Journal of Advances in Medicine and Medical Research

33(20): 1-13, 2021; Article no.JAMMR.72400
ISSN: 2456-8899
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

Insulin-Like Growth Factor Binding Protein-2 in Systemic Lupus Erythematosus Patients as a Marker of Lupus Nephritis Disease

Zeinab N. ELRefeai ELgody[1*], Ghadah Mahmoud Alghzaly[1], Mohammed Attia Saad Attia[2] and Mohammed Mohammed Albedawey[1]

[1]Internal Medicine Department, Faculty of Medicine, Tanta University, Tanta, Egypt.
[2]Clinical Pathology Department, Faculty of Medicine, Tanta University, Tanta, Egypt.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMMR/2021/v33i2031099
Editor(s):
(1) Dr. Rameshwari Thakur, Muzaffarnagar Medical College, India.
Reviewers:
(1) Bhanu Patibandla, Oregon Health & Science University, USA.
(2) Chun Ouyang, Nanjing Medical University, China.
(3) Enmanuel Jimenez Castro, National University of Costa Rica, Costa Rica.
Complete Peer review History: https://www.sdiarticle4.com/review-history/72400

Original Research Article

Received 06 July 2021
Accepted 16 September 2021
Published 27 September 2021

ABSTRACT

Background: One of the members of Insulin-like Growth Factor Binding Protein family is IGFBP-2 that binds to the Insulin-like Growth Factor (IGF) receptors to regulate IGF biological activities. In nephrotic syndrome IGFBP-2 has also been reported to be increased in children and IGFBP-2 considers as predictor for longitudinal deterioration of kidney function in Type 2 Diabetes. The aim of the work was to assess insulin like growth factor binding protein-2 as a marker for activity of lupus nephritis.
Methods: A cross-sectional study was carried out on 80 subjects and was divided on: Group1: 60 patients with Systemic lupus erythematosus which were subdivided into: (a) 40 Systemic lupus patients with nephritis. (b) 20 Systemic lupus patients without nephritis. Group 2: 20 healthy persons as control (Healthy controls).
Results: there were statistically significant difference in ILGRFBPs2 P1, P2 while P3 was insignificant, Regarding the Systemic Lupus Erythematosus Disease Activity Index (SLEDI) score, there was significant difference between group IA and IB while statistically significant positive

**Corresponding author: E-mail: zeinab.nagib23@gmail.com;*

correlation between ILGFBPs2 and renal SLEDI score. Regarding ILGFBPs2, Anti-ds DNA Ab titer, renal biopsy classes and activity index, there was a statistically significant positive correlation. Regarding chronicity index and renal SLEDI score, there was insignificant correlation.
Conclusion: Serum IGFBP-2 is a promising biomarker for lupus nephritis, reflecting disease activity and chronicity changes in renal pathology.

Keywords: Insulin-like growth factor; lupus nephritis disease; renal pathology.

1. INTRODUCTION

Systemic lupus erythematosus is a chronic auto immune disease in which there is multiple auto antibodies against self-directed antigen and affect many vital organs in the body causing tissue damage and inflammation [1].

Lupus nephritis consider one of the most sever manifestations of systemic lupus erythematosus. It occurs at any age and 20% to 75% of systemic lupus patients develops renal affection [2]. Patients with lupus nephritis are at high risk for developing cardiovascular complications, malignancy and death [3].

One of the members of insulin-like growth factor binding protein family is IGFBP-2 that binds to IGF receptors to regulate the Insulin-like Growth Factor (IGF) biological activities. The second most abundant the Insulin-like Growth Factor Binding Protein (IGFBP) in serum is IGFBP-2 which has both regulatory activities on malignancy and metabolism [4]. IGFBP-2 is expressed in most normal tissues of the body including both humans and animals' glomerulus. In nephrotic syndrome IGFBP-2 has also been reported to be increased in children and IGFBP-2 considers as predictor for longitudinal deterioration of kidney function in type 2 diabetes [5].

The aim of the work is to assess insulin like growth factor binding protein-2 as a marker for activity of lupus nephritis.

2. PATIENTS AND METHODS

This cross-sectional study was carried out on 80 subjects and was divided on: Group 1: 60 patients with Systemic lupus erythematosus (The diagnosis of SLE was established according to ACR criteria for SLE) which were subdivided into: (a) 40 Systemic lupus patients with nephritis (Clinical nephritis was suspected if urine analysis showed proteinuria > 0.5 gm. on a 24-hour urine collection and/or hematuria or cellular casts with or without increased serum creatinine.) (b) 20 Systemic lupus patients without nephritis. Group 2: 20 healthy persons as control (Healthy controls).

The Exclusion criteria was Patients with the chronic kidney disease (CKD) while the Inclusion criteria were SLE patients with and without nephritis.

All the participants were subjected to:

Thorough history taking: Regarding age, sex, associated diseases and duration of the disease. Complete clinical examination: Particularly for the presence of; butterfly rash, photosensitivity, discoid rash, hair loss, oral ulcers, peripheral edema, serositis, arthritis, fever, central nervous system (CNS) affection and hypertension.

Laboratory investigations including:

Complete blood count (CBC)- Erythrocyte sedimentation rate (ESR)- C-reactive protein (CRP)- INR, PT- 24-hour urine collection for proteins- Complete urine analysis- Serum creatinine level- Urinary Albumin / creatinine ratio- Serum C3 and C4 levels- Levels of serum anti-nuclear anti bodies (ANA)- Anti-dsDNA antibodies.

Renal biopsy: for histopathological examination, detection of LN class, activity and chronicity indices was done by an expert physician in nephrology unit of internal medicine department.

Measurement of serum IGFBP-2 levels: whole blood was collected from each patient into vacationer tubes without any additives. After 20 min of incubation at room temperature, the tubes were centrifuged for 10 min at 1,000 g. the supernatant was separated carefully and stored at -80 c until use .in order to avoid protein degradation from multiple freeze-thaw cycles.

2.1 Statistical Analysis

Data were fed to the computer and analyzed using IBM SPSS software package version

20.0.(Armonk, NY: IBM Corp). Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation, median and interquartile range (IQR). Significance of the obtained results was judged at the 5% level.

The used tests were: Chi-square test: For categorical variables, to compare between different groups. Fisher's Exact or Monte Carlo correction: Correction for chi-square when more than 20% of the cells have expected count less than 5. F-test (ANOVA): For normally distributed quantitative variables, to compare between more than two groups. Mann Whitney test: For abnormally distributed quantitative variables, to compare between two studied groups. Spearman coefficient: To correlate between two distributed abnormally quantitative variables. Receiver operating characteristic curve (ROC).

3. RESULTS

Regarding gender and age of studied groups there was statistical insignificant difference between group IA, IB and II. Table 1.

Regarding the ANA test, C3 and C4 levels, there was significant difference between the studied groups, but regarding anti-ds DNA ab titer, the difference between studied groups was not statistically significant. Table 2.

Regarding platelets, there was a statistically significant difference between groups. The p1 was statistically significant, while p2 and p3 were not statistically significant but regarding hemoglobin level and WBCs, there were no statistically significant difference between the groups. Regarding kidney function, there was a statistically significant difference between the studied groups regarding blood urea and serum creatinine Table 3.

Regarding Erythrocyte Sedimentation Rate (ESR) and C-reactive protein (CRP) titer, there was statistically insignificant difference between group IA and IB 1sthour, ESR 2ndhour. Moreover, PT and INR show no statistically significant difference between groups. Table 4.

Correlation between ILGFBPs2 with ACR in nephritis group shown in Fig. 1

Correlation between ILGFBPs2 with Creatinine (mg/dl) in nephritis group shown in Fig. 2.

Regarding lipid profile, there was statistically significant difference between the studied groups regarding cholesterol blood level. P1 was not statistically significant, while p2 and p3 were statistically significant but regarding triglycerides, there was no statistically significant difference between the studied groups. While regarding ILGRFBPs2, P1 was statistically significant, p2 was statistically significant, while p3 was statically insignificant. Table 5.

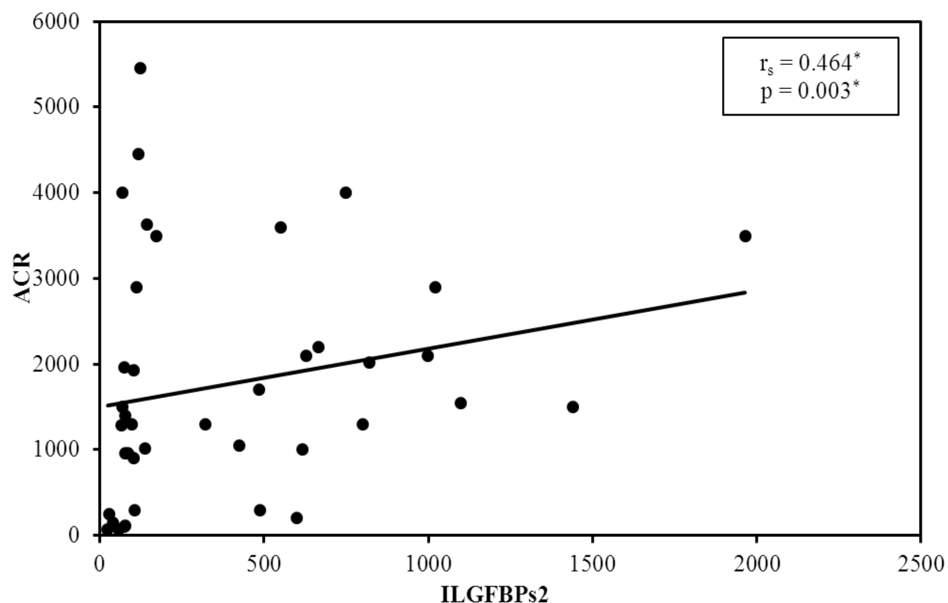

Fig. 1. Correlation between ILGFBPs2 with ACR in nephritis group (n = 40)

Table 1. Comparison between the two studied groups according to demographic data

	Group I				Group II (n = 20)		Test of Sig.	P-Value
	A(n = 40)		B(n = 20)					
	No.	%	No.	%	No.	%		
Gender								
Male	6	15.0	2	10.0	1	5.0	χ2=	MCp=0
Female	34	85.0	18	90.0	19	95.0	1.167	0.596
Age (years)								
Min. – Max.	19.0 – 55.0		21.0 – 50.0		19.0 – 56.0		F=	0.474
Mean ± SD.	33.58 ± 9.43		32.05 ± 8.78		30.55 ± 8.88		0.755	
Median (IQR)	32.50(26.50–40.50)		30.50(25.50–36.50)		32.0(22.0–34.50)			

Table 2. Comparison between the two groups according to ANA, Anti-ds DNA Ab titer, C3 and C4 levels

	Group I				Group II (n= 20)		Test of Sig.	P- value
	A (n = 40)		B(n = 20)					
	No.	%	No.	%	No.	%		
ANA								
Negative	22	55.0	3	15.0	20	100.0	χ2=	<0.003*
Positive	18	45.0	17	85.0	0	0.0	29.410*	
Anti-ds DNA Ab titer								
Min. – Max.	12.0 – 430.0		89.0 – 427.0		–		U=	0.101
Mean ± SD.	158.9 ± 105.5		201.3 ± 86.21		–		295.50	
Median (IQR)	152.5(87.0–210.0)		173.0(144.5–259.0)		–			
C3								
Not consumed	3	7.5	7	17.5	20	100.0	59.286*	<0.001*
Low	37	92.5	33	82.5	0	0.0		
C4								
Not consumed	4	10.0	6	30.0	20	100.0	46.720*	<0.001*
Low	36	90.0	14	70.0	0	0.0		

Table 3. Comparison between the two studied groups according to CBC and kidney function

CBC	Group I		Group II (n = 20)	Test of Sig.	P value
	A (n = 40)	B (n = 20)			
HB (gm/dl)					
Min. – Max.	6.50 – 12.60	6.0 – 12.0	8.30 – 13.0	F= 2.302	0.107
Mean ± SD.	9.46 ± 1.60	9.46 ± 1.73	10.33 ± 1.26		
Median (IQR)	9.70(8.20–10.35)	9.75(8.30–10.80)	10.0(9.55 –11.0)		
Platelet x103(mm)					
Min. – Max.	600.0 – 4900.0	950.0 – 9990.0	1550.0 – 3100.0	H= 8.476*	0.014*
Mean ± SD.	1952.5 ± 921.4	2954.5 ± 1953.8	2001.5 ± 394.9		
Median (IQR)	1775.0(1290.0–2390.0)	2590.0(1875.0–3330.0)	1930.0(1740.0–2100.0)		
Sig. bet. Grps.	p1=0.004*, p2=0.439, p3=0.065				
WBC (mm)					
Min. – Max.	2600.0 – 13200.0	2500.0 – 15000.0	4200.0 – 9400.0	H= 0.677	0.713
Mean ± SD.	7180.0 ± 2936.1	6785.5 ± 3393.4	6634.5 ± 1304.0		
Median (IQR)	7100.0(4900.0–9800.0)	6150.0(4400.0–8355.0)	6450.0(5665.0–7300.0)		
Urea (mg/dl)					
Min. – Max.	20.0 – 168.0	13.0 – 80.0	22.0 – 50.0	H= 16.112*	<0.001*
Mean ± SD.	63.98 ± 35.79	39.15 ± 18.09	32.0 ± 7.63		
Median (IQR)	54.0 (35.0 –95.0)	35.50 (25.0 –51.0)	30.0 (26.50 – 37.0)		
Sig. bet. Grps.	p1=0.008*, p2<0.001*, p3=0.341				
Creatinine (mg/dl)					
Min. – Max.	0.60 – 3.10	0.60 – 1.40	0.50 – 1.10	F= 16.813*	<0.001*
Mean ± SD.	1.55 ± 0.74	0.90 ± 0.22	0.79 ± 0.19		
Median (IQR)	1.35(0.95–2.05)	0.85(0.70–1.08)	0.80(0.60 –0.90)		
Sig. bet. Grps.	p1<0.001*, p2<0.001*, p3=0.767				
WBC (mm)					
Min. – Max.	2600.0 – 13200.0	2500.0 – 15000.0	4200.0 – 9400.0	H= 0.677	0.713
Mean ± SD.	7180.0 ± 2936.1	6785.5 ± 3393.4	6634.5 ± 1304.0		
Median (IQR)	7100.0(4900.0–9800.0)	6150.0(4400.0–8355.0)	6450.0(5665.0–7300.0)		

p1: p value for comparing between Group I (a) and Group I (b); p2: p value for comparing between Group I (a) and Group II; p3: p value for comparing between Group I (b) and Group II

Table 4. Comparison between the two subgroups according to ESR, CRP titer, PT and INR

	Group I		U	P-Value
	A(n = 40)	**B (n = 20)**		
ESR				
1st				
Min. – Max.	10.0 – 106.0	15.0 – 80.0	341.50	0.357
Mean ± SD.	49.40 ± 28.40	40.75 ± 20.02		
Median (IQR)	42.50(24.0–70.0)	40.0(25.0–60.0)		
2nd				
Min. – Max.	18.0 – 138.0	30.0 – 115.0	348.50	0.417
Mean ± SD.	81.30 ± 28.63	74.75 ± 24.09		
Median (IQR)	77.50(60.0–102.0)	75.0(60.0–90.0)		
CRP Titer				
Min. – Max.	2.0 – 24.0	2.0 – 24.0	354.5	0.465
Mean ± SD.	10.70 ± 7.71	9.10 ± 6.03		
Median (IQR)	12.0(4.0 –12.0)	9.0(4.0 –11.0)		
PT (sec)				
Min. – Max.	11.0 – 14.10	11.0 – 14.0	11.0 – 14.0	F=
Mean ± SD.	12.55 ± 0.89	12.46 ± 0.75	12.42 ± 0.83	0.176
Median (IQR)	12.06(12.0–13.10)	12.09(12.0–13.02)	12.0(11.96–13.0)	
INR				
Min. – Max.	1.0 – 1.60	1.0 – 1.70	1.0 – 1.60	H=
Mean ± SD.	1.09 ± 0.14	1.13 ± 0.21	1.11 ± 0.17	0.281
Median (IQR)	1.02(1.0 –1.15)	1.03(1.0 –1.10)	1.01(1.0 –1.20)	

U: Mann Whitney test

Table 5. Comparison between the studied groups according to lipid profile and ILGFBPs2

Lipid profile	Group I		Group II(n = 20)	Test of Sig.	P-Value
	A (n = 40)	**B (n = 20)**			
TG (mg/dl)					
Min. – Max.	59.0 – 286.0	45.0 – 251.0	98.0 – 210.0	H=	0.199
Mean ± SD.	139.9 ± 60.47	125.0 ± 59.31	138.9 ± 29.34	3.226	
Median (IQR)	116.0(92.0–184.5)	107.5(81.0–177.5)	135.5(117.5–147.5)		
Cholesterol (mg/dl)					
Min. – Max.	106.0 – 313.0	91.0 – 250.0	170.0 – 260.0	F=	<0.001*
Mean ± SD.	176.2 ± 43.92	172.3 ± 48.28	222.0 ± 28.71	9.548*	
Median (IQR)	176.0(148.5–197.5)	180.0(129.5–207.5)	214.5		
Sig. bet. Grps.	p1=0.940, p2<0.001*, p3=0.001*				
ILGFBPs2				H	
Min. – Max.	23.19 – 2801.50	23.80 – 299.23	23.19 – 102.0	45.494*	<0.001*
Mean ± SD.	1686.01 ± 775.20	67.69 ± 97.76	64.58 ± 23.29		
Median (IQR)	2044.45	27.30	66.65		
Sig. bet. Grps.	p1<0.001*, p2<0.001*, p3=0.059				

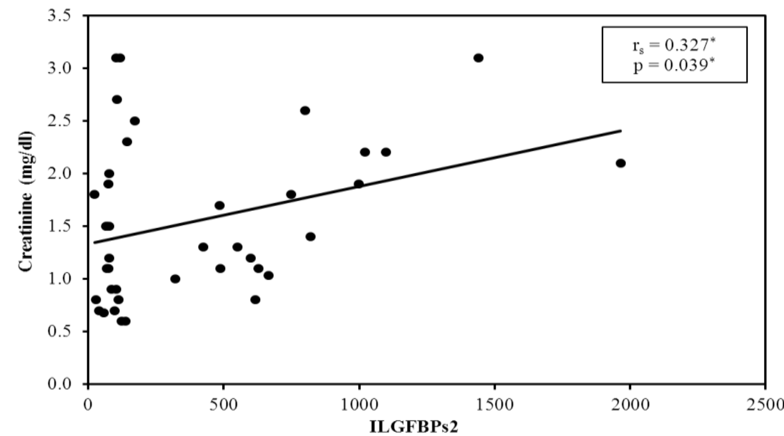

Fig. 2. Correlation between ILGFBPs2 with Creatinine (mg/dl) in nephritis group (n = 40)

Regarding the Systemic Lupus Erythematosus Disease Activity Index (SLEDI) score, there was statistically significant difference between group IA and IB. Table 6.

Regarding the Relation between ILGFBPs2 and renal biopsy classes in lupus nephritis group, there was statistically significant difference between renal biopsy classes and ILGFBPs2 for group IA. Table 7.

Regarding correlation between ILGFBPs2 with SLEDI score and Anti-ds DNA Ab titer in lupus nephritis group, there was statistically significant positive correlation between ILGFBPs2 and the three of renal SLEDI score and Anti-ds DNA Ab titer and renal biopsy. Regarding different parameters, there was statistically significant correlation between ILGFBPs2 and activity index while there was insignificant correlation with chronicity index and renal SLEDI score. Table 8.

ILGFBPs2 at >281.91 can significantly (P <0.001) detect lupus nephritis with 80% sensitivity, 85% specificity, 91.89% positive predictive value, 73.91% negative predictive value and 0.949 AUC (95% CI: 0.891-1). Fig 3.

4. DISCUSSION

Systemic lupus erythematosus (SLE) is a chronic autoimmune inflammatory disease characterized by the production of auto-antibodies and the formation of immune complexes due to the polyclonal activation of T and B lymphocytes, which results in tissue and organ damage; SLE also affects multiple organs. The kidney is the most commonly affected organ with 35 % of patients presenting with lupus nephritis (LN) at the time of diagnosis; 50–60 % develop LN during the first 10 years and up to 25 % develop end-stage renal disease within 10 years of the onset of renal symptoms [6].

It's important to identify biomarkers that have a high specificity for the early diagnosis of LN and can reflect renal activity in follow-up monitoring. Insulin-like growth factor (IGF) is composed of 2 ligands (IGF1, IGF2), 2 receptors (IGF-1R, IGF-2R), and 6 IGF binding proteins (IGFBP-1 to 6). IGF-1R acts by facilitating cell proliferation, differentiation, survival, migration, and metabolic processes. The second most abundant IGFBP found in serum is IGFBP-2 which has been found to be a strong diagnostic and prognostic biomarker for several malignant tumors. In addition, IGFBP-2 has been reported to be increased in nephrotic syndrome and to be a predictor of the longitudinal deterioration of renal function in type 2 diabetes. Although the above reports suggest that IGFBP-2 is a dependable biomarker of renal deterioration, it is still unclear if it has high sensitivity and specificity for discriminating SLE-caused kidney disease from other-cause kidney disease [7].

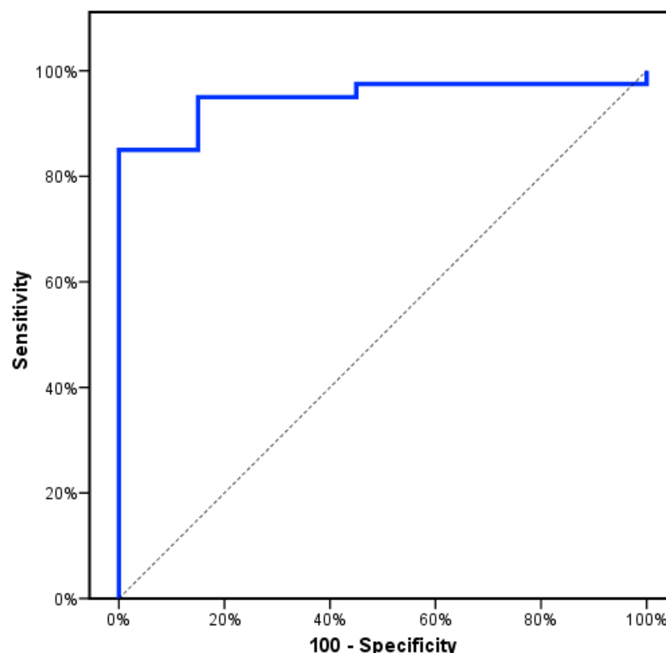

Fig. 3. Receiver operating characteristics (ROC) curve analysis

Table 6. Comparison between the two diseased groups according to SLEDI score

SLEDI score	Group I		U	P-Value
	A (n = 40)	B (n = 20)		
Min. – Max.	0.0 – 30.0	6.0 – 20.0	254.50*	0.022*
Mean ± SD.	16.43 ± 8.87	13.15 ± 4.08		
Median (IQR)	20.0(9.0 –22.0)	12.50(10.50 –15.0)		

Table 7. Relation between ILGFBPs2 and renal biopsy in lupus nephritis group (n = 40)

Renal biopsy	N	ILGFBPs2			H	p
		Min. – Max.	Mean ± SD.	Median		
Class 1	10	39.20 – 1820.00	1028.12 ± 895.98	1550.00	11.298*	0.023*
Class 2	10	56.40 – 2487.00	1684.26 ± 895.87	2081.68		
Class 3	10	23.19 – 2801.50	1565.80 ± 837.56	1807.20		
Class 4	7	1141.78 – 2441.10	2025.73 ± 362.48	2075.05		
Class 5	3	2118.50 – 2170.50	2136.83 ± 29.19	2121.50		

H: H for Kruskal Wallis test; p: p value for association between different categories

Table 8. Correlation between ILGFBPs2 with SLEDI score and Anti-ds DNA Ab titer and different parameters in lupus nephritis group (n = 40)

	ILGFBPs2	
	rs	P
SLEDI score	0.352	0.026*
Anti-ds DNA Ab titer	0.341	0.031*
Renal biopsy	0.369	0.019*
Activity index	0.419	0.052
Chronicity index	0.305	0.167
Renal SLEDI score	-0.195	0.228

*rs: Spearman coefficient, *: Statistically significant at p ≤ 0.05*

Our results were supported by study of Soliman et al., [8] reported that variations regarding age and sex between the studied groups have no significant differences. In this cross-sectional research, 270 participants were enrolled into the research after exclusion of 70 patients; the included patients were classified into four groups: 80 patients with lupus nephritis (LN) diagnosed by renal biopsy, 12 active lupus patients without renal involvement, 28 lupus patients on remission, and 80 healthy participants as controls. Yet, they discovered a statistically significant difference between the studied groups regarding ANA and Antids DNA. Also, 24 h urinary proteins had statistically significant association with the advanced classes of renal pathology in SLE patients. Still the CRP in the LN group remained at lower levels than in the active SLE group.

Furthermore, Choe & Kim, [9] as they reported that this study included 70 female patients with SLE (mean age, 40.4 ± 11.2 years) and 61 female healthy controls (43.6 ± 9.1). The mean age was not significantly different between the two groups (p, 0.05).

In agreement with Bertsias et al., [10] current guidelines for LN diagnosis and management depend largely upon renal pathology, which requires renal biopsy. Although renal biopsy remains the gold standard for the diagnosis and management of LN, it has several disadvantages. Renal biopsy is invasive, with complications such as bleeding and infection. It is also not feasible to perform renal biopsies repeatedly or serially. Last, but not least, renal biopsy reflects only existing pathology, but cannot predict imminent renal flare in LN patients. Given that LN has an unpredictable disease course, the lack of reliable markers that can predict renal flares precludes the development of preventive strategies for disease relapses. Conventional biomarkers for LN, including anti-double-stranded DNA antibodies (dsDNA) and complement components 3 and 4 (C3, C4), are neither sensitive nor specific in reflecting concurrent renal activity or predicting impending renal flare. Therefore, it is important to identify biomarkers that have high specificity for the early diagnosis of LN, can reflect renal activity in follow-up monitoring and are predictive of renal pathology and impending renal flare.

Our results were in line with study of Ata Bora et al., [11] as they reported that there were statistically significant differences among their studied groups as regard Mean platelet volume. The study included a total of 108 SLE patients (8 males, 100 females; mean age 35.3±10.2 years; range 16 to 64 years) including 78 patients with renal involvement (8 males, 70 females; mean age 33.9±10.6 years; range 16 to 64 years) (SLEn+ group) and 30 patients without renal involvement (30 females; mean age 39.1±8.2 years; range 22 to 55 years) (SLEn- group). There was a statistically significant difference between their studied groups as regard ESR yet, not significant regarding the CRP.

In the study of Xuejing et al., [12], the SLE patients (n = 46) were recruited into two groups: SLE patients with active lupus nephritis (active group) and those patients with inactive or nonrenal involvement (nonactive group). They reported that statistically, significant differences were found between both groups in the following variables: red blood cell count in urine (/HP), 24 h urinary proteins (g/24 h), C3 (mmol/L), C4 (mmol/L), serum BUN (mmol/L), and serum creatinine level (µmol/L).

Stojan and Petri, 2017 [13] found out that SLE nephritis affects almost 50% of the SLE patients, and increases the risk of developing renal failure, cardiovascular complications and death. Interestingly, repeated “pulse” steroid was associated with higher renal damage and deleterious effect on central nervous system and bone in Egyptian SLE patients. Persistent national efforts are ongoing to raise the standard of clinical practice, optimize the use of biologics and to develop tailored and targeted therapies for this vulnerable rheumatic disease.

Our results were in agreement with study of Abdulrahman et al., [14], as they reported that there was a statistically significant difference between the three groups as regard creatinine, C3 and C4.

In the study of Mok et al., [15], clinically active SLE, defined as a SLEDAI score of ≥6 or the presence of mild/moderate/severe flares as assessed by the SELENA flares instrument, was present in 52 patients (55%). The mean ± SD SLEDAI scores of the SLE patients was 8.3 ± 1.1. Mok also found that IGFBP-2 was significantly elevated in patients with active SLE than in patients with inactive SLE and controls; in this study, SLEDAI ≥ 6 was considered active SLE.

Our results were supported by study of Ding et al., [5] as they reported that serum IGFBP-2

levels were elevated significantly in LN patients compared to CKD patients and healthy controls. Serum IGFBP-2 was a potential indicator of both global disease activity and renal disease activity in LN patients, correlated with serum creatinine levels ($r = 0{\cdot}658$, $P < 0{\cdot}001$, $n = 85$) and urine protein-to-creatinine levels ($r = 0{\cdot}397$, $P < 0{\cdot}001$, $n = 85$). More importantly, in 19 concurrent patient samples, serum IGFBP-2 correlated with the chronicity index of renal pathology ($r = 0{\cdot}576$, $P = 0{\cdot}01$, $n = 19$) but not renal pathological classification. In the ROC analysis, we found the maximum area under the curve (AUC) values for LN versus healthy controls were 0.742 and 0·841 for anti-dsDNA and complement C3, respectively (assuming all negative for healthy controls). However, when they combined IGFBP2, anti-dsDNA and complement C3 together as a composite marker using logistic regression analysis, the AUC value was increased to 0·986. All these data indicate that IGFBP2 could indeed add diagnostic values significantly to current yardsticks.

Furthermore, Goma et al., [16] showed a significant difference between the 3 groups with respect to IGFBP-2, except for ILGFBP-2, where no significant difference was noted between the CKD and control groups. There was a significant increase in IGFBP-2 with an increase in the SLEDAI score ($p < 0.002$ and $p < 0.006$ respectively). Moreover, there was no significant difference between PGRN and IGFBP-2 and classes of renal biopsy. These findings agreed with the findings of some studies on PGRN [17]. However, in contrast with Ding et.al, findings, the sensitivity of ILGFBPs2 as a marker of activity of lupus nephritis was 100% and its specificity was 100% using the cut off value of > 12.5. PPV was 100% and NPV was 100%.

Fujinaka et al., 2010 [18] demonstrated IGFBP-2 is a member of the insulin-like growth factor binding protein (IGFBP) family and regulates IGF's biological activities through IGF receptors. IGFBP-2 is the second most abundant IGFBP found in serum, which has both regulatory activities of IGFs and IGF-independent activities on metabolism and malignancy. IGFBP-2 is expressed in a wide range of normal tissues, including the glomerulus in both humans and animals. Interestingly, animal model studies have demonstrated the increased expression of IGFBP-2 in the glomerulus in anti-glomerular basement membrane (GBM) glomerulonephritis in the rat 42 and Murphy Roths Large lymphoproliferation (MRL/lpr) lupus mice [18].

Narayanan et al., [19] found that in human immunoglobulin (Ig)A nephropathy, glomerular expression levels of IGFBP-2 mRNA were increased significantly compared to normal glomeruli. IGFBP-2 has also been reported to be increased in nephrotic syndrome in pediatric patients and as a predictor of longitudinal deterioration of renal function in type 2 diabetes. Although the above reports suggest that IGFBP-2 is a reliable biomarker of renal deterioration, our results still indicate that it had high sensitivity and specificity in discriminating kidney disease caused by SLE from other origins.

SLE is a potentially fatal disease with the deposition of immune complexes and inflammation leading to severe tissue damage. In spite of contemporary treatment using immunosuppressive drugs for LN, results are unsatisfactory regarding disease activity with remission and drug intolerance. Thus, new biomarkers to identify early renal involvement in SLE patients are being sought. An ideal biomarker should detect disease activity and renal involvement and damage as early as possible to enable prompt treatment and minimize organ damage. In LN, glomerular immune complexes, at their site of deposition on the kidneys, are considered the main mediators of renal involvement. The progression of LN, leading to renal failure, is due to renal infiltration by macrophages, dendritic cells, and T cells [20].

In agreement with Russo et al., 2015 [21] IGFBP-2 belongs to the IGFBPs family, which binds insulin-like growth factors (IGFs) with high affinity. It is the second most abundant IGFBP found in serum, and has been found to be a robust diagnostic and prognostic biomarker for several malignant tumors. IGFBP-2 has also been reported to be increased in nephrotic syndrome 19 and to be a predictor of longitudinal deterioration of renal function in type 2 diabetes.

There were some limitations in our study. First, the sample size was relatively small. Secondly, all our patients were from a single institution. Several follow-up studies are needed to estimate levels of IGFBP-2 in all SLE patients with and without LN. Moreover, studies could compare these biomarkers with the chronicity index in LN patients.

5. CONCLUSION

Serum IGFBP- 2 is a promising biomarker for lupus nephritis, reflecting disease activity and chronicity changes in renal pathology.

CONSENT

Informed written consent was obtained from all patients after a full explanation of the benefits and risks of the study.

ETHICAL APPROVAL

Permission obtained from Research Ethics Committee as a part of Quality Assurance Unit in Faculty of Medicine at Tanta University to conduct this study and to use the facilities in the hospital.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Tawfik MG, Nasef SI, Omar HH, Ghaly MS. Serum Interleukin-37: A new player in Lupus Nephritis? International Journal of Rheumatic Diseases. 2017;20:996-1001.
2. Jebali H, Hajji M, Rais L, Hamida FB, Beji S, Zouaghi MK. Clinicopathological findings and outcome of lupus nephritis in Tunisian children: a review of 43 patients. Pan African Medical Journal. 2017;27:153-7.
3. Babaei M, Rezaieyazdi Z, Saadati N, Saghafi M, Sahebari M, Naghibzadeh B, et al. Serum alpha-actinin antibody status in systemic lupus erythematosus and its potential in the diagnosis of lupus nephritis. Caspian Journal of Internal Medicine. 2016;7:272-7.
4. Mok CC, Ding HH, Kharboutli M, Mohan C. Axl, Ferritin, Insulin-Like Growth Factor Binding Protein 2, and Tumor Necrosis Factor Receptor Type II as Biomarkers in Systemic Lupus Erythematosus. Arthritis Care & Research (Hoboken). 2016;68:1303-9.
5. Ding H, Kharboutli M, Saxena R, Wu T. Insulin-like growth factor binding protein-2 as a novel biomarker for disease activity and renal pathology changes in lupus nephritis. Clinical & Experimental Immunology. 2016;184:11-8.
6. Stohl W. Future prospects in biologic therapy for systemic lupus erythematosus. Nature Reviews Rheumatology. 2013;9:705-20.
7. Forbes B, McCarthy P, Norton R. Insulin-like growth factor binding proteins: a structural perspective. Frontiers in Endocrinology. 2012;3:38-42.
8. Soliman M, Makarem Y, El Wafaa A, Khairallah M. Platelet-to-lymphocyte and neutrophil-to-lymphocyte ratios as noninvasive predictors for renal involvement in systemic lupus erythematosus in health clinics. The Egyptian Journal of Internal Medicine. 2019;31:927-.
9. Choe J-Y, Kim S-K. Serum TWEAK as a biomarker for disease activity of systemic lupus erythematosus. Inflammation Research. 2016;65:479-88.
10. Bertsias GK, Tektonidou M, Amoura Z, Aringer M, Bajema I, Berden JHM, et al. Joint European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. Annals of the Rheumatic Diseases. 2012;71:1771-82.
11. Ata Bora A, Ermurat S, Coşkun BN, Harman H, Pehlivan Y. Neutrophil to lymphocyte ratio and mean platelet volume as inflammatory indicators in systemic lupus erythematosus nephritis. Archives of rheumatology. 2017;32:21.
12. Xuejing Z, Jiazhen T, Jun L, Xiangqing X, Shuguang Y, Fuyou L. Urinary TWEAK level as a marker of lupus nephritis activity in 46 cases. Journal of Biomedicine and Biotechnology. 2012;2012:359647.
13. Stojan G, Petri M. The risk benefit ratio of glucocorticoids in SLE: have things changed over the past 40 years? Current Treatment Options in Rheumatology. 2017;3:164-72.
14. Abdulrahman MA, Afifi N, El-Ashry M. Neutrophil/lymphocyte and platelet/lymphocyte ratios are useful predictors comparable to serum IL6 for disease activity and damage in naive and relapsing patients with lupus nephritis. The Egyptian Rheumatologist. 2020;42:107-12.
15. Mok CC, Ding HH, Kharboutli M, Mohan C. Axl, Ferritin, Insulin-Like Growth Factor Binding Protein 2, and Tumor Necrosis Factor Receptor Type II as Biomarkers in Systemic Lupus Erythematosus. Arthritis care & research. 2016;68:1303-9.
16. Goma SH, Abdelaziz MM, El-Hakeim EH, El Zohri MH, Sayed SK. Progranulin and insulin-like Growth Factor Binding Protein-2 as Biomarkers of Disease Activity and

Pathological Changes in Lupus Nephritis. Aktuelle Rheumatologie. 2019;44:121-7.
17. Qiu F, Song L, Ding F, Liu H, Shu Q, Yang N, et al. Expression level of the growth factor progranulin is related with development of systemic lupus erythematosus. Diagnostic Pathology. 2013;8:88-93.
18. Fujinaka H, Katsuyama K, Yamamoto K, Nameta M, Yoshida Y, Yaoita E, et al. Expression and localization of insulin-like growth factor binding proteins in normal and proteinuric kidney glomeruli. Nephrology. 2010;15:700-9.
19. Narayanan RP, Fu B, Heald AH, Siddals KW, Oliver RL, Hudson JE, et al. IGFBP2 is a biomarker for predicting longitudinal deterioration in renal function in type 2 diabetes. Endocrine connections. 2012;1: 95-102.
20. Monroy Trujillo JM, Fine DM. Lupus Nephritis in the Era of Biomarkers. Clinical Journal of the American Society of Nephrology. 2016;11:4-5.
21. Russo VC, Azar WJ, Yau SW, Sabin MA, Werther GA. IGFBP-2: The dark horse in metabolism and cancer. Cytokine & Growth Factor Reviews. 2015;26:329-46.

© 2021 ELgody et al.; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle4.com/review-history/72400