The Egyptian Journal of Hospital Medicine (April 2022) Vol. 87, Page 1328-1335

Urinary Ferritin Creatinine Ratio as a Potential Biomarker for Lupus Nephritis

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ABSTRACT

Background: Systemic lupus erythematosus (SLE) can affect multiple systems and major organs, among which lupus nephritis (LN), which is a common major organ manifestation and a main cause of the morbidity and mortality of the disease. In this regard, LN affects 40– 80% of SLE patients and result in chronic kidney disease, which sequentially increases the morbidity and mortality in SLE patients.

Objective: The aim of this study was to evaluate the value of urinary ferritin/creatinine ratio (UFCR) in diagnosis and evaluation of lupus nephritis.

Patients and Methods: This study was conducted in the Internal Medicine Department, Zagazig University Hospitals. The study included 36 patients complaining of SLE diagnosed according to the American College of Rheumatology (ACR) revised criteria for the classification of SLE. Patients were divided into two equal groups; group (**I**) included 18 SLE patients without LN (17 of them were females and one was male) with a mean age of 32.33 ± 6.47 years, and group (**II**) included 18 SLE patients with LN (18 of them were females) with a mean age of 29.28 ± 6.56 years. They were compared to 18 healthy control participants (16 of them were females and two were males) with mean age of 32.28 ± 6.03years. Urinary ferritin creatinine ratio (UFCR) was measured for all of them.

Results: There was a statistical significance increase in urinary ferritin among LN group compared to other groups. UFCR was significantly higher in the LN group than control group. There was a statistically significance positive correlation between UFCR and SLEDAI score, serum ferritin, blood urea and serum creatinine among LN group.

Conclusion: UFCR level can be considered as a potential biomarker for the kidney injury in LN, and it is significantly increased in LN patients.

Keywords: Urinary ferritin creatinine ratio, Biomarker, Lupus nephritis.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with unknown etiology, which can be characterized by producing various autoantibodies against self-antigens (autoantigens) [(1)]. SLE can affect multiple systems and major organs, among which lupus nephritis (LN) is a common major organ manifestation and a main cause of the morbidity and mortality of the disease [(2)]. In this regard, LN affects 40– 80% of SLE patients, and an immunosuppressive treatment for LN may have an adverse effect on kidney and result in chronic kidney disease, which sequentially increases the morbidity and mortality in SLE patients [(1)]. Therefore, an involvement of renal disease activity is one of the most important prognostic factors for patients with SLE, and the diagnosis of SLE patients with LN has an important clinical implication in guiding the treatment of SLE in clinical settings [(3)].

Urinary biomarkers are easily obtained and probably are best at reflecting the current renal status, as they specifically represent local inflammatory activity [(4)]. In recent years, ferritin has gained increasing attention in the studies of autoimmune diseases. Elevated serum ferritin levels were well established as an acute-phase reactant in antiphospholipid syndrome (APS), rheumatoid arthritis (RA) and adult onset Still's disease (AOSD). There were several studies that reported elevated levels of serum ferritin in SLE patients, but few studies have investigated the clinical significance of urinary ferritin in SLE and LN [(5)].

The aim of this study was to evaluate the value of urinary ferritin/creatinine ratio (UFCR) in diagnosis and evaluation of lupus nephritis.

PATIENTS AND METHODS

This retrospective case-control study was carried out in Internal Medicine Department, Faculty of Medicine, Zagazig University Hospitals between February 2021 and August 2021.

Study population: This study was conducted on 54 participants including both females and males and their ages ranged from 18-45 years old. Thirty six participants were diagnosed to have SLE and fulfilled at least four of 11 American College of Rheumatology (ACR) revised criteria for SLE. We divided them into three groups. **Group I** included 18 SLE patients without LN (17 were females and 1 was male). They were admitted to due lupus flares with arthritis, proteinuria < 0.5 g/day, no hematuria or urinary casts sediment and all of them had a normal kidney function (serum creatinine <1.1 mg/dl in female or < 1.2 mg/dl in male) with estimated GFR > 90 ml/min/1.73 m^2. **Group II** included 18 SLE patients with LN (18 were females with no males) and all had evident clinical nephritis (proteinuria > 0.5 g/day and some patients had elevated serum creatinine level > 1.1 mg/dl in female and > 1.2 mg/dl in males). **Group III** included 18 apparently healthy control population, which were age- and sex-matched with patients' groups.

Received: 15/10/2021
Accepted: 13/12/2021

Inclusion Criteria: Male and female patients aged > 18 and < 40 years old. All lupus patients fulfilled the American College of Rheumatology (ACR) 1997 criteria for the diagnosis of SLE. Clinically persistent proteinuria > 0.5 g/24 h for patients with lupus nephritis. Healthy people who had no clinical or laboratory evidence of any chronic disease.

Exclusion Criteria: All the enrolled individuals had never taken any iron supplements in nearly six months. Patients with diabetes mellitus, cardiovascular and cerebrovascular diseases, liver disease, blood diseases, and other severe concomitant diseases. Patients with a diagnosis of overlap syndrome. Patients with urinary tract infections, urinary stones or any urological problem, acute renal failure and dehydration, end-stage renal disease patients whether on hemodialysis or not and patients with malignancies. Exclusion was done according to medical history, medical examination and routine laboratory investigations indicating any of the exclusion criteria.

All subjects of the study were subjected to full history and thorough clinical examination as well as drug prescriptions. General examination and local examination of different systems with thorough cardiovascular, respiratory, abdominal and neurological examination was performed. Routine investigations were done according to protocol of clinical pathology and laboratories of Zagazig University Hospital. This included CBC, fasting blood glucose and glycated hemoglobin (Hb A1c), liver function tests, erythrocyte sedimentation rate (ESR), serum creatinine and blood urea and estimated glomerular filtration rate (eGFR). Moreover, iron study to exclude iron overload including serum iron, total iron binding capacity and transferrin saturation, antinuclear antibodies (ANA) and anti-double stranded deoxyribonucleic acid (dsDNA) antibodies by indirect immunofluorescence (Inova Diagnostics, USA). Also, serum complements levels (C3, C4) were measured by turbidimetry on Cobas 6000 analyser (Roche Diagnostics, Switzerland). In addition, urinary and serum ferritin levels were measured by commercial ELISA kits according to manufacturer instructions (Sunred Biotechnology, China). Urinary ferritin was standardized by urinary creatinine to get urinary ferritin creatinine ratio (UFCR). Also, ultrasonography on the abdomen and pelvis was done to determine renal medical disease grades. Estimated GFR (eGFR) was calculated for all participants in the study using the MDRD equation of the National Kidney Foundation eGFR mobile application [(6)]. "GFR (mL/min/1.73 m^2) = 175 × (Scr)-1.154 × (Age)-0.203 × (0.742 if female) × (1.212 if African American)".

Assessment of the SLE disease activity: Assessment of the disease activity was done using the systemic lupus erythematosus disease activity index (SLEDAI), which is a validated model among experienced clinicians for global assessments of disease activity in patients with SLE [(7)].

Ethical consent:

Approval for performing the study was obtained from Internal Medicine Department, Zagazig University Hospitals after taking Institutional Review Board (IRB) approval. All participants were informed of the various aspects of the study, and they were enrolled only after providing a signed consent form. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis:

The collected data were revised, coded, tabulated and introduced to a PC using Statistical Package for Social Science (SPSS version 20.0 for windows; SPSS Inc., Chicago, IL, 2001). Data were presented and suitable analysis was done according to the type of data obtained for each parameter. Continuous variables were expressed as mean ± SD and categorical variables were expressed as numbers (percentages). Continuous data were checked for normality. All normally distributed data were analyzed using independent student (t) test. Data formed non-normally distributed were analyzed using the Mann Whitney (MW) test. One way ANOVA was used to compare normally distributed variables between more than two groups if data were normally distributed. Kruskal–Wallis H test (KW) was used to compare non-normally distributed ones. Percentage of categorical variables was compared using the chi square (X^2) test. The Spearman rank correlation and Pearson correlation coefficient were calculated to assess correlation between UFCR and other parameters. Receiver operating characteristic (ROC) curve analysis was used to identify the utility of UFCR for prediction of SLE and LN with maximum sensitivity and specificity of generated cut off values. Multivariate regression analysis was performed to check the association between UFCR and different study parameters among the studied groups. All p-value calculations were 2 tailed and considered statistically significant (S) if ≤ 0.05, and if p ≥ 0.05 then was considered non-statistically significant (NS).

RESULTS

We included fifty-four individuals' [3 males (5.6%) and 51 females (94.4%)] in the current study. The mean age of the study participants was 31.3 ± 6.35 years. Participants with SLE were divided into two equal groups; group I included 18 SLE patients without LN (17 of them were females and one was male) with mean age 32.33 ± 6.47 years, and group II included 18 SLE patients with LN (18 of them were females) with mean age 29.28 ± 6.56 years. They were compared to 18 healthy control participants (16 were females and 2 two were males) with mean age of 32.28 ± 6.03 years.

ANA titers were found to be higher in patients with LN (group II) (Mdn=26.95) compared to

those with SLE but without LN (group I) [(Mdn=15.85); U=117, p=0.13], without statistical significance. As regards C3 levels, there was statistical significant difference between patients with SLE and LN (Mdn=0.8) and patients with SLE but without LN (Mdn=1.02), (p=0.01). Other comparison of immunological profile and inflammatory markers between both the two main groups (SLE patients with or without LN) are summarized in table (1).

The SLEDAI score in SLE patients with LN varied between 6 and 36 with a mean of 16.83 ± 8.23. In SLE patients without LN it varied between 4 and 28 with a mean of 10.17 ± 6.16. SLEDAI score was found to be higher in group II (Mdn=14) compared to group I [(Mdn=9), p=0.004]. The most frequent classes founded among LN group were class V (33.3%) followed by class III-s (16.7%) and class V early (III-s) as shown in figure (1).

There was a statistical significance increase in blood urea, 24 h protein and S. creatinine and decrease in GFR among LN group compared to SLE group as shown in table (2).

A Kruskall Wallis H test showed that there was a statistically significant difference in UFCR between the three groups (including control group III), UFCR was higher among LN group compared to other groups and among SLE group compared to control group as shown in table (3).

The correlation between UFCR and other study parameters were tested using appropriate correlation analysis. There were positive correlation between UFCR and SLEDAI in total SLE patients (n= 36, r = 0.62, P < 0.001), UFCR and serum ferritin (n= 36, r = 0.52, P<0.001) and UFCR and serum creatinine (n= 36, r = 0.41, P = 0.01). While, there was negative correlation between UFCR and eGFR (n= 36, r = -0.36, P = 0.03). Other correlation analyses between UFCR and study parameters were summarized in table (4.

To detect the ability of UFCR to predict LN, we utilized the receiver operating characteristic curve. We found that UFCR at cut off > 5.99 mg/mol had sensitivity 72.2%, specificity 88.9% and accuracy 84.6% in diagnosis of LN (Table 5 & figure 2).

Table (1): Comparison of immunological profile and inflammatory markers among the studied cases group

Variable		Group I (SLE) (n=18)		Group II (LN) (n=18)		Test	P
		No	%	No	%		
ANA	-	2	11.1	0	0	χ^2	
	+	4	22.2	2	11.1	3.29	0.35
	++	8	44.4	10	55.6		NS
	+++	4	22.2	6	33.3		
Titer:	Median(IQR)	15.85(7.53-30.73)		26.95(12.38-44.63)		MW 1.52	0.13 NS
dsDNA	-	5	27.8	0	0	χ^2	
	+	3	16.7	2	11.1	6.59	0.09
	++	7	38.9	11	61.1		NS
	+++	3	16.7	5	27.8		
Titer:	Median(IQR)	75.5(21-100.45)		76(42.5-87)		MW 0.29	0.78 NS
C3:	Median(IQR)	1.02(0.7-1.17)		0.80(0.56-0.90)		MW 2.53	0.01*
C4:	Median(IQR)	0.14(0.10-0.29)		0.11(0.06-0.18)		MW 1.48	0.14 NS
ESR: (mm)	Median(IQR)	4.5(2.49-9)		14.8(10.05-18.63)		MW 0.30	0.76 NS
CRP: (mg/dl)	Median(IQR)	4(3-6.33)		4.5(2.49-9)		MW 0.22	0.83 NS
SD: Standard deviation IQR: Interquartile range MW: Mann Whitney test χ^2: Chi square test NS: Non significant (P>0.05) *: Significant (P<0.05)							

Table (2): Comparison of KFTs among the studied groups

Variable	Group I (SLE) (n=18)	Group II (LN) (n=18)	Test	P

Blood urea: (mg/dl)	Mean ± SD Median(IQR)	24.98±5.34 23.58(18.91-31.34)	54.63±4.18 42.43(22.77-64.34)	**MW** **2.74**	**0.006***
eGFR: (ml/min/1.73m^2)	Mean ± SD Median(IQR)	106.06±21.49 113(85-121.5)	71.67±12.71 79(49.25-90)	**MW** **3.55**	**<0.001****
24 hour Protein: (mg/24h)	Mean ± SD Median(IQR)	167.71±13.65 112.95(72.75-285.25)	1081.62±131.68 1280.7(587.3-2563)	**MW** **4.4**	**<0.001****
S.Creatinine: (mg/dl)	Mean ± SD Median(IQR)	0.73±0.19 0.67(0.57-0.92)	1.14±0.39 0.9(0.71-1.41)	**MW** **2.71**	**0.007***
SD: Standard deviation IQR: Interquartile range MW: Mann Whitney test χ^2: Chi square test NS: Non significant (P>0.05) *: Significant (P<0.05) **: Highly significant (P<0.001)					

Table (3): Comparison of UFCR among the studied groups

Variable		**Group I (SLE) (n=18)**	**Group II (LN) (n=18)**	**Group III (Control) (n=18)**	**KW**	**P**	**LSD**
UFCR: (mg/mol)	Mean ± SD Median(IQR)	3.91±0.84 3.57(2.25-5.43)	10.63±0.6 10.2(4.82-17.3)	0.6±0.16 0.53(0.32-0.84)	35.59	<0.001**	0.001* <0.001**^{2} <0.001**^{3}
SD: Standard deviation IQR: Interquartile range KW: Kruskal wallis test LSD: Least significant difference P1: Group I versus group II P2: Group I versus garoup III P3: Group II versus Group III *: Significant (P<0.05) **: Highly significant (P<0.001)							

Table (4): Correlation between different parameters and UFCR among cases groups:

Variable	**UFCR Group II (n=18)**		**All cases Group I&II (n=36)**	
	r	**P**	**r**	**P**
Age (years)	0.28	0.27 NS	0.31	0.06 NS
ANA	0.33	0.18 NS	0.08	0.63 NS
dsDNA	0.23	0.37 NS	0.04	0.81 NS
C3	-0.25	0.32 NS	-0.14	0.43 NS
C4	-0.18	0.46 NS	-0.16	0.36 NS
SLEDAI	0.80	<0.001**	0.62	<0.001**
Hb: (gm/dl)	0.21	0.41 NS	0.08	0.63 NS
Platelets:(x10^3/mm^3)	0.17	0.50 NS	0.16	0.36 NS
WBCs:(x10^3/mm^3)	0.34	0.16 NS	0.32	0.06 NS
Lymphocyte:(x10^3/mm^3)	0.19	0.26 NS	0.14	0.41 NS
RBCs:(x10^6/mm^3)	0.17	0.49 NS	-0.03	0.88 NS
FBS: (mg/dl)	0.30	0.23 NS	0.27	0.12 NS
HbA1c: (%)	0.16	0.54 NS	0.10	0.55 NS
T. protein: (gm/dl)	-0.13	0.61 NS	-0.17	0.33 NS
Albumin: (gm/dl)	-0.14	0.57 NS	-0.31	0.06 NS
ALT: (µ/l)	0.13	0.61 NS	0.08	0.64 NS
AST: (µ/l)	0.09	0.70 NS	-0.01	0.99 NS
ESR: (mm)	0.09	0.73 NS	0.07	0.70 NS
CRP: (mg/dl)	0.14	0.57 NS	0.14	0.44 NS
S.Iron:(µg/dl)	0.15	0.54 NS	0.10	0.58 NS
TIBC:(µg/dl)	0.11	0.67 NS	0.22	0.20 NS
TS:(%)	-0.10	0.72 NS	-0.10	0.57 NS
S. Ferritin:(ng/ml)	0.54	0.02*	0.52	<0.001**
Blood urea:(mg/dl)	0.50	0.03*	0.23	0.19 NS
eGFR: (ml/min/1.73m^2)	-0.58	0.01*	-0.36	0.03*
24 hour Protein:(mg/24h)	0.46	0.06 NS	0.27	0.11 NS
S. Creatinine: (mg/dl)	0.64	0.004*	0.41	0.01*
r: Spearman'e correlation coefficient NS: non-significant (P>0.05) *: Significant (P<0.05) **: Highly significant (P<0.001)				

Table (5): Validity of UFCR in diagnosis of LN among the studied cases groups:

Cut off	AUC (95%CI)	P	Sensitivity	Specificity	PPV	NPV	Accuracy
>5.99	0.82 (0.68-0.97)	0.001*	72.2%	88.9%	86.7%	76.2%	80.6%

AUC: Area under curve PPV: +ve predicted value NPV:-ve predicted value
*: Highly significant (P<0.5)

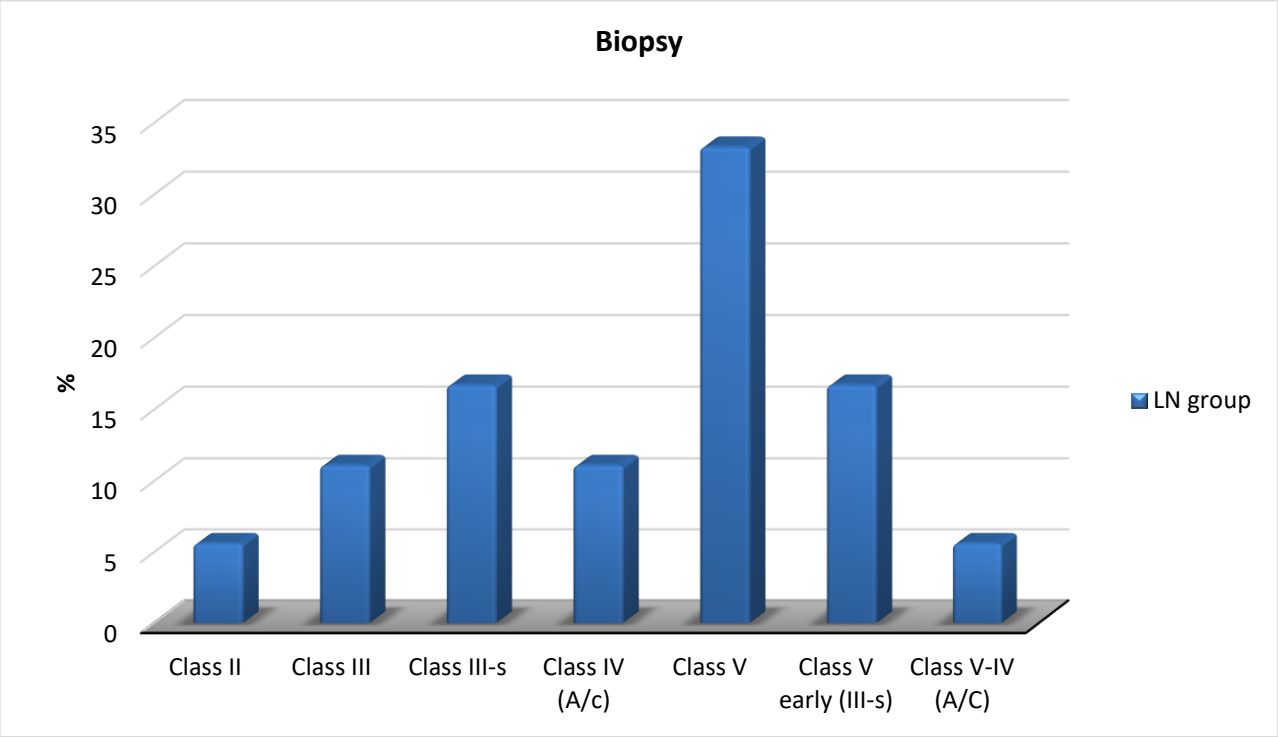

Figure (1): Bar chart showed biopsy results among LN group.

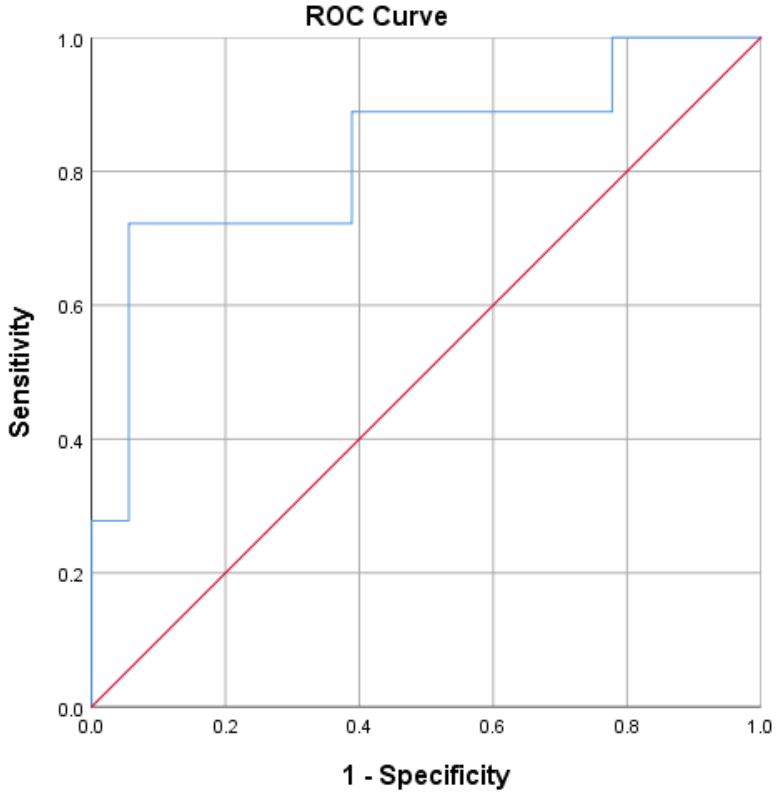

Figure (2): Roc curve for validity of UFCR in diagnosis of LN among the studied cases groups

DISCUSSION

Involvement of renal disease activity is one of the most important prognostic factors for patients with SLE, and the diagnosis of SLE patients with LN has an important clinical implication in guiding the treatment of SLE in clinical settings. Regarding demographic data, there was no significant difference between the three groups regarding age and sex distribution (p-value: 0.27 and 0.35 respectively).

As regards immunological profile and inflammatory markers, our results showed that there was no statistical significant difference between both cases groups regarding ANA and anti-dsDNA incidence and titer. Our results are supported by **Pradhan *et al.*** [8] who found that the prevalence of ANA is 100% in the SLE patients studied. Regarding anti-dsDNA, our results are in agreement with **Hewala *et al.*** [9] and **Chi *et al.*** [10] as they found that the titer of anti-dsDNA antibodies was higher in the active SLE and LN groups in comparison with the inactive SLE and non-LN groups, respectively. Anti-double stranded DNA antibodies (anti-dsDNA) are highly specific for SLE and are included in past and new ACR classification criteria [11]. Anti-dsDNA have proven to exert pathogenic effect and their serum levels correlate with overall disease activity, so that they are included in most of clinical assessment tools for SLE and serial measurement of them is part of EULAR recommendations (European League Against Rheumatism) and ACR guidelines [12; 6].

Also, there was no statistical significant difference between both cases groups as regard complement C4 (p-value: 0.14), while there was a statistical significant difference between them regarding complement C3 (p-value: 0.01).

As regarding ESR and CRP, our results showed that there were no statistically significant differences between both groups (p-value: 0.76 and 0.83 respectively). Regarding ESR, our result is in agreement with studies done by **Mirzayan *et al.*** [13] and **Chang *et al.*** [14] where they couldn't demonstrate any association between ESR and disease activity. While against our results, **Nasiri *et al.*** [15] concluded that a combination of anti-dsDNA, serum complement C3 and C4, ESR, and CRP is most commonly used and probably provides the most useful clinical information on SLE disease activity, in particular patients with lupus nephritis. Also in conflict with our results, **Stojan *et al.*** [16] reported in their study on 1865 different patients over 35,373 visits were analyzed in a large scale cross sectional study. There was a strong association between ESR and disease activity but in the same study he concluded that ESR associates with both global and organ specific disease activity.

Regarding iron parameters, our results showed that there was a statistical significance increase in transferrin saturation among control group compared to cases groups. Also there was a statistical significance increase in urinary & serum ferritin among LN group compared to other groups. Finally, there was a statistical significant increase in serum & urinary ferritin among SLE group compared to control group. There was no statistical significant difference between studied groups as regard serum iron and total iron binding capacity.

As regard kidney function tests, our results showed that there was a statistical significant difference between both cases groups regarding blood urea, serum creatinine, estimated GFR and collected 24 hour protein in urine (p-value: 0.006, 0.007, <0.001 and <0.001 respectively). Similar to our finding, **Alalfy *et al.*** [17] reported that there was a significant difference concerning serum creatinine and eGFR between groups of the study with higher serum creatinine and lower eGFR in active lupus nephritis group. Explaining the previous finding that kidney involvement in the setting of lupus is suspected by an abnormal urine analysis and/or elevation of serum creatinine and confirmed by histopathological findings on renal biopsy [18]. In the majority of studies, renal function has been defined by the level of serum creatinine as a surrogate for glomerular filtration rate (GFR). In the steady state, there is a reciprocal relationship between GFR and serum creatinine, but since creatinine generation and tubular secretion can have an influence on the level of creatinine in the serum, serum creatinine alone can be an inaccurate marker of renal function [19].

As regards proteinuria, it goes in harmony with **Medina-Rosas *et al.*** [20], **Alalfy *et al.*** [17] and **Chi *et al.*** [10] who found high statistical significance concerning proteinuria being high and specific for active renal flares in SLE patients explaining these finding that Nephrotic syndrome is a common sign of LN, which is usually associated with immune complex deposition in the glomerular capillary wall and is frequently accompanied by endocapillary proliferation or necrosis. Nephrotic syndrome is particularly characteristic of proliferative LN (class III, class IV) or membranous LN (class V) [21].

There was no statistical significant difference between both groups regarding urinary casts, RBCs and pus cells.

Regarding urinary ferritin creatinine ratio (UFCR), our results showed that there was a statistical significant difference between the three studied groups (p-value: <0.001). It was significantly higher in the LN group than in the other two groups (SLE and control groups). Also, it was significantly higher in the SLE group than the control group. These findings are in agreement with **Qi *et al.*** [5] who reported that The UFCR level was significantly higher in severely (n = 28) or non-severely active SLE patients (n = 34) than that in HC (both $P < 0.01$). Also, they reported that the UFCR levels were significantly different among LN, SLE without nephritis and healthy control ($P < 0.01$). UFCR level in LN patients (n = 35) was significantly higher than that in lupus patients without LN (n = 27) (15.25 mg/mol (5.18, 33.25) vs. 2.01 mg/mol (0.69, 2.75), $P < 0.01$). At least three factors contributing to the increased

UFCR in LN. Firstly, because ferritin cannot be filtered by the normal glomeruli, the glomerular damage should be the base of increased UFCR. Secondly, many chronic kidney diseases, including LN, have tubulointerstitial lesions in the meantime, and tubular iron deposition has been found to be one of the causes of tubulointerstitial change in these diseases [(22)]. Therefore, it is reasonable to presume that tubular iron deposition promotes ferritin formation and secretion in LN. In addition, it has been demonstrated that activated macrophages increase in the kidneys of LN patients. These local macrophages may be important cells in charge for increased ferritin production and increased UFCR [(23)].

In LN group there was a statistical significance positive correlation between UFCR and SLEDAI score, serum ferritin, blood urea and serum creatinine among LN group. Also there was a statistical significance negative correlation between UFCR and eGFR. Finally, in both groups there was a statistical significance positive correlation between UFCR and SLEDAI score, serum ferritin, and serum creatinine and a statistical significance negative correlation between UFCR and eGFR. In the study done by **Qi *et al.*** [(5)] they reported that the relationship between UFCR and related inflammatory markers and laboratory indicators were investigated by correlation analysis and found that UFCR level was significantly positively correlated with SLEDAI, rSLEDAI, serum ferritin, 24 h urine protein, serum creatinine, and serum cystatin C, but negatively correlated with GFR and hemoglobin.

Regarding validity of UFCR in diagnosis of LN, UFCR has 72.2% sensitivity, 88.9% specificity, 86.7% PPV, 76.2% NPV and 80.6% accuracy in diagnosis of LN. **Qi *et al.*** [(5)] reported that the AUC of UFCR was 0.831, and a cutoff of 4.09 mg/mol yielded a sensitivity of 82.9% and specificity of 81.5% for diagnosing LN. And in the ROC curve of LN disease activity, the AUC of UFCR was 0.720, indicating that UFCR can be used as a reliable indicator for evaluating LN disease activity.

CONCLUSION

UFCR level can be considered as a potential biomarker for the kidney injury in LN, and it is significantly increased in LN patients.

Financial support and sponsorship: Nil.
Conflict of interest: Nil.

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