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A comparative study of Integrin-linked kinase 1 and anti-smith antibody as diagnostic biomarkers in Iraqi patients with systemic lupus erythematosus

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Abstract

Systemic lupus erythematosus (SLE) is the prototypical multisystem autoimmune disease, with a broad spectrum of clinical manifestations affecting virtually all organs and tissues. Determination of integrin-linked kinase 1 (ILK-1) and anti-smith antibody (ASAB) levels in serum of Iraqi patients with systemic lupus erythematosus; that ILK-1 may serve as a diagnostic marker for SLE disease; and evaluation of the impact of systemic lupus erythematosus on renal function in these patients. This study included 100 female patients with systemic lupus erythematosus from the Rheumatology Unit at the Baghdad Teaching Hospital, Medical City, (Baghdad), as well as 30 healthy females without any chronic diseases who served as the control group. All study participants' ages ranged between 18 and 48 years. Using Rheuma Helper, all patients were classified based on the SLE disease activity index (SLEDAI) severity into 30 female patients with mild stage (G1), 40 female patients with moderate stage (G2), and 30 female patients with severe stage (G3). (G3). **Results:** As compared to the control (C) group, the G1, G2, and G3 patient groups in the current investigation showed a substantial increase in the levels of dsDNA, ANA, ASAB, ILK-1, urea, and uric acid. Comparing the control group to G1, G2, and G3, the levels of creatinine did not differ. The current results showed that there were various significant comparisons between ILK-1 and other study parameters in the control and patient groups. ROC test for ILK-1 and ASAB markers showed a perfect cut-off value with 100% sensitivity and 100% specificity. **Conclusions**: TK-1 may be helpful as a novel biomarker in the diagnosis of SLE disease, and there was a positive correlation between ILK-1 with urea and creatinine which are considered factors of renal damage. As a result, these patients may be at risk for renal failure at a severe stage. This indicates that SLE disease has an impact on kidney function.

Keywords:

systemic lupus erythematosus, integrin-linked kinase 1, anti-smith antibody, lupus nephritis

Systemic lupus erythematosus (SLE) is the prototypical multisystem autoimmune disease with a broad spectrum of clinical manifestations affecting nearly all organs and tissues. Some researchers have suggested

that SLE reflects a syndrome rather than a single disease as a result of the high variety of the condition. With a 9:1 female predominance, it is more common among women of childbearing age [1] There is a possibility that SLE will affect any body tissue or cell. The following systems were affected: skeletal, hematological, cutaneous, renal, vascular, nervous, gastrointestinal, pulmonary, and ocular[2] . Uncertainty surrounds the precise etiology of this disease. The excessive production of damaging autoantibodies by B cells and the dysregulation of cytokines that results in damage to tissue and organs are all indications of immune responses that are triggered by a combination of environmental and inherited variables, claims the research. Antibodies to cytoplasmic and nuclear antigens are indicative of SLE [3]. Age, gender, and ethnicity have a significant effect on the clinical outcome and management of the condition. SLE is more prevalent in women than in men, but men's disease progresses more rapidly and severely, resulting in a poor prognosis[4]. Anti-dsDNA, anti-RNA, anti-RNP, anti-Smith antigen (anti-Sm), and anti-nucleosome autoantibodies are detected in SLE patients. Antibodies are a crucial component of the disease. The diagnosis of SLE as a disease mediated by B lymphocytes follows. These antibodies are included in the most recent revisions to the classification criteria for SLE because they are a specific autoantibody detected only in SLE patients.[5]. Anti-Sm antibodies have historically and continue to be a component of the SLE classification parameters. They are exclusively generated in SLE patients and are targeted at the same proteins that make up RNP antibodies' shared nucleus.[6]

Instead of being a singular protein, the Sm antigen is a protein complex made up of several constituent proteins. All cells' nuclei have been found to exhibit the proteins SmB1 (SmB), SmB2 (SmB'), SmB3 (SmN), SmD1, SmD2, SmD3, SmE, SmF, and SmG..[7].

Integrin-linked kinase (ILK) is a multifunction molecular participant in cell adhesion, cell-matrix connections and cell development that is reliant on anchoring. It combines the roles of a signal transmitter and a scaffold protein by interacting with integrins and making it easier for other proteins to join the ILK-PINCH-Parvin complex. ILK takes part in fundamental cellular functions like multiplying, enduring, dividing, moving, infiltrating, and sprouting, which result in systemic alterations in the kidney, heart, muscle, epidermis, and arterial system as well as throughout fetal development. ILK is still a key component of focal adhesion and is frequently present on cell membranes.[8]. The most prevalent version of β1 interacts with signaling proteins like integrin-linked kinase (ILK), focal adhesion kinase (FAK), and adapter proteins as well as focal adhesion complex proteins like -actinin and talin. Particularly ILK has been demonstrated to be essential for the development and upkeep of the integrin-actin link [9]. and sustained upregulation of ILK in murine podocytes caused a substantial behavioral shift in mouse progressive glomerulosclerosis as well as a reduction in matrix adherence.

One of the most prevalent and well-known clinical symptoms of SLE is lupus nephritis. About 50% of people with SLE experience it as one of the initial symptoms[10]. The most frequent cause of renal dysfunction in SLE, although not the only one, is lupus nephritis (LN), which impacts 50% of SLE patients[11]. Those with SLE who also have LN usually manifest sooner than those with SLE who do not have nephritis. LN may also be present at the time of the initial diagnostic and appears early in the course of the illness, frequently in the first 6 to 36 months[12]. Lupus nephritis (LN), a frequent and serious sign of systemic lupus erythematosus (SLE), affects the kidneys in affected individuals[13]. LN incidence is believed to range from 35 to 60%and depends on factors like age, gender, and race. From silent sickness to rapidly advancing nephropathy, the clinical appearance differs widely[14].

Materials and Methods

Study design and patients' selection

Study design: From September 2022 to February 2023, the present analysis cross-sectional research was conducted at the rheumatologist department of the Baghdad Teaching Hospital in Medical City (Baghdad). Thirty participants acted as subjects in the present research, which included 130 participants with ages varying from 18 to 48. Of these, 100 participants were female patients with systemic lupus erythematosus (SLE). Each SLE patient had their diagnosis determined by a rheumatologist based on their clinical

examinations and test results.Using Rheuma Helper, all patients were categorized into the following categories based on the seriousness of their condition as determined by the SLE disease activity index (SLEDAI):1. Thirty female patients with mild stage as (G1).

2. Forty female patients with moderate stage as (G2).

3. Thirty female patients with severe stage as (G3).

Rheuma Helper is an application in smart phone is based on the existence of 24 descriptors during the course of the past 10 days in nine organ systems (Petri et al., 2005).

Sample collection:

The venous blood were obtained from patients and healthy volunteers. Then serum was frozen for using later in laboratory assessments, which encompassed dsDNA, ANA, ILK-1, (anti-Sm) antibodies, urea, creatinine, and uric acid in serum. Samples and data collection is subject to the ethics of scientific research. Participants consent was taken for inclusion in the study.

Exclusion criteria: Male, and all females' patients who suffer from other autoimmune diseases such as (rheumatoid arthritis and scleroderma), thyroid diseases, hematological diseases, pregnant women and tumors.

Statistical Analysis

The information was displayed as mean standard error of mean. (SEM). The sick and control groups were contrasted using the student t-test, the LSD test, and the Pearson correlation coefficient. Statistics were deemed to be significant when the P-value was ($P > 0.05$) or ($P \leqslant 0.05$), respectively. The receiver operating characteristics (ROC) graph was used to calculate the cut-off number, sensitivity, and specificity.

Results

dsDNA, ANA, (anti-Sm) antibody, urea, creatinine, and uric acid levels were found in SLE female patients with mild disease activity as (G1), SLE female patients with moderate disease activity as (G2), and SLE female patients with severe disease activity as (G3), as well as in the control (C) groups. The present study's findings show a significant ($P \leqslant 0.05$) increase in dsDNA and ANA levels in patient groups G1, G2, and G3 when compared to the control group (C), but no significant ($P > 0.05$) variations in dsDNA and ANA levels between patient groups. Additionally, there was a significant ($P \leqslant 0.05$) rise in anti-Sm antibodies and ILK-1 levels in the patient groups G1, G2, and G3 compared to the control (C) group; however, there were no significant ($P > 0.05$) variations in anti-Sm antibodies and ILK-1 levels between the patient groups.

In all phases of disease activity, data in Table (1) revealed a significant ($P \leqslant 0.05$) increase in urea and uric acid levels in patient groups when compared with the control group (c), but no significant ($P > 0.05$) difference in urea and uric acid levels between patient groups. When compared to the control group (c), creatinine levels in the G1, G2, and G3 groups did not vary, but the difference between the G2 and G3 groups was significant ($P \leqslant 0.05$).

As shown in table 2, the present findings revealed several statistically meaningful differences between ILK-1 and other research factors in the control and sick groups.

This result was similar to the ROC test for ASAB (the common parameter in the diagnosis of SLE), which suggests that ILK-1 may be considered a good diagnostic marker for SLE disease in addition to ASAB. ROC test for ILK-1 marker showed a perfect cut off value with 100% sensitivity and 100% specificity (Table 3 and figure 1), and this result was similar to the ROC test for ASAB. (Table 4 and Figure 2).

Discussion

Evaluation of disease activity in lupus erythematosus is crucial for the clinician because it provides the basis for treatment options. Disease activity must be distinguished from injury, as this distinction has crucial implications for long-term prognosis and treatment. In the context of long-term observational studies, the Disease Activity Index (SLEDAI) and other validated global activity indices have been developed and shown to be significant predictors of harm and mortality, as well as indicators of disease activity change. Moreover, they have been validated against one another[15]. The astonishingly high prevalence of SLE in females suggests that sex

variables, specifically hormones and genetic factors, play a crucial role in the disease's etiology and pathogenesis. Due to the scarcity of SLE in males, physicians should have a low investigational threshold in order to avoid delayed diagnosis[16].

Systemic lupus erythematosus (SLE) is frequently found in young women of reproductive age. Peak incidence in men occurs between 45 and 60 years of age, whereas it occurs between 20 and 30 years of age in women. The disparity in ages at presentation may indicate that physicians have less suspicion for the diagnosis. Men's illness is more severe, with brief relapse rates[17].

Rare antibodies in the blood are one of the most prevalent symptoms of lupus. Although the causes of systemic lupus erythematosus are unknown, medications, ultraviolet radiation, viruses, and heredity are all possible contributors[18] . Antinuclear antibody (ANA) testing, which is sensitive but not specific for SLE, and other autoantibody tests must be positive. Anti-Sm and anti-DNA antibody tests are required for a precise diagnosis of SLE disease.[19]. Both the activation of B-cells, which are hyperactive and more prevalent in lupus patients, and plasma cells, which secrete immunoglobulin in the peripheral blood, contribute to the production of antibodies[20]. Anti-Sm antibodies, however, are frequently present before a diagnosis of SLE and are particularly specific for the disease. Both the old and new SLE categorization criteria rely heavily on these factors[21]. Anti-Sm antibodies are relatively specific for SLE, especially those that target the SmD antigen; however, their sensitivity is limited. Anti-Sm antibodies' clinical relevance is still up for dispute. Anti-Sm antibodies in SLE patients target primarily the SmB (B1, B2, and B3) and SmD (D1, D2, and D3) proteins, which are believed to be the most disease-specific antigens.[22]. Focal adhesions are formed with the help of a protein kinase called integrin-linked kinase (ILK), which is an adaptor protein that connects the cell's exterior to the extracellular matrix. Interestingly, ILK modulates the activation and transmits signals of two downstream targets, Akt and glycogen synthase kinase 3 (GSK3), in a phosphatidylinositol 3-kinase (PI3K)-dependent manner route. Both our own research and that of others have pointed to ILK as a proinflammatory molecule essential for NF-kappaB activation and inflammatory signaling[23]. Inegrin-linked kinase (ILK) is a serine/threonine kinase that controls cell cycle progression, survival, migration, and invasion. Protein kinase B/Akt and other proteins are phosphorylated by ILK, and this phosphorylation regulation is known to be a mechanism by which ILK performs its tasks. Through its serine/threonine kinase activity, ILK stimulates many signaling pathways downstream of integrins[24]. The findings of Afsar et al. (2017) indicate that ILK is required for the migration of neutrophils from the bloodstream to sites of inflammation. Signaling mediated by integrins is crucial for promoting leukocyte emigration from peripheral tissues.[25] . In the Sergio de Frutos et al. (2019) study, they used a mouse experimental model in which ILK was transgenically reduced at both the beginning and end of the disease to evaluate the essential role of ILK in the etiology and progression of chronic renal diseases. (CKD). Our findings indicate that ILK expression in renal tissue increases as CKD progresses, and this increased ILK content is positively correlated with a large number of molecules deemed to be renal impairment indicators or contributors. ILK depletion eventually halts the progression of renal disease.[26]. integrin-linked kinase (ILK), an important scaffold protein linking extracellular matrix (ECM) and intracellular signaling pathways, is involved in a variety of pathophysiological mechanisms during kidney injury. The most common organ afflicted by autoimmune disease is the liver Systemic Lupus Erythematosus (SLE) patients with lupus nephritis (LN) have a dismal prognosis overall. Lupus nephritis (LN) is the most prevalent organ affected, and is associated with a poor prognosis for patients with SLE[27]. One of the most common clinical complications is lupus nephritis (LN), which affects up to 74% of SLE patients. It increases morbidity and mortality significantly, particularly among ethnic minorities. According to the current paradigm, LN is caused by immune complex deposition in the renal glomeruli, which activates complement, causes chronic inflammation, and ultimately results in renal insufficiency, which is identified by histology, proteinuria, and cellular casts[28]. The significance of genetic variation in the etiology of SLE and LN is now better supported by data [29]. SLE and LN have a genetic basis, as supported by multiple indirect lines of evidence. Monozygotic twins are projected to have a 24%–35% higher incidence of SLE concordance than

dizygotic twin pairs (2%–5%), according to twin studies[30]. There was a significant difference in the levels of urea and creatinine between male and female SLE patients with lupus nephrotic syndrome, which is consistent with previous research indicating that men have a greater risk of developing certain conditions. In cases with more severe lupus nephritis, the following multivariate logistic regression analysis was conducted to investigate the relationships between urea, creatinine, and other factors, taking gender into account. Males were positively independent risk variables for blood creatinine levels after accounting for other characteristics, which was a surprising finding. Independent of renal function impairment, this finding revealed that sex hormones may interact with creatinine but not with urea or uric acid. This finding may also suggest that being a male may enhance the severity of lupus nephritis by increasing creatinine levels, at least in part.[31].

In SLE, damage may be caused by the disease itself or by medication treatment. There is currently no index to quantify the effects that medications have on lupus patients. The change must have been noticeable for at least six months and be confirmed by clinical or simple examinations. According to research, early development of injury is indicative of a poor prognosis.[32].

Conclusions

This study was the first to determine human serum ILK-1 levels in female patients with SLE disease by evaluating previous literature. TK-1 may be useful as a novel biomarker for the diagnosis of SLE disease, as the current study demonstrated a highly significant increase in ILK-1 levels in SLE patients compared to healthy controls. The levels of urea, creatinine, and uric acid increase in patients with SLE, particularly in the severe stage, and there is a positive correlation between ILK-1 and urea and creatinine, which are considered indicators of renal injury. This indicates that SLE disease has an effect on kidney function, and therefore these patients may be at risk for kidney dysfunction at this stage.

Table 1. Mean ± SEM of levels of studied parameters in control (C) , and SLE patients groups G1, G2, and G3.

Groups / Parameters	C No.(30)	G1 No.(30)	G2 No.(40)	G3 No.(30)
dsDNA	7.0±0.61	68.56±1.86 *a**	75.38±2.33 *a**	80.70±3.50 *a**
ANA	0.32±0.03	1.45±0.07 *a**	2.09±0.50 *a**	2.12±0.22 *a**
ASAB	1.06±0.27	23.94±1.65 *a**	24.94±1.36 *a**	24.10±1.74 *a**
ILK-1	306.00±21.29	1299.15±83.42 *a**	1324.18±75.69 *a**	1261.36±89.76 *a**
Urea	33.65±1.07	51.42±1.12 *a**	51.91±0.90 *a**	51.51±0.85 *a**
Creatinine	0.71±0.02	0.75±0.07	0.62±0.02	0.86±0.12 *d**
Uric Acid	4.35±0.10	6.95±0.11 *a**	7.17±0.10 *a**	7.17±0.12 *a**

^{a}LSD test between patients groups and control, ^{d} LSD test between G2 and G3 patients.
*Significant: * $P \leq 0.05$; No significant: $P>0.05$.*

Table 2. Pearson correlation coefficient (r) and P-value between ILK-1 and all studied parameters in control and SLE patients groups.

Parameters	Control		Patients groups	
	r	P-value	r	P-value
dsDNA	0.267	0.000	-0.065	0.000
ANA	-0.010	0.000	0.030	0.000
ASAB	0.699	0.000	0.345	0.000
Urea	0.504	0.005	0.012	0.907
creatinine	0.234	0.212	0.135	0.181
Uric acid	-0.181	0.337	-0.292	0.003

*Significant: * $P \leq 0.05$; No significant: $P>0.05$.*

Table 3. Sensitivity, specificity & cut-off value of ILK-1 for diagnosis of SLE.

Test results	Area under curve%	Sensitivity %	Specificity %	Cut-off value	Asymptotic Sig.	Accuracy	
						Lower Bound	Upper Bound
ILK-1	100%	100%	100%	534.5	.000	1.0	1.0

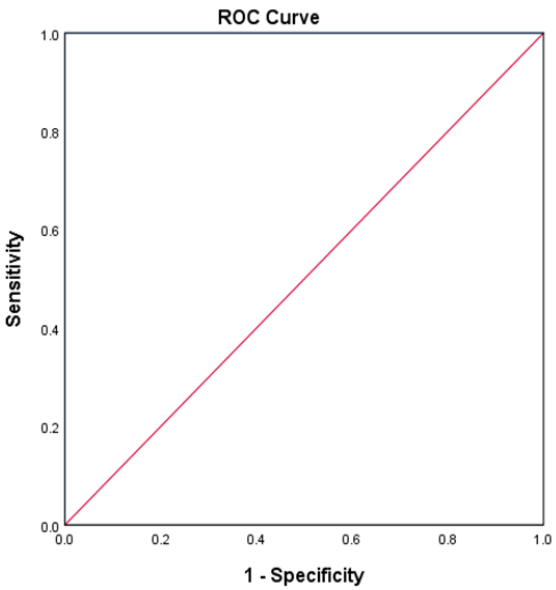

Figure 1. The Roc curve of ILK-1 in SLE and control groups

Table 4. Sensitivity, specificity & cut-off value of ASAB for diagnosis of SLE.

Test results	Area under curve%	Sensitivity %	Specificity %	Cut-off value	Asymptotic Sig.	Accuracy	
						Lower Bound	Upper Bound
ASAB	100%	100%	100%	3.96	.000	1.0	1.0

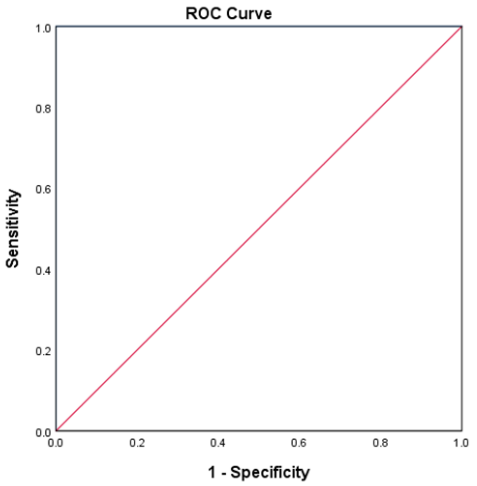

Figure 2. The Roc curve of ASAB in SLE and control groups

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