (LC/MS/MS), this technology used as a comparatively less time-consuming procedure with greater sensitivity for smaller proteins molecules. In proteomics, eight types of peptides/proteins molecular of different weights were recognized. Some of them were included albumin or albumin fractional products, transferrin (TF), ceruloplasmin (CP),  $\alpha$ 1-acid-glycoprotein (AGP), and lipocalin type prostaglandin D-synthetase (LPGDS). Suzuki et al. demonstrated that these biomarkers were remarkably higher in patients with nephritis in contrast with controls and those without nephritis [18]. Hepcidin is an acute phase reactant and upregulated by IL-6 and IL-1, these cytokines incriminated in pathogenesis of LN [18].

### VCAM

**Vascular Cell Adhesion Molecule:** It is a chemotactic agent for leukocytes and when it activated cause liberate proteases, reactive oxygen molecules causing to tissue injury and fibrosis [19]. Many studies reported that SLE patients had remarkably greater VCAM-1 levels than the controls. VCAM-1 amounts also corroborated with u-PCR ratios, SLEDAI scores, and active lupus nephritis who displayed the greater amounts of VCAM-1 in the urine [20]. Similarly, Ikeda et al. reported that greater amounts of serum VCAM-1 corroborate with expanded illness activity in humans with active LN (WHO class III and IV) in comparison to patients with inactive or mild LN (WHO class I and II) [21].

### CXCL16

**CXC chemokine ligand 16:** It is a chemokine presented on antigen presenting cells, with play an important role in T-cell and NK-cell enrolment and intracellular adherence arbitrated by combine with CXC receptor 6 (CXCR6) [22]. Few studies found that urine amounts of CXCL16 were increased in the urine of mice with unprompted LN (B6.Sle1.lpr, and MRL.lpr models) and were greater than the congenerous serum amounts of CXCL16 [21]. CXCL16 was over expressed in kidney tissue of diseased mice, and in urine of SLE patients, it was also correlated with SLEDAI scores and has batter sensitivity and specificity to discriminate between SLE patients and healthy controls [21].

## IP-10

**Interferon- $\gamma$ -inducible protein 10 or CXCL10 (chemokine (C-X-C Motif) ligand 10):** It is a chemokine produced by monocytes, interferon- $\gamma$ -stimulated endothelial cells, and fibroblasts [23]. Along with its receptor, CXC receptor 3 (CXCR3), IP-10 encourages the emigration of T lymphocytes at the place of inflammatory reaction and is also down-regulated in angiogenesis [24]. Serum amounts of IP-10 are expanded in patients with LN [24].

## Proteinuria

Proteinuria is a chief urine biomarker for lupus glomerulonephritis [25]. Proteinuria is utilized in various ratified scoring systems to evaluate illness activity, like British Isles Lupus Assessment Group index (BILAGI) and the SLEDAI [26]. A recent study reported that 65% of urine dipstick uses to screen for proteinuria, while 17% used a spot (untimed) U-PCR (protein to creatinine ratio), and only 12% of those observed used a timed 24-h urine collection to see for proteinuria [27]. The dipstick was an unreliable method in evaluation of proteinuria whereas 24-h urine protein collection is a gold standard method for proteinuria or a 24-h U-PCR is insufficient for collection [28]. The 24-h urine collection is a complex for patients and generally unsuitable method, mainly to the analysis of spot quantification [5].

## Urinary T cell flowcytometry

In SLE patients with proliferative LN T cells count can be used as a new urinary biomarker [29]. The flowcytometry of urine T cells detection is a noninvasive probe for cellular elements of the inflammatory kidney lesions and may yield prognostic parameters for the patients' consequence, therapeutic retaliation or future nephritis glare [30]. Dolf et al. reported the urinary sediment in active renal disease showed increased numbers of CD4<sup>+</sup> T-cells (134  $\pm$  71 cells/ml) and CD8<sup>+</sup> T-cells (287  $\pm$  220 cells/ml), while in HC (healthy controls) and patients without active renal disease almost no T-cells were present [31]. They concluded that CD8<sup>+</sup> effector memory cells migrate from the peripheral blood to the kidney and appear in the urine during active renal disease in SLE patients [31].

**Urinary soluble CD163:** Endo et al. reported that increased number of glomerular CD163<sup>+</sup> macrophages were correlated with LN severity, as determined by the biopsy activity index ( $r=0.635$ ) [32]. Urinary (u-) sCD163 level was strongly correlated with glomerular CD163<sup>+</sup> cell counts and histological disease score as well as urinary monocyte chemoattractant protein 1 levels ( $r = 0.638$  and  $0.592$ , respectively) and u-sCD163 level was greater in patients with active LN in comparison to other diseases [32].

## Other urinary biomarkers

**Urine osteoprotegerin (OPG):** Few studies reported that OPG robustly correlated with kidney activity rubric of the SELENA SLEDAI; the amounts of OPG prognosticative of a U-PCR of  $\geq 0.5$  [11].

**FOXP3 mRNA:** It is expressed remarkably greater in the urinary sediments of active (proliferative) than inactive (non-proliferative) LN patients, FOXP3 mRNA amount also corroborated with histological activity index and proteinuria; continual increased level of FOXP3 correlated with poor outcomes [33].

**Urine endothelin-1:** Dhaun et al. demonstrated aliquot evacuation of endothelin-1 and urine endothelin-1/creatinine ratio greater in a

patient of LN in comparison to normal kidney function and another chronic inflammatory kidney disease [34].

**Urine TGF $\beta$ -1:** Hammad et al. reported significantly higher Urine TGF $\beta$ -1 level in patients of proliferative than non-proliferative LN, and it corroborated with the amounts of anti-ds DNA and C3 [35].

## Significance of urine biomarkers in lupus nephritis

Usually, urine stuff is more appropriate to ratify renal injury superior than serum constitute. Urine is an origin of biomarker that is simple to collect and the presence of urinary biomarkers are generally ratify the kidney function straight in different type of kidney diseases. Urinary biomarkers are more sensitive for lupus nephritis; they can appear in urine before functional derangement. Different current urine biomarkers have been described like transferrin, lipocalin-type prostaglandin D-synthetase (L-PDGS) and  $\alpha$ 1-acid-glycoprotein (AGP) that may deliver as probable biomarkers for imminent glare in pediatric LN [36]. The urine VCAM-1 amount is corroborated with LN activity in SLE patients [21]. Moreover, urine MCP-1 amounts were remarkably correlated with both extremity of lupus nephritis glare and lupus nephritis class, thence, urinary MCP-1 levels are highly specificity and a non-invasive biomarker for considering lupus nephritis glare and lupus nephritis class [37]. In accession, urine TWEAK (tumor necrosis factor-like weak inducer of apoptosis) was suggesting as a peculiar biomarker of active lupus nephritis, because its amounts were corroborated with all active signs of lupus nephritis [38]. Furthermore, ISN/RPS (International Society of Nephrology and Renal Pathology Society) recommends urine free light chains (FLCs) are probably helpful biomarkers for proliferative or class III/IV lupus nephritis [39].

## Conclusion

Urinary biomarkers are easy to harvest, can be acclimated as serially monitoring LN, safe for patient, and cost-effective for LN. We are cheering that urinary biomarker will arrive with the capability to emphatically enrapture Eco management and reduced the morbidity and mortality of LN. Urine biomarkers arrive to be additional invigorated, in comparison to serum biomarkers perhaps because these markers are the straight produce, or sequences of renal inflammation or damage. Future studies must be centre of attention on a conjunction of innovative markers with orthodox clinical features to increase the sensitivity and specificity for the prognostication of kidney glares and prognosis in LN for SLE patients.

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