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Original Article

Impact of serum level of Dickkopf-1 in patients with Lupus nephritis

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ABSTRACT

Background: Early management of lupus nephritis (LN) depends on accurate and early diagnosis. Laboratory biomarkers such as Anti ds-DNA antibody and complement are not sensitive or specific enough for prediction of lupus nephritis flare. This study aimed to evaluate the value of the serum level of Dickkopf-1 in the diagnosis of systemic lupus erythematosus (SLE) and LN.

Subjects and methods: This case-control study was carried out on forty-two SLE patients, 21 of them were complicated with nephritis (proved by renal biopsy), and 21 healthy age and sex matched individuals as a control group. Serum DKK-1 concentration was measured, for all participants, by enzyme linked immunosorbent assay (ELISA).

Results: SLE patients (nephritis and non-nephritis) had significantly higher serum DKK-1 levels (median was 56.3 ng/ml in nephritis group and 112 ng/ml in non-nephritis group) than healthy controls (median was 44.4 ng/ml) P-value 0.003, also Serum DKK-1 level was significantly higher in non-nephritis group as compared to nephritis group P-value = 0.001. Serum DKK-1 level was negatively correlated with 24-hour urine proteins (p-value <0.001).

Conclusions: Serum Dkk1 may be a highly sensitive and specific SLE diagnostic marker that is dependable, promising, and non-invasive. It has a good sensitivity for LN diagnosis. Further studies are still needed to ensure these findings.

Keywords: Biomarkers; DKK-1; Dickkopf-1; Lupus nephritis; Systemic lupus erythematosus

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease. It is characterized by the presence of autoantibodies against self-antigens forming an antigen-antibody complex which then causes various organ damage; its clinical course can vary between exacerbation and remission [1].

The kidney is a major organ affected by SLE and Lupus nephritis (LN) is a severe sequelae of SLE [2]. The molecular basis for the onset and development of LN is mainly unclear [3]. The Wingless (WNT) signaling pathway is important in the growth and physiology of different body organs [4]. According to recent researches suggesting the importance of the WNT signalling pathway in preserving the homeostasis of the renal extracellular matrix, this system may be involved in the predisposition to LN [5].

The WNT signaling pathway was suggested to be implicated in the generation of some autoimmune diseases, such as rheumatoid arthritis RA, SLE, LN, and ankylosing spondylitis (AS), as it is involved in the formation of immune cells [6].

Aberrant WNT signaling will cause excessive production of matrix metalloproteinases (MMPs) and result in the rebuild of the extracellular matrix and the glomerular membrane integrity will be reduced [7].

Extracellular antagonists can influence WNT signalling, including the Dickkopf (DKK) family, which consists of four proteins, DKK-1, DKK-2, DKK-3, and DKK-4, which are produced as primitive proteins and activated by the breakdown of protein bonds [8]. The DKK-1 proteins are group of this family, which can block WNT signalling and have thus been regarded as prospective targets in disorders characterized by abnormal WNT signalling activity [9].

Many investigations have shown that auto-antibodies to double-strand DNA (dsDNA), histone, and complement were closely connected with renal disorders in SLE patients and might be utilized to predict the prognosis of individuals with LN [10]. However, non-LN patients and SLE patients with clinically inactive SLE were also shown to have antibodies to dsDNA and a decrease in complements in a rather high percentage. Therefore, it was crucial to look for more reliable biomarkers for diagnosing SLE cases with active LN [11].

Diagnosis, prognosis, and therapy of LN have mainly depended on renal biopsy, but renal biopsy has some disadvantages; being costly, risky, and invasive procedures [12].

This made the search for novel, available, and noninvasive biomarkers for LN diagnosis and prognosis is mandatory [13].So, this work aimed to assess the role of DKK-1 as a biomarker for the detection of lupus nephritis in SLE patients and its relation to disease activity.

SUBJECTS AND METHODS

SUBJECTS:This case-control study was carried out at Clinical Pathology and Rheumatology Departments, Zagazig University Hospitals from December 2021 to December 2022.

Inclusion criteria: Adult patients ≥ 18 years diagnosed with SLE according to the American College of Rheumatology (ACR) criteria for SLE were included.

Exclusion criteria: Patients who were younger than 18 years old, refused to participate in the study,and patients with other rheumatological or autoimmune diseases, or with any other chronic kidney disease were excluded.

The current study was approved by the Zagazig University- Institutional Review Board (ZU-IRB) (#8040/31-8-2021). This work has been carried out following The Code of Ethics of the World Medical Association (Declaration of Helsinki). Written informed consent was obtained before carrying out the study.

METHODS

Data collection and Routine laboratory investigation: All participants in this study underwent a thorough history taking, thorough clinical examination, and laboratory tests, including both routine laboratory tests (the complete blood count, liver and kidney functions, a full urine analysis, and 24 h urinary proteins) and immunological

laboratory tests (the erythrocyte sedimentation rate, C3, C4, CRP, ANA, and anti-dsDNA).

Diagnosis of SLE and Lupus nephritis: SLE was diagnosed according to the new 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for SLE (EULAR/ACR). Lupus nephritis was confirmed by renal biopsy.

Assessment of SLE activity: The SLE disease activity in patients was assessed each visit by SLE disease activity index 2000 (SLEDAI-2K) which measures the disease activity within the last 10 days.

Patients disease activity were defined as no activity SLEDAI score = 0, mild activity SLEDAI score 1 – 5 , moderate activity SLEDAI score 6 – 10, high activity SLEDAI score 11 – 19 and very high activity SLEDAI score > 20 [14].

Measurement of DKK-1 serum level : Two milliliters of whole blood were collected into plain tubes from controls and patients upon diagnosis; separated sera were stored at -20°c until analysis, Serum levels of Dickkopf-1 (DKK1) protein were assayed for both patient and control groups using human DKK-1 ELISA kit (Sun Red) that depends on the sandwich ELISA technique.

STATISTICAL ANALYSIS

Data was analyzed using SPSS version 26. Numbers and percentages are utilized to describe qualitative facts. To confirm the normality of the distribution; The range, mean, standard deviation, and median of quantitative data were used. When comparing various groups using categorical data, chi-square or Fisher exact test and Monte Carlo tests when appropriate were employed. Spearman rank correlation coefficients (for not normally distributed data) were used to determine the degree and direction of correlation between two continuous variables. The Kruskal Wallis test (for not normally distributed data) and the one-way ANOVA test (for regularly distributed data) were used to evaluate quantitative data between two groups. The ROC curve was used to establish the best cutoff for a specific quantitative parameter in diagnosing a health concern. The results were significant with $p<0.05$.

RESULTS

This study was performed on 42 patients with SLE and 21 normal volunteers as control, patients were divided into two groups, 21 were presented with LN, and 21 SLE without nephritis, their ages ranged from 19-56 years old, with female predominance "95% of cases were female". Demographic features are presented in Table 1.

There was no significant difference regarding the presenting symptoms of patients among both patient groups except for pleural effusion, which was significantly higher in the LN group. p= 0.03, Cases with LN presented more frequently with high levels of protein, pus cells, RBCs and blood casts in urine. P values (< 0.001, 0.03, 0.03, and 0.04) respectively. Presenting symptoms, urine analysis results and distribution of LN stages are presented in Table 2.

Apart from kidney function tests, 24-hour urine protein, serum total protein, and frequency of AntidsDNA antibody, none of the laboratory tests showed significant differences among the patient groups. Serum creatinine, blood urea nitrogen, and 24-hour protein in urine were significantly increased in the LN group (P value of 0.003, 0.015, and

< 0.001) respectively. Serum total protein was significantly higher in non-nephritis group than LN p (0.03). Positive AntidsDNA antibody was significantly higher in the LN group (group I) than in non-nephritis group (group II). P= 0.013, ANA results were positive in all patients in both groups except for 3 patients in non nephritis group. Those patients were diagnosed as SLE by typical clinical presentation, positive AntiRo (SSA) Ab and low complement level according to old criteria that do not require ANA as entry criteria. Laboratory investigation results are summarized in Tables 3 and 4.

Regarding the serum DKK-1 level, both patient groups had significantly higher levels than normal controls, p<0.001, and non-nephritis group (II) had a significantly higher serum level of DKK-1 than LN group (I), p 0.003, medians and ranges of serum DKK-1 level in all the studied groups are illustrated in Table 5.

By testing the correlation of serum DKK-1 with all the numerical variables in both patient groups it was demonstrated that; there was a statistically negative correlation between serum DKK-1 level and 24-hour urinary protein among patients with LN. P <0.001, data are illustrated in Table 6.

The validity of serum DKK-1 in the diagnosis of SLE and LN was estimated by ROC curve analysis, serum DKK-1 level at cutoff ≥ 51.707 ng/ml could have 78.6% sensitivity for diagnosis of SLE with high significance, 85.7% specificity, and 81% accuracy (p<0.001). Serum DKK1 level at cutoff ≤ 89.3 ng/ml could diagnose LN at a statistically significant level with 85.7% sensitivity, 71.4% specificity, and 78.6% accuracy (p<0.001), data are summarized in Table 7.

Table (1): Demographic data of the studied groups

Parameter	**SLE**		**Group III control subjects n=21**	F	P
	Group I with nephritis n=21	**Group II without nephritis n=21**			
	Mean ± SD	**Mean ± SD**	**Mean ± SD**		
Age (year)	29.67 ± 8.4	35.95 ± 9.99	30.48 ± 8.27	3.084	0.053
Disease duration(year)	8.64 ± 4.96	8.1 ± 5.94	NA	0.105	0.747
	N=21 (%)	N=21 (%)	N=21 (%)	χ^2	P
Gender **Female** **Male**	 20 (95.2%) 1 (4.8%)	 20 (95.2%) 1 (4.8%)	 18 (85.7%) 3 (14.3%)	MC	0.419

Table (2): Clinical data urine analysis, and renal biopsy findings among patients with LN among the studied patient groups

	SLE		χ^2	P
	Group I with nephritis(n=21)	**Group II without nephritis(n=21)**		
Fever	13 (61.9%)	12 (57.1%)	0.099	0.753
Fatigue	18 (85.7%)	15 (71.4%)	Fisher	0.454
Anorexia	**11 (52.4%)**	10 (47.6%)	**0.095**	**0.758**
Weight loss	11 (52.4%)	11 (52.4%)	0	>0.999
Lymphadenopathy	5 (23.8%)	3 (14.3%)	Fisher	0.697
Malar rash	11 (52.4%)	9 (42.9%)	0.382	0.537
Discoid rash	8 (38.1%)	3 (14.3%)	Fisher	0.159
Photosensitivity	13 (61.9%)	12 (57.1%)	0.099	0.753
Oral ulcers	9 (42.9%)	5 (23.8%)	1.714	0.19
Alopecia	10 (47.6%)	7 (33.3%)	0.889	0.346
Vasculitis	8 (38.1%)	4 (19%)	1.876	0.172
Arthritis	20 (95.2%)	18 (85.7%)	Fisher	0.606
Arthralgia	20 (95.2%)	18 (85.7%)	Fisher	0.606
Myalgia	9 (42.9%)	4 (19%)	2.785	0.095
Depression	9 (42.9%)	3 (14.3%)	Fisher	0.085
Seizures	2 (9.5%)	2 (9.5%)	0	>0.999
Neuropathy	6 (28.6%)	3 (14.3%)	Fisher	0.454
Headache	12 (57.1%)	7 (33.3%)	2.403	0.121
Cough	10 (47.6%)	5 (23.8%)	2.593	0.107
Chest pain	4 (19%)	2 (9.5%)	Fisher	0.663
Dyspnea	6 (28.6%)	3 (14.3%)	Fisher	0.454
Pleural effusion	8 (38.1%)	2 (9.5%)	4.725	0.03*
Pneumonia	6 (28.6%)	2 (9.5%)	Fisher	0.238
Serositis	9 (42.9%)	6 (28.6%)	0.933	0.334
Abdominal pain	8 (38.1%)	4 (19%)	1.867	0.172
Hepatosplenomegaly	3 (14.3%)	2 (9.5%)	Fisher	>0.999
Recurrent abortion	5 (23.8%)	3 (14.3%)	Fisher	0.697
Urine analysis				
	SLE	χ^2	P	
	Group I (n=21)	**Group II (n=21)**		
Physical				
Aspect: Clear Turbid	 1 (4.8%) 20 (95.2%)	 7 (33.3%) 14 (66.7%)	Fisher	0.045*
Chemical examination				
PH Abnormal	 11 (52.4%)	 6 (28.6%)	 2.471	 0.116
Protein	17 (81%)	5 (23.8%)	13.745	<0.001**
Sugar	3 (14.3%)	2 (9.5%)	Fisher	>0.999
Microscopic examination				
Pus cells	14 (66.7%)	7 (33.3%)	4.667	0.031*
RBCs	13 (61.9%)	6 (28.6%)	4.709	0.03*
Epithelial cells	11 (52.4%)	7 (33.3%)	1.556	0.212
Blood cast	7 (33.3%)	1 (4.8%)	Fisher	0.045*
Ca oxalate	4 (19%)	7 (33.3%)	Fisher	0.484
Uric acid	3 (14.3%)	6 (28.6%)	Fisher	0.454
Renal Biopsy	N=21		%	
Class I	2		9.5 %	
Class II	4		19%	
Class III	5		23.8%	
Class IV	4		19%	
Class V	3		14.3%	
Class VI	3		14.3%	

χ^2Chi square test *p<0.05 is statistically significant

Table (3): Liver and kidney functions among the studied patient groups

	SLE		T	P
	Group I (n=21)	Group II (n=21)		
	Mean ± SD	Mean ± SD		
Total protein	7.15 ± 0.86	7.68 ± 0.64	-2.249	0.03*
S. albumin	3.92 ± 0.47	4.15 ± 0.52	-1.527	0.135
	Median (IQR)	Median (IQR)	Z	P
T. bilirubin	0.26 (0.18 – 0.6)	0.27 (0.2 – 0.4)	-0.05	0.96
D. bilirubin	0.12 (0.09 – 0.2)	0.11 (0.11 – 0.14)	-0.152	0.88
ALT	14 (9.7 – 22)	15.3 (10.85 – 24.15)	-0.616	0.538
AST	17.5 (12.8 – 22.5)	20.2 (16.2 – 25.65)	-1.535	0.125
Creatinine	0.78 (0.69 – 1.02)	0.55 (0.5 – 0.65)	-2.995	0.003*
BUN	13.4 (11.5 – 25.8)	11.5 (8.2 – 13.1)	-0.088	0.015*
24-hr urinary protein	420 (224.5 – 625)	106.5 (77.6 – 150)	-4.717	<0.001**

ALT: alanine transaminase, AST: aspartate aminotransferase, TLC: Total leukocytes count, D. bil: direct bilirubin, T. bil: total bilirubin, S. albumin: serum albumin,
IQR interquartile range, Z Mann Whitney test t independent sample t test *p<0.05 is statistically significant

Table (4): Complete blood count and immunological markers among the studied patients

	SLE			
	Group I (n=21)	Group II (n=21)		
	Mean ± SD	Mean ± SD		
Platelet count	**289.43 ± 93.11**	**285.48 ± 77.8**	**-1.25**	**0.219**
Hemoglobin	**11.13 ± 1.91**	**11.84 ± 1.79**	**0.149**	**0.882**
	Median (IQR)	**Median (IQR)**	**Z**	**P**
Total leukocytes count (TLC)	**6.4 (5.35 – 9.75)**	**6.5 (4.6 – 9.45)**	**-0.616**	**0.538**
	Mean ± SD	**Mean ± SD**	**T**	**P**
C3	0.973 ± 0.35	1.13 ± 0.36	-1.386	0.173
C4	**0.157 ± 0.1**	**0.21 ± 0.122**	**-1.52**	**0.136**
	Median (IQR)	**Median (IQR)**	**Z**	**P**
ESR	**26 (23 – 38)**	**27 (23.5 – 50)**	**-0.442**	**0.659**
CRP	4.67 (2.5 – 11.45)	8 (3.78 – 12.5)	-0.881	0.379
	N=21(%)	N=21(%)	χ^2	P
Positive ANA	21 (100%)	18 (85.7%)	Fisher	0.232
Positive anti dsDNA	16 (76.2%)	8 (38.1%)	6.222	0.013*

C3: complement 3, C4: complement 4, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, ANA: antinuclear antibody, BUN: blood urea nitrogen, anti-dsDNA: anti-double-stranded DNA antibody, RBCs: red blood corpuscles, Ca: calcium, SLE: Systemic lupus erythematosus.
IQR interquartile range, Z Mann Whitney test t independent sample t test *p<0.05 is statistically significant

Table (5): Serum DKK-1 level among the studied groups

Parameter	SLE		Group III Control group (n=21)	KW	p
	Group I with nephritis(n=21)	Group II without nephritis(n=21)			
	Median (IQR)	Median (IQR)	Median (IQR)		
DKK1 (ng/ml)	56.3(37.46 – 75.45)	112 (85.15 – 132)	44.44 (30.94-51.05)	25.449	<0.001**
Pairwise	P_1 0.003*	P_2 <0.001**	P3 0.047*		

KW Kruskal Wallis test **p≤0.001 is statistically highly significant p1 difference between SLE nephritis and non-nephritis p2 difference between SLE non-nephritis and control group p3 difference between SLE nephritis and control group *p<0.05 is statistically significant

Table (6): Correlation between serum DKK1 and different parameters among the studied patient groups

Parameter	DKK1			
	SLE With nephritis		SLE Without nephritis	
	R	P	R	p
Age	0.174	0.449	0.329	0.145
TLC	-0.087	0.708	-0.141	0.542
Hemoglobin	-0.381	0.088	-0.092	0.690
Platelet count	0.051	0.827	0.283	0.213
T. bilirubin	-0.063	0.786	0.105	0.650
D. bilirubin	-0.074	0.64	-0.249	0.276
Total protein	0.186	0.418	-0.359	0.110
Serum albumin	-0.185	0.48	0.233	0.310
ALT	-0.01	0.967	-0.285	0.211
AST	-0.055	0.812	-0.017	0.942
Creatinine	-0.255	0.264	0.404	0.069
24hr urinary protein (mg/24 hour)	-0.699	<0.001**	-0.241	0.292
Blood urea nitrogen	0.001	0.998	0.216	0.347
CRP	0.183	0.428	-0.136	0.555
ESR	0.022	0.926	-0.267	0.241
C3	0.014	0.951	0.120	0.604
C4	0.105	0.65	0.147	0.525

ALT: alanine transaminase, AST: aspartate aminotransferase, TLC: Total leukocytes count, T.bil: total bilirubin, S. albumin: serum albumin, C3: complement 3, C4: complement 4, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate.
r Spearman rank correlation coefficient **p≤0.001 is statistically highly significant *p<0.05 is statistically significant

Table (7): Validity of serum DKK-1 in diagnosis of SLE and LN among the studied groups

Cutoff	AUC	Sensitivity	Specificity	PPV	
diagnosis of SLE					
≥51.707	0.814	78.6%	85.7%	91.7%	
diagnosis of LN					
≤89.3	0.807	85.7%	71.4%	75%	

SLE: Systemic lupus erythematosus, LN: lupus nephritis.
AUC area under curve PPV positive predictive value NPV negative predictive value

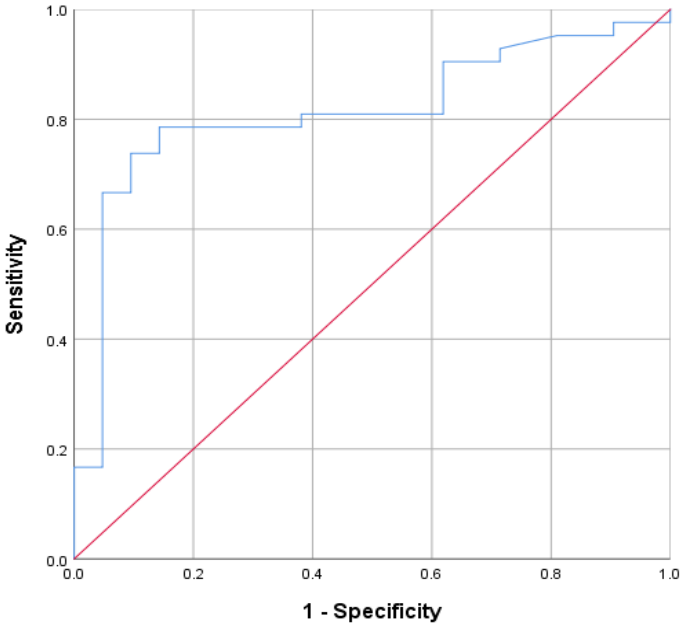

Figure (1) :ROC curve for validity of serum DKK1 in diagnosis of SLE among the studied groups

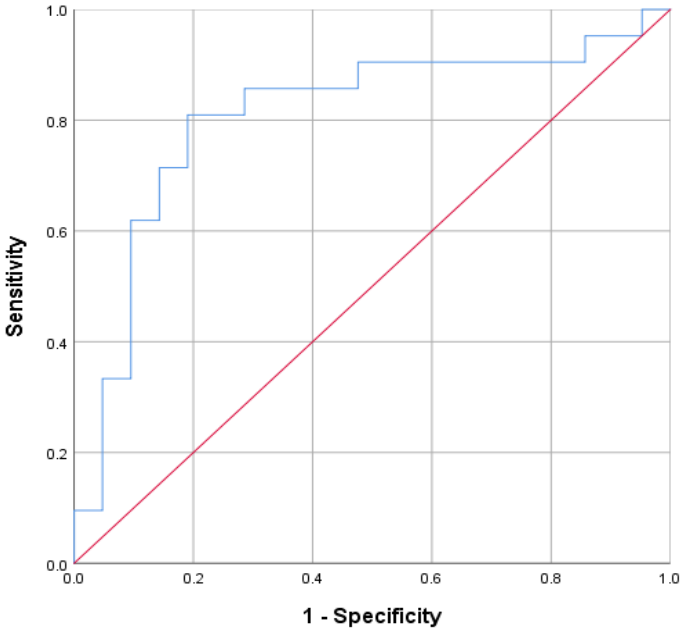

Figure (2): ROC curve for validity of serum DKK1 in diagnosis of LN among the studied patient groups

DISCUSSION

Lupus nephritis is a severe sequelae of SLE and can lead to chronic renal disease and renal failure. The main diagnostic procedure for LN is renal biopsy, however, it is annoying to patients and many patients refuse it [15] **,** this led to the need for search for novel diagnostic markers for SLE and LN among them is DKK-1. This work aimed to assess the value of serum DKK-1 protein in the detection of SLE patients and patients with LN. This study was performed on 42 SLE patients (21 diagnosed with LN, and 21 patients without nephritis) and 21 normal

subjects as a control group. 95% of our patients were females, while only 5% were males.

It has been thought that traditional markers such as Anti-dsDNA antibodies and complements (C3 & C4) reduction were not specific for LN as they present by high percentage in lupus patients without nephritis and lupus patients with low disease activity [16].

In our study, there was a significant increase in 24-hour urinary protein, pus cells, RBCs, and blood casts in LN (group I) as compared to non-nephritis (group II) p values <0.05, This was the same as reported by Kamel et al. [17] who proposed that 24h urinary protein could be important diagnostic marker for lupus nephritis activity. The current work showed that Anti-dsDNA Ab was positive in 16 cases of group I while in only 8 cases of group II and this was statistically significant (p <0.05). These results are near to what was stated by Abdelazeem et al. [18] who reported 20 cases of his LN group were positive anti-ds DNA Ab compared to 1 case of the non-nephritis group (P<0.001).

Renal biopsies for Lupus patients in our work revealed that 43% of our patients were with class III and IV, in the contrast to study of Abdelazeem et al. [18] who stated that class III and IV represent 80% of their patients.

Serum DKK-1 was higher in patient groups (LN and non-LN) than in healthy and this was significant P< 0.001; This was consistent with studies of Xue et al. [19] and Abdelazeem et al. [17] who reported that DKK-1 was higher in serum of SLE patients than control subjects. Serum DKK1 levels in non-LN patients (group II) were significantly higher than in LN patients (group I) p-value =0.003, The same finding was obtained by Hou et al. [20] who reported lower serum DKK1 levels in diabetic nephropathy patients having proteinuria when compared to diabetic patients without proteinuria.

Although some previous studies concluded that the serum level of DKK-1 in patients with LN was more than its level in non-nephritis patients, some of these studies were in different populations and some were experimental as in the study of Tveita and Rekvig [20].

The conflict between previous research and ours can be related to the discrepancy in geographical distribution and genetic differences and the small sample size of our study, Future researches with increasing sample size are needed to ensure or deny our results.

Knowing the role that DKK-1 plays in LN can open the doors to new researches to validate the potential benefits of DKK-1 as a marker for disease diagnosis and even as a goal of therapy [22].

Wang et al. [23] discussed the possible pathogenic mechanisms that may cause nephritis in lupus patients, they demonstrated hyperactive WNT pathway in renal biopsies for a group of SLE patients by immunohistochemistry of glomeruli and western blot technique as compared to normal subjects and patients with some types of renal neoplasms. They claimed that this hyperactivation can be responsible for collagen synthesis and fibrosis in the kidneys of lupus patients, and DKK-1 may preserve kidney function by disrupting the exaggerated amount of matrix metalloproteinase. Dai et al. [24] in the murine model emphasized the implication of hyperactive WNT signaling pathway in the pathological changes that occur in the kidney of LN patients, causing podocyte dysfunction and proteinuria, while DKK-1 protects the kidney by limitation of podocyte lesion and maintaining membrane integrity.

The low serum DKK-1 in our LN patients could be reasoned by an overactive WNT pathway leading to the exhaustion of its antagonist DKK-1 and decreasing in its serum level, this could be shown in our results in a relatively higher level of serum DKK-1 in LN patients with early stages (1-3) more than later stages (4-5), Although the relation between DKK1 and renal biopsy was non significant in our study. due to small number of patients in each group. In agreement with our study, Hamada-Ode et al. [24] showed in their study on chronic kidney disease in Japanese patients that Dkk1 levels

were significantly lower at later Stages 4 and 5 than at early Stages 1–3 B.

The significant negative correlation between serum DKK-1 and 24-hour urine protein among patients with LN P<0.001 goes with a lower concentration of DKK-1 in the serum of patients with lupus nephritis than lupus patients without nephritis and highlights the conclusion of Hou et al., that serum DKK-1 concentrations are independently and negatively correlated with urinary albumin/creatinine ratio and successively decrease with progression of proteinuria.

We suggest that serum Dkk-1 could be a sensitive and specific marker for the diagnosis of SLE, For diagnosis of LN it is a better positive biomarker with high sensitivity.

As our study had some drawbacks such as the low number of patients in each group, and a short period of follow-up, Future studies with a bigger sample size are recommended to confirm the value of DKK-1 in diagnosis of SLE and LN.

Because of the heterogeneity and complexity of LN, It is difficult to depend on one single marker to capture the whole range of features of LN, so we recommend future studies to analyze different molecules that may be involved in disease pathogenesis and so can be applied as a biosignature for disease diagnosis. We recommend measuring DKK-1 in urine and synovial fluid in addition to serum.

CONCLUSIONS

Serum Dkk1 may be a highly sensitive and specific SLE diagnostic marker that is dependable, promising, and non-invasive. Regarding LN ,it is mainly a sensitive marker for LN diagnosis. however, this finding requires confirmation in further studies on a larger scale in the future.

Conflict of Interest: None

Financial Disclosures: None

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