Soluble Urokinase Plasminogen Activator Receptor as a Predictor of Renal Damage in Systemic Lupus Patients

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Abstract

Background: Systemic lupus erythematosus (SLE) is a chronic inflammatory disorder of autoimmune etiology with multisystemic affection. SLE represents a high burden on general health world widely as it causes high morbidity and mortality rates. Lupus nephritis (LN) is a severe organ lesion form which affect high percentage of SLE patients and may end by developing of end-stage renal disease (ESRD) or even death. Urokinase plasminogen activator receptor (uPAR) is a membrane-bound receptor which is mainly expresses on the membrane of immunologically active cells and is involved in many physiological and pathological processes, such as inflammation and immune responses. Soluble urokinase plasminogen activator receptor (suPAR) is derived from shedding of the uPAR and is expressed on a variety of cells, including neutrophils, lymphocytes, macrophages, and endotheliocytes. Recent evidences indicate that suPAR is involved in various biological functions, including cell adhesion, migration, and chemotaxis, and its elevated level is associated with poor clinical outcomes in various inflammatory diseases, such as sepsis, bacteremia, and systemic inflammatory response syndrome. Assessment of disease activity and organ damage in SLE remains challenging due to lack of reliable biomarkers and to heterogeneity of the disease. Additionally, it can be difficult to distinguish ongoing inflammation from permanent organ damage caused by previous flares or medication side effects. The suPAR has emerged as a potential marker of inflammation and disease severity, as well as a predictor of outcome of several disparate conditions.

Key words: Soluble Urokinase Plasminogen Activator Receptor - Predictor – Renal Damage – Systemic Lupus Patients
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Introduction:

Systemic lupus erythematosus (SLE) is a systemic chronic autoimmune disease. Genetic, immunological, endocrinal, and environmental factors influence the loss of immunological tolerance against self-antigens leading to the formation of pathogenic autoantibodies that cause tissue damage through multiple mechanisms. clinical presentations vary from mild mucocutaneous manifestations to sever multiorgan involvement [(1)].

SLE diagnosis and treatment still can be challenging, even with several classification criteria which have been posed and several agents which have been shown to be efficacious in treating SLE, the disease still poses significant morbidity and mortality risk in patients [(1)]. The overall global incidence of SLE ranges between 1.5 and 11 per 100,000 person-

year, and the global prevalence ranges from 13 to 7,713.5 per 100,000 individuals. Mortality among patients with SLE is still unacceptably high, being two to three times higher than that of the general population [(2)].

Lupus nephritis (LN) is a type of glomerulonephritis that affect up to 50% of SLE patients and considers as one of the most serious organ manifestations of SLE. SLE patients may develop LN within 5 years of SLE diagnosis and, in many cases, LN is the presenting manifestation leading to diagnosis of SLE [(3)]. Within 15 years of diagnosis with LN, 10% to 30% of patients can progress to end-stage renal disease (ESRD). In fact, LN is the most important predictor of mortality in patients with SLE [(4)].

Epidemiology:

LN develops early is the disease's course, usually within the first 6 to 36 months. The prevalence of SLE and the chances of developing LN vary considerably between different regions of the world and different races and ethnicities. In the United States, the incidence of LN is higher in black (34%-51%), Hispanic (31%-43%), and Asian (33%-55%) compared with white (14%-23%) patients. Black and Hispanic patients tend to have worse outcomes and are more likely to develop kidney failure than white patients. The reasons for these racial and ethnic differences are not completely understood, but genetic and socio-economic factors may have a role in these differences [(5)]. In Egypt, a study was done on 770 SLE patients at Kasr Alainy Hospital, there were 707 (91.8%) female patients. The mean age at disease onset was 22.1 ± 8.6 and the disease duration was 6.1 ± 4.5 years. 67.8% of patients developed LN. The 5- and 10-year survival rates for the total cohort were 97.4% and 96.3%, respectively, and were 96% and 92%, respectively, for those with LN [(6)]. LN prevalence is higher in childhood SLE (cSLE) than in adult-onset SLE. Up to 80% of cSLE patients develop LN within 5 years of diagnosis, with more active lesions than adult LN [(7)].

Prognosis:

Over the past 4 decades, changes in the LN treatment and general healthcare have greatly improved both renal involvement and overall survival. The mortality rate has declined from 11.1 in 1995-1999 to 6.7 per 100 patients in 2010-2014. Deaths due to cardiovascular disease declined by 44% and deaths due to infection declined by 63% [(8)]. Certainly, mortality rate is higher in LN patients than SLE patients without LN. Death caused directly due to renal disease occurs in 5-25% of proliferative LN patients (class III, IV, or III/IV + V) which are also at higher risk of developing ESRD. A complete clinical response is essential for preserving long term kidney health as it has 92% kidney survival at 10 years compared to 43% in partial responders and 13% in non-responders [(5)]. Regarding to mortality rates, **Moghazy and Ibrahim, 2021** [(9)] had found that 14.7% of deaths in SLE were of renal causes.

Sadly, LN is usually unrecognized before full-blown nephritis and/or renal flare nephrotic syndrome emerges. Moreover, current therapies for LN are not sufficiently efficacious in inducing remission or preventing new flares and not all patients show adequate treatment responses. In fact, fewer than 30% achieve complete remission within 6 months of therapy. Despite decelerating rates over the last decades, up to 20% of patients who have been afflicted by LN will ultimately develop ESRD within the first decade of their disease course. For these reasons, the need for reliable predictive biomarkers of LN had grown, as early prediction of LN will help in early diagnosis and better response to therapies, which in turn will help in decreasing ESRD developing rates and mortality rates [(10)].

Soluble Urokinase Plasminogen Activator Receptor (suPAR):

Generation of suPAR:

Plasminogen activation system (PAS) is an extracellular proteolytic enzyme system which plays an important role in many physiological and pathological processes, such as extracellular matrix degradation,

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cell migration, tissue remodeling, wound healing, inflammation, and tumor cell migration. This system consists of two main plasminogen activators which are urokinase plasminogen activator (uPA) and tissue plasminogen activator (tPA), beside the plasminogen activator inhibitor 1 (PAI-1) and 2 (PAI-2), and the protease nexin-1 (PN-1) [(11)]. Plasminogen activators uPA and tPA are serine proteases, their main function is catalyzing of the conversion of plasminogen into plasmin via proteolytic cleavage of its zymogen. Plasmin is a broad-spectrum protease; it has an important role in fibrinolysis and extracellular matrix degradation [(12)].

uPA is synthesized in kidneys by large amounts, and present in blood and extracellular matrix (ECM). uPAR is a membrane-bound receptor that interacts with uPA and many other soluble and membrane proteins as vitronectin, integrins, and thrombospondin. It has three extracellular domains (D1, D2 and D3) linked to a glycosylphosphatidylinositol (GPI) anchor in the cell membrane. Cleavage of uPAR from cell surface by proteases at GPI anchor release a soluble form of uPAR called soluble urokinase plasminogen activator receptor (suPAR). GPI anchor cleavage is regulated by various proteases as GPI-specific phospholipase-D (GPI-PLD), transmembrane phospholipase-C GDE3, cathepsin G and phosphatidylinositol-specific phospholipase-C [(13)].

Structure of suPAR:

Soluble urokinase plasminogen activator receptor (suPAR) is found in three forms, full-length suPARI-III, which is almost structurally identical to uPAR as it contains three domains (D1, D2 and D3) of uPAR, suPARI and suPAR Ⅱ-III which are formed by cleavage of the link between D1 and D2-D3 resulting in fragment D1 (suPARI) and fragment D2-D3 (suPAR Ⅱ-III). suPARI-III has a molecular mass of 55-60 KDa. It can still bind to uPA as the uPA-binding domain D1 is still present and also can still bind to vitronectin in a complex with uPA. The suPARI has a molecular mass of 16 KDa. It also can still bind to uPA but in a very weak form as D3 is required for strong binding. It has a very short half-life and so a very limited expression. The suPAR Ⅱ-III has a molecular mass of 40-45 KDa. It may be generated by cleavage from membrane-bound uPAR or from suPARI-III [(14)].

Physiological role of suPAR:

The exact physiological role of suPAR is still unclear. However, there are strong evidences that suPAR act as chemotactic agent. It can activate G protein-coupled chemotactic receptor FPRL1/LXA4R. Production of suPAR Ⅱ-III by neutrophils at acute inflammation site shares in chemotaxis of monocytes to site of inflammation during the inflammatory response [(6)].

Direction of signaling induced by suPAR is affected by type of cell and different suPAR fragments. Full-length suPAR downregulates promigratory signaling in cells where uPA-uPAR is active. This downregulation takes place by competitive displacement of the uPA-uPAR complex from signaling adaptor proteins. The suPAR Ⅱ-III has more signaling activity, mostly because it has a similar signaling ability like that of uPA [(13)].

Serum suPAR as an inflammatory marker:

Serum suPAR is a novel inflammatory biomarker that reflects inflammation and immune activation. While healthy individuals have low blood levels of suPAR, it is elevated in various acute, chronic, non-communicable and infectious diseases. Most of common inflammatory biomarkers are short-lived and rapidly up and down-regulated, which may complicate chronic inflammation assessment precisely. In contrast with CRP, which is the gold-standard inflammation marker, suPAR seems to be more correlated with chronic rather than acute inflammation, as suPAR is not an acute phase reactant and is less rapidly affected by acute changes and short-term events. In addition, high blood levels of suPAR are more associated with early-life stress factors (as adverse childhood experiences, early-life stress and violence)

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and poor health habits (as unhealthy diet, smoking, and physical inactivity) than CRP and IL-6 [15] [16].

Furthermore, suPAR is considered as a prognostic marker that is important to predict the course of disease and response to the therapy. The higher the suPAR level, the worse the prognosis. In several diseases, suPAR level discriminates non-survivors from survivors. There are evidences of association between high levels of suPAR and mortality in both healthy and patients' populations. As suPAR is still a relatively new clinical biomarker, its application into clinical guidelines is still lacking. However, it is expected to be involved in new clinical guidelines as an important chronic inflammation marker and a prognostic marker with a well-described association with mortality, which of course will help in clinical decision making [15].

Serum suPAR and kidney diseases:

Chronic kidney disease (CKD) is defined as gradual kidney damage lasting for more than 3 months. In 2017, the global prevalence of CKD was 9.1%, CKD resulted in 1.2 million deaths and was the 12th leading cause of death worldwide [17]. Recently, suPAR has been linked to renal diseases, first in focal segmental glomerulosclerosis (FSGS), then as a predictor of the rate of progression in CKD. In renal biology, there is evidence that uPAR binds to and activates b3 integrin on the podocyte cell surface, leading to changes in podocyte motility and proteinuria in mouse models. However, it has not been established that suPAR directly causes proteinuria in humans, despite of high circulating levels of suPAR in different kidney diseases. The source of high circulating suPAR is difficult to confirm in CKD human patients. However, there are data that uPAR is upregulated in different kidney diseases, as minimal change disease, diabetic nephropathy (DN) and immunoglobulin A nephropathy, in glomeruli and tubules, raising the possibility that some of the increased suPAR production could arise from the kidney itself. Also, high levels of suPAR have been found in renal biopsy samples, especially in DN correlating with increasing proteinuria and with severity and staging of DN [13]. Plasma level of suPAR has been found to be significantly higher in CKD patient group compared to healthy individuals in several studies, even in stage 1 CKD patients, suPAR was higher than control group despite of normal serum creatinine, blood urea, and GFR. This shows that suPAR is a promising biomarker of progression of CKD [18].

World widely, about 2 million people suffering from ESRD with increasing rate 5-7% per year and mortality rate 15-20%. As inflammation and innate immunity are linked to mortality and cardiovascular (CV) complications in ESRD patients, suPAR has been found to be a strong predictor for all-cause and both CV and non-CV mortality in ESRD patients as it is strongly linked to innate immunity activation, atherosclerosis and CV events in various populations [19].

According to the National Organ Procurement and Transplantation Network, the kidney transplant with a living-donor (LD) kidney success rate was reported as 97% at 1 year and 86% at 5 years and after transplant with a deceased-donor (DD) kidney was 96% at 1 year and 79% at 5 years. Serum suPAR is improved significantly after kidney transplantation with increasing renal functions. However, high serum suPAR levels after one year of transplantation is an independent risk factor for decreasing GFR >30% in the following three years [21].

Serum suPAR as a Predictor of Renal Damage in Systemic Lupus Patients:

SLE disease activity assessment remains challenging due to lack of reliable biomarkers and disease heterogeneity and differentiation between ongoing inflammation and permanent organ damage can be difficult. There is significant association between high serum suPAR levels and organ damage in SLE patients comparing with C-reactive protein (CRP) levels which have no association

with any isolated organ damage. In addition, suPAR acts as a predictor of organ damage in recent-onset lupus patients. Patients with high score on the Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology (ACR) Damage Index (SDI) ≥1 have higher levels of circulating suPAR. These data are strengthening the value of serum suPAR as indicator and predictor of organ damage in SLE patients [(21)].

Several studies had proved the relation between suPAR and SLE disease activity and renal damage in SLE patients. suPAR levels had been proved to be higher in SLE patients than controls and corelated with disease activity [(22)]. SLE associated organ damage, specifically renal damage and musculoskeletal damage, have a great impact on suPAR levels in recent studies [(21)]. suPAR had been found to be negatively correlated with GFR in LN patients, higher in nephrotic syndrome patients and shows a significant association with different histopathological classes of LN as it was the highest in proliferative LN especially class IV [(23)].

LN is generally caused by immune-complex deposition and complement activation which result eventually in glomerular damage. Podocytes injury had been observed in different classes of LN histologically, as there are strong evidences that podocytes are targets for immune-complex deposition either directly or indirectly. As podocytes genetics play an important role in podocytes injury in LN pathogenesis, **Hayek et al., 2017** [(24)] had found that suPAR considers as a potential injury molecule in LN contributing podocytes damage by direct interaction with pathogenic variants of apolipoprotein L1 (ApoL1) shown to be associated with integrin activation and podocyte detachment [(24)]

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