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Review Article

Advances in Study of Biomarkers for Lupus Nephritis

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Abstract

Lupus Nephritis (LN) is one of the most common and serious manifestations in SLE patients that causes significant morbidity and mortality. Current conventional biomarkers for lupus nephritis like urine sediments proteinuria, anti-dsDNA antibodies, and levels of C3 or C4 in serum still have limitations to reflect intrarenal injury very well. Renal biopsy is still the gold standard for LN diagnosis. Kidney biopsy, kidney functions and proteinuria measurements were usually used to assess the disease activity and organ damage. As kidney biopsy is an invasive operation and has various complications, such as bleeding, infection and allergic reactions to anesthetics or sedatives. Also, some patients cannot accept it, which may result in inaccurate diagnosis and treatment. Therefore, compare to kidney biopsy, biomarkers to predict renal damage and direct medication obviously have advantages in LN. Thus, study in novel biomarkers for SLE LN attracted many researchers attention, and made some progression in recent years. In this review, we summarized new findings about biomarkers for LN in recent years, and hope to update knowledge in this aspect for clinicians who treat SLE patients in their daily work.

Keywords: Biomarkers; Lupus nephritis; Systemic lupus erythematosus

Introduction

Systemic Lupus Erythematosus (SLE) is a multifactorial autoimmune disease characterized with immune tolerance broken and large amount of auto antibodies production. Excessive production of auto antibodies to nuclear antigens such as anti-double-stranded DNA (dsDNA) and his tones auto antibodies, leading to detrimental inflammation and multi-organ injuries [1]. Lupus Nephritis (LN), the kidney injury with SLE, is one of the most common and serious manifestation in SLE patients, which causes increasingly level of morbidity and mortality [2,3]. Renal manifestations range from asymptomatic proteinuria to nephritic or nephrotic syndromes, ultimately produce end-stage renal disease [4], which may differ among patients in different age and gender [5]. The pathogenesis of LN is still incompletely understood. Accurately and earlier diagnosis is important and necessary to decrease morbidity and mortality of SLE patients. To date, percutaneous renal biopsy is gold standard for LN diagnosis, disease activity evaluation, prognosis and therapy feedback of LN [6-9]. However, biopsy is an invasive operation and has various complications, such as bleeding, infection and allergic reactions to anesthetics or sedatives [7]. There are still some patients cannot accept it, which may resulted in inaccurate diagnosis and treatment. Therefore, biomarkers to predict renal damage and direct medication obviously have advantages in LN. Biomarkers are biologic, genetic, epigenetic or a chemical characteristic and conveniently detectable, to serve as measures of disease diagnosis, disease activity or prognosis evaluation or predict the flare of LN [9-11]. Some current biomarkers like urine sediments proteinuria, anti-dsDNA antibodies, C3 and C4 levels in sera, are conventional biomarkers used for LN. However, they can not reflect the real-time renal pathological alterations [9,12]. New surrogate non-invasive biomarkers that closely parallel to renal pathology in LN are still in need [8,13]. In recent years, researchers have done many studies on biomarkers in LN. In this review, we summarize the recent finding of biomarker for LN, with focus on novel biomarkers in serum and urine.

Conventional biomarkers IN LN

Conventional serum biomarkers of LN: The current laboratory markers such as proteinuria, anti-cardiolipin, anti- ribosomal P, complete blood count, Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP), anti-Sm, anti-dsDNA antibodies, and the complement components C3 and C4 are related to LN [12-14]. And both anti-dsDNA level and reduced level of C3 were not independent risk factor for LN [15]. Serum C3 can indicate Juvenile-onset Systemic Lupus Erythematosus (JSLE) with renal involvement [16]. However, most of these biomarkers lack of sensitivity and specificity to identify renal activity and damage in LN [17].

Conventional urinary biomarkers of LN: Proteinuria is the most commonly used urinary biomarker for LN. And the widely accepted criteria of the American College of Rheumatology for LN includes: persistent proteinuria of greater than 0.5 g in 24h (or greater than 3+ urine dipstick reaction for albumin), or spot urine protein/creatinine ratio >0.5, and/or urinary cellular casts, including red blood cell, hemoglobin, granular, renal tubular cell, or mixed(4, 7). Meanwhile, it reflects renal inflammation when there are Red Blood Cells (RBCs) >5/high-power filed (hpf), White Blood Cells (WBCs) >5/hpf and/or≥1 cellular casts show in urine, it reflects renal inflammation. Though urinary RBCs or WBCs are easy to detect, it may cause false positive result, especially easy to be polluted after menstrual period. Proteinuria was the current standard indicating glomerular or tubular pathology. Spot urine protein/creatinine ratio is another convenient method to estimate the degree of proteinuria [4]. There may also exist false positive of proteinuria and these biomarkers still couldn't predict LN flares accurately or reflect the disease activity, as well as missing the real-time renal pathology [12].

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Table 1: New serum biomarkers in SLE LN.

Serum Bimarkers	Detection Method	Correlated to Disease Activity (SLEDAI)	Change After Treatment	Related to	References
Anti-C1q	ELISA	yes	/	C4, mucocutaneous manifestations, protein-to-creatinine ratio, anti-dsDNA antibody	[22-24]
Anti-NCS	ELISA	no	/	pLN activity(when disease actived)	[22,42]
Anti-GBM	ELISA	yes	/	LN activity, anti-dsDNA, anti-NuA	[22,24]
Anti-mCRP antibodies	ELISA	yes	yes	lupus nephritis pathogenesis	[25,26]
Adiponectin	ELISA	yes	/	serum creatinine, proteinuria	[45,46]
AOPPs	Spectrophotometric method	yes	/	proteinuria, eGFR, anti-dsDNA antibody	[15]
BAFF/BLyS	Flow Cytometry	controversy	yes(responders)	C3, dosage of immunosuppressant, eGFR	[18-20]
Capric acid	LC-HRMS	/	/	/	[36]
CD4(+)CD25-Foxp3(+) Treg cells	Flow Cytometry	yes	no	proteinuria, anti-dsDNA antibody, ECLAM	[34,35]
CXCL13	ELISA	yes	yes	C3, number of B cells/HP in the renal tissue	[39-41]
Dickkopf-1	ELISA	no	/	/	[38]
human epididymis protein 4	ELISA	yes	/	serum creatinine, eGFR, IgG	[44]
HMGB1 protein	ELISA	yes	/	pLN activity	[22,24]
Leptin	ELISA	no	/	body mass index, corticosteroids doses	[45,46]
IGFBP-2	ELISA	yes	/	the anti-dsDNA, C3, physician's global assessment	[8,27]
IGFBP-4	ELISA	no	/	glomerular filtration rate, the chronicity index of renal pathology	[8,27,28]
NGAL	ELISA	yes	yes	urinary NGAL	[30-33]
Oxidized glutathione	LC-HRMS	/	/	/	[36]
resistin	ELISA	no	/	urinary resistin, measures of renal dysfunction	[45,46]
sAPRIL	ELISA	controversy	yes	histological activity, proteinuria	[18-21]
sCD72	ELISA	yes	/	SLEDAI score	[29]
SLAM	Flow Cytometry	no	yes	/	[43]
theophylline	LC-HRMS	/	/	/	[36]
Thiols	the Ellmans method	yes	no	serum creatinine, C3	[2]
Tumor necrosis factor receptor type II	ELISA	yes	/	conventional serological markers such as anti-dsDNA and C3	[27]

"/": not mentioned in the article.

AOPPs: Advanced Oxidation Protein Products; APRIL: A Proliferation-Inducing Ligand; Anti-NCS: Antibodies Against Nucleosomes; Anti-GBM: Glomerular Filtration Membrane; BAFF/BLyS: B-cell-Activating Factor; ELISA: Enzyme-Linked Immunosorbent Assay; eGFR: estimated Glomerular Filtration Rate; ECLAM: Consensus Lupus Activity Measurement; HMGB1: High Mobility Group Box 1; IGFBP: Insulin-like Growth Factor Binding Proteins; NGAL: Neutrophil Gelatinase-Associated Lipocalin; SLAM: Signalling Lymphocyte Activation Molecule; SLEDAI: the Systemic Lupus Erythematosus Disease Activity Index.

Novel Blood Biomarkers for LN: Due to the limitation of conventional serum biomarkers and the invasive risk of renal biopsy, the more sensitivity and specificity biomarker are still needed. Many researchers had found the novel potential biomarkers in blood in these years. Here, we will introduce the detail of novel biomarkers found in researches, and summarize in Table 1.

BAFF, APRIL

B-cell-Activating Factor (BAFF), also called B Lymphocyte Stimulator (BLyS), as well as A Proliferation-Inducing Ligand (APRIL), are both belong to Tumor Necrosis Factor (TNF) family protein. It plays critical roles in helping B cell activation, development, maintenance and plasma cell survival. It also proved that the up-regulation of B cells is associated with kidney damage in LN patients [18]. Researches had proved that serum levels of BAFF (sBAFF) and its mRNA levels in peripheral blood mononuclear cell (PBMC) were much higher in LN patients [19,20]. Some researchers had proved that levels of serum APRIL (sAPRIL) were also highly expressed in SLE patients [20]. The sAPRIL and renal mRNA expression were changed after a 6 months follow-up study with similar drugs, high APRIL level predicted treatment failure through the Receiver Operating Characteristic (ROC) analysis [19]. Levels of

Table 2: New urinary biomarkers in SLE LN.

Urinary Bimarkers	Detection Method	Correlated to Disease Activity (SLEDAI)	Change After Treatment	Related to	References
Alpha-1-acid-glycoprotein	ELISA	yes	/	Renal Domain Score	[48]
Alpha-1 anti-chymotrypsin (ACT)	ELISA	yes	yes	protein creatinine (PC) ratio	[52]
CXCL16	ELISA	yes	/	urine protein, protein-creatinine ratios	[51,52]
Haptoglobin (HAP)	ELISA	yes	yes	protein creatinine (PC) ratio	[52]
Cleaved form of osteopontin	The Human Osteopontin N-Half Assay Kit	no	/	thrombin or MMP-3 activity	[48]
P-selectin	ELISA	yes	/	protein-creatinine ratios	[50,51]
Retinol binding protein (RBP)	ELISA	yes	yes	protein creatinine (PC) ratio	[52]
Tumor necrosis factor receptor-1	ELISA	yes	/	protein-creatinine ratios	[51,52]
APRIL	ELISA	yes	yes	conventional disease activity markers and histology	[21]
BAFF	ELISA	no	yes(responders)	conventional disease activity markers and histology	[21]
MCP-1	ELISA	yes	yes	SLEDAI Renal Domain Score	[16,47,48]
NGAL	ELISA	yes	yes	the FE NGAL/FE protein ratio, serum creatinine, Upro:Ucre ratio	[31,32,48]
sCD163	ELISA	yes	/	the biopsy histological active score, levels of urinary chemoattractant protein 1	[50]
TWEAK	ELISA	yes	/	C4, C3, and proteinuria	[53]

"/": not mentioned in the article.

MCP-1: Monocyte Chemo-attractant Protein 1; TWEAK: Tumor Necrosis Factor-Like Weak Inducer of Apoptosis

sAPRIL were positively related to degree of histological activity and proteinuria [19]. However, the sBAFF and sAPRIL and its correlation with the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) still controversy(18, 20). Vincent, F.B.'s study showed that levels of sAPRIL decreased among LN patients(18). It may due to the difference of severity and ethnicity [21]. Meanwhile, the research also found that both urinary APRIL (uAPRIL) and urinary BAFF (uBAFF) levels raised significantly in proliferative lupus nephritis. The uBAFF and uAPRIL both outperformed C3, C4 and anti-dsDNA antibodies on ROC analysis when differentiating between nephritis and non-nephritis [21].

Anti-C1q: The complement Component 1q (C1q) is a protein complex involved in the complement system. When the antibodies bind to antigen forming an antigen-antibody complex, the C1 complex activated, which initiates the classical complement pathway [22]. Researches had displayed that the anti-C1q antibody levels in serum increased in LN. Also, it had been proved that the anti-C1q levels in serum were significantly associated with global disease activity protein-to-creatinine ratio, anti-dsDNA antibody levels and mucocutaneous manifestations [22-24]. The results above suggested that serum anti-C1q levels could be a potential biomarker for LN diagnosis and disease activity monitoring.

Anti-mCRP antibodies: Antibodies against Monomeric C Reactive Protein (anti-mCRP) may directly damage the kidney in LN patients by binding to endogenous antigens such as mCRP and C1q [25]. And present studies showed the levels of serum anti-mCRP antibodies increased in LN patients but not related to the level of CRP [25,26]. Serums with the higher level of anti-mCRP had higher titer of ANA , anti-dsDNA antibody and the TNF-α concentrationI [25]. Moreover, the results proved that the anti-mCRP participated in the pathogenesis of LN. It may be a better indicator biomarker than the classical indicators. The research also proved that the levels of anti-mCRP were significantly decreased after efficient treatment [25].

IGFBP-2 & IGFBP-4

Insulin-like Growth Factor Binding Proteins (IGFBP), one of the insulin-like growth factor binding protein family members, play important roles in reproductive physiology, bone formation and so on. The concentration of IGFBP-4 and IGFBP-2 in serum were significantly higher in LN patients [8,27]. IGFBP-4, the smallest IGFBP, could prolong the half-life of Insulin-like Growth Factors (IGFs) [8,28]. It positively correlated with the chronicity index of renal pathology, while negatively with estimated Glomerular Filtration Rate (eGFR) [8]. IGFBP-2 was proved to be a potential biomarker of active lupus nephritis which more specific than anti-dsDNA or C3 [27].

Soluble CD72: CD72, one of the regulatory co-receptors on B cells, carries an Immune receptor Tyrosine-based Inhibition Motif (ITIM). But the significance of soluble CD72 (sCD72) in SLE has not been clearly illustrated. Vadasz Z, et al. had proved that sCD72 was significantly increased in SLE patients mainly in large numbers of those with renal involvement than normal SLE, Rheumatoid Arthritis (RA) patients, or healthy adults. Also the level of sCD72 positively correlated with the SLEDAI scores [29].

NGAL: Neutrophil Gelatinase-Associated Lipocalin (NGAL), belong to the lipocalin super family, highly expresses in kidney

especially after ischemia or nephrotoxic injury. It triggers kidney damage and associates with kidney disease progression [30]. Serum NGAL (sNGAL) and urinary NGAL (uNGAL) had been proved to be a predictor of existing renal disease progression and related to eGFR [31]. Both NGAL concentrations were significantly elevated in SLE patients with renal involvement. The uNGAL correlated with sNGAL. And the high level of sNGAL was a good marker to predict LN and significantly associated with other laboratory markers for LN, such as anti-dsDNA antibody, anti-C1q IgG antibodies, and serum creatinine [32,33]. However, there are another research didn't show difference of uNGAL levels between LN and SLE without renal flare [32]. The Fractional Excretion (FE) NGAL/FE protein ratio was first proved in 2014 to be a reliable marker for disease activity and remission, even better than anti-dsDNA antibody [32].

CD4+CD25-Foxp3+ Treg

Regulatory T cells (Treg) play critical roles in self-tolerance and preventing immune-mediated inflammation, which are characterized by high expression levels of fork head family transcription factor (Foxp3) and the IL-2 receptor α-chain (CD25) [34,35]. However, Bonelli, M., et al had firstly identified a new subset of CD4+Foxp3+ Treg that does not express CD25 surface molecules (CD4+CD25−Foxp3+) were higher in active SLE, especially in LN and correlated with the levels of proteinuria. Though the levels of this cluster of Treg did not change after prednisone treatment. CD4(+)CD25-Foxp3(+) Treg might be acted as potential diagnose biomarker for LN [34].

Metabolomics: Metabolites are related to glycolysis, amino acid and lipid metabolism [36]. Metabolic profiling is proved to participated in some disease, like arthritis [37] and SLE [36]. There are three metabolomics, namely theophylline, oxidized glutathione and capric acid, could be predictive markers for LN with area under curve (AUC) values ranged from 0.70 to 0.80 by Ultra-High-Performance Liquid Chromatography coupled with High-Resolution Mass Spectrometry (UPLC-HRMS), while the combination of this three metabolomics was of better diagnostic accuracy with 87.5% sensitivity and 67.86% specificity and the AUC values of 0.85 [36].

Dickkopf-1: The Dickkopf-1 (DKK-1), a kind of Wnt antagonists, has four members of proteins namely DKK1, DKK2, DKK3, and DKK4, which all play important roles in the initiation and progression of LN. The serum levels of DKK-1 protein significantly elevated in LN patients when compared with SLE patients without renal involvement or Healthy Controls (HCs). Though the levels were not correlated with disease activity [38]. The serum DKK-1 may be a biomarker for identification of SLE patients with active LN.

CXCL13: B-lymphocyte chemokine CXC ligand 13 protein (CXCL13) is a member of the chemokine family. Its main function is effectively chemo attracting B cells and induced production of pro-inflammatory factors [39]. Serum concentrations of CXCL13 was significantly higher in SLE patients, especially in LN [39,40]. CXCL13 combining its receptor CXCR5 promoted the proliferation of a human renal mesangial cell [40]. The results suggest that CXCL13 act as a new therapeutic target in LN [41] and a biomarker for diagnosis of LN.

HMGB1, Anti-NCS, Anti-GBM

C1q can bind to the Glomerular Filtration Membrane (GBM) and contribute to the ongoing kidney inflammation. High Mobility Group Box 1 (HMGB1) protein might also induce the inflammation in LN by binding with pathogenic anti-dsDNA antibody [24]. Recently, serum levels of HMGB1 protein, antibodies against Nucleosomes (anti-NCS), and anti-GBM were exhibited significantly higher in paediatric LN (pLN) than in paediatric SLE (pSLE) without renal involvement. Moreover, the HMGB1 levels were positively correlated with pSLE and pLN disease activity [22]. However, Keusseyan et al. also showed the titer of anti-NCS in serum related to pLN only in the active pLN [42].

There are many other novel biomarkers such as the Signalling Lymphocyte Activation Molecule (SLAM) gene family [43], human epididymis protein 4 (HE4) [44], TNF receptor type II [27], adipokines like adiponectin, leptin and resistin [45,46], Advanced Oxidation Protein Products (AOPPs) [15], and oxidative stress related markers like thiols in LN [2] had been found. The novel serum biomarkers might give a new sight in LN diagnosis and treatment.

Novel Urine Biomarker for LN

More and more researches had focus on the biomarkers in urine because urine is easier to get and detected. We summarized the biomarkers latest found in urine in Table 2.

MCP-1: Monocyte Chemo-attractant Protein 1 (MCP-1) were proved to be a reliable marker of renal disease activity over time [16]. And the combination of some novel urinary biomarkers MCP-1, Alpha-Acid Glycoprotein (AAG), and ceruloplasmin levels plus protein: creatinine ratio in urine were better marker in predicting LN activity (AUC 0.85). NGAL (as we have mentioned earlier in the serum part) together with creatinine clearance plus MCP-1 was an excellent diagnostic test for chronic LN (AUC 0.83), and the combination of MCP-1, AAG, transferrin, and creatinine clearance plus C4 was a good diagnostic test for membranous LN (AUC 0.75). These potential urinary biomarkers may be a good way to diagnose kidney biopsy [47].

OPN N-half: Osteopontin is secretory glycoprotein, and secreted by osteoblasts, macrophages, activated T cells, or tubular epithelial cells. It plays a role for normal and dysregulated immune responses, which would promote macrophages and T cells infiltrating to inflammatory sites. Cleaved form of osteopontin (OPN N-half) concentration in urine were significantly higher in LN patients than HC, IgA nephropathy, minimal change nephrotic syndrome, or diabetic nephropathy. Patients with higher proteinuria (urine protein/creatinine ratio: P/C > 0.5), the level of OPN N-half was higher. Urinary OPN N-half might be a reliable specific biomarker for LN [48].

SCD163: Macrophages play important roles in the pathogenesis of LN. CD163 is a marker of M2 macrophages marker. Endo, N., et al. had revealed the urinary level of soluble CD163 (u-sCD163) level was higher in active LN patients than other autoimmune diseases. And both the increased number of glomerular CD163+ macrophages and the u-sCD163 were significantly correlated to the biopsy histological active scores and levels of urinary chemo attractant protein. More importantly, there were more than 60% of CD68+ macrophages with CD163+ in immunohistological analysis of glomeruli in LN patients. LN is a glomerular inflammation related to macrophage and

u-sCD163 can act as a biomarker for LN [49].

There are many other novel urinary biomarkers for LN. Urinary levels of P-selectin, Tumour Necrosis Factor Receptor-1(TNFR-1), as well as CXCL16 all increased in spontaneous lupus nephritis both in patients and LN mice models with excellent sensitivity and specificity AUC values [50,51]. Aggarwal, A., et al. found the level of Retinol Binding Protein (RBP), Haptoglobin (HAP), and Alpha-1 anti-chymotrypsin (ACT) in urine highly expressed in patients with active LN and decreased at 6 and 12 months after treatments [52]. Other urine biomarkers like tumor necrosis factor-like weak inducer of apoptosis (TWEAK) [53].

Urine is more easier to get and detected than blood sample, so the research about the specificity and sensitively biomarker in urine for the early diagnosis and disease activity evaluation is still needed.

Conclusion

In this review, we summarized the conventional and novel non-invasive biomarkers for LN. The development of promising potential diagnostic biomarkers for LN in recent years has been exhibited above and summarized in the tables. These biomarkers were related to functions of B cell, T cells and others immune cells. Remaining biomarkers were correlated with cytokines, such as complement, TNF, IFN, interleukin and so on. Besides, the combination of different biomarkers might earn a higher AUC rate on ROC analysis, which provided a better solution to diagnosis of lupus nephritis and could improve evaluative accuracy. Some of these novel markers identified as markers for early loss of kidney function and suitable to the histological biopsy changes during follow up. It may give a new strategy for SLE patients, especially for refractory LN patients. Even though, the biomarkers found in these years still have many limitations, it may effect by different age, race, sex or disease activity. Also, it is still a critical task to translate the potential biomarkers for LN into clinical practice and replace renal biopsy. Therefore, to replace renal biopsy with biomarkers still a long way to go.

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