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The Value of Lipocalin-2 in Patients with Systemic Lupus Erythematosus.

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Abstract

Background: Systemic lupus erythematosus (SLE) is a chronic autoimmune multisystem disease predominantly affecting women in the childbearing period. The majority of the pathology in SLE is related to deposits of immune complexes in various organs, which trigger complement and other mediators of inflammation. SLE is characterized by a very large spectrum of clinical manifestations accompanied by prototypic abnormalities of the immune system. **Methods:** This study was conducted on thirty SLE patients who were diagnosed according to the American College of Rheumatology (ACR) revised criteria**.** The patient was selected from the outpatient clinic of Rheumatology and Rehabilitation of Ain Shams University Hospital. Fifteen subjects, matched for age and sex, were included in the study and served as a control group. Comparison of quantitative variables between the study groups was done using the Kruskal Wallis analysis of variance (ANOVA) test with Mann Whitney *U* test for independent samples as posthoc multiple 2-group comparisons. A probability value (p-value) less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel 2007 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows. **Results and Discussion:** Our results come in agreement with the study done by Farzaneh and his colleagues in 2013, who studied fifty-two lupus patients; urinary lipocalin-2 levels in LN patients were significantly higher than those in non-LN patients. Also, our results were in accordance with the study done by Hammad, who studied 33 children with active SLE (22 with and 11 without LN) and compared them with 15 matched controls. Levels of urinary NGAL were higher in patients with LN than those without LN. These findings come in consistent with previous work done by Youssef and his co-worker in 2015, who studied 44 SLE patients and divided them into two groups, group I (twenty-two patients with LN) and group II (twenty-two patients without LN), the urinary lipocalin-2 had the highest mean levels in LN patients (group I) compared to group II and controls with a statistically significant difference. Also, between SLE patients without nephritis (group II) and controls. **Conclusions:** In this study, urinary lipocalin-2 was significantly higher in the SLE patients compared to the control group, and the lupus nephritis patients, when compared to the patients with SLE without nephritis, showed significantly higher levels of urinary lipocalin-2. The significant association of the urinary lipocalin-2 with the renal SLEDAI shows that urinary lipocalin-2 can be an early biomarker to diagnose patients with lupus nephritis and to detect renal disease activity.

Keywords: Systemic lupus erythematosus (SLE); urinary lipocalin-2; and NGAL.

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune multisystem disease predominantly affecting women in the childbearing period. The majority of the pathology in SLE is related to deposits of immune

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complexes in various organs, which trigger complement and other mediators of inflammation [1]. SLE is characterized by a very large spectrum of clinical manifestations accompanied by prototypic abnormalities of the immune system [2]. While recent advances in therapeutic approaches have taken place, SLE still has a profound impact on the quality of life and life expectancy of affected persons. Renal involvement occurs in 40–70% of all SLE patients and is a major cause of morbidity and hospital admissions. Its clinical presentations are highly variable, ranging from mild asymptomatic proteinuria and/or hematuria [3,4] to rapidly progressive uremia. Early diagnosis and prompt treatment may dramatically modify the course of renal disease and improve long-term survival. Approximately 10 to 30 % of patients with lupus nephritis progress to end-stage renal disease (ESRD) [5]. The accepted routine measures of assessing patients with SLE include acute phase markers, erythrocyte sedimentation rate (ESR), C-reactive protein, plasma/serum complement component 3 (C3) and component 4 (C4), and presence of antibodies to double-stranded DNA (anti-dsDNA) such markers help in a variety of ways [6], including early detection of flare, distinction between flare and chronic damage and monitoring response to therapy. However, improved new markers are required to assist clinicians in the diagnosis of lupus patients. Among these new markers, lipocalin-2 is a promising one [7,8]. The lipocalin protein family is a large group of mostly secreted soluble proteins that carry small molecules to specific cells. Lipocalin-2, also known as neutrophil gelatinase-associated lipocalin (NGAL), is expressed in neutrophils and in low levels in the kidneys. NGAL has been evaluated as an early biomarker of acute kidney injury after cardiopulmonary bypass and kidney transplantation. It is also a candidate biomarker for chronic kidney diseases, such as immunoglobulin nephropathy and membranous and membranoproliferative glomerulonephritis [9,10]. Based on these findings, Lipocalin-2 may be a potential biomarker for renal damage/ inflammation in lupus nephritis. The aim of the present study is to assess serum and urinary lipocalin-2 levels in patients with Systemic lupus erythematosus (SLE) and its correlation to disease activity and lupus nephritis (LN).

Method:

This study was conducted on thirty SLE patients who were diagnosed according to the American College of Rheumatology (ACR) revised criteria**.** The patient was selected from the outpatient clinic of Rheumatology and Rehabilitation of Ain Shams University Hospital. Fifteen subjects, matched for age and sex, were included in the study and served as a control group. Patients with diabetes mellitus, malignancies, other connective tissue diseases, polycystic kidneys, acute kidney injury (AKI), post-renal transplantation, and ischemic heart diseases were excluded by history and routine examination as there is an increase in the level of NGAL in these conditions. Data were statistically described in terms of range, mean ± standard deviation (± SD), frequencies (number of cases), and percentages when appropriate. Comparison of quantitative variables between the study groups was done using the Kruskal Wallis analysis of variance (ANOVA) test with Mann Whitney *U* test for independent samples as posthoc multiple 2-group comparisons. For comparing categorical data, the Chi-square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than 5. Correlation between different variables was done using the Pearson moment correlation test. Accuracy was represented using the terms sensitivity and specificity. Receiver operator characteristic (ROC) analysis was used to determine the optimum cut-off value for the studied diagnostic markers. A probability value (*p*-value) less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel 2007 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows. Patients considered to have lupus nephritis if they had a renal SLEDAI of ≥ 8 (i.e., at least two abnormal results for renal parameters on at least two seperate occasions). So according to the renal SLEDAI, the patients were divided into two groups: ***Group I:*** SLE patients with lupus nephritis (renal SLEDAI ≥8): this group comprised fifteen patients. ***Group II:*** SLE patients without lupus nephritis (renal SLEDAI < 8): this group comprised fifteen patients. The extra-renal SLEDAI was also calculated, where the renal component of the total SLEDAI score was removed in order to determine the dependency of lipocalin-2 on the renal component of the score. In the Biovendor Human Lipocalin-2/NGAL ELISA, Standards, Quality Controls, and samples were incubated in microplate wells with polyclonal anti-human Lipocalin-2 antibody. After one hour of incubation and washing, a biotin-labeled polyclonal anti-human Lipocalin-2 antibody was added and incubated with captured Lipocalin-2 for one hour. After another washing, streptavidin-HRP conjugate was added. After 30 minutes of incubation and the last washing step, the remaining conjugate was allowed to react with the substrate solution (TMB). The reaction was stopped by the addition of an acidic solution, and the absorbance of the

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resulting yellow product was measured spectrophotometrically at 450 nm. The absorbance was proportional to the concentration of Lipocalin-2. A standard curve was constructed by plotting absorbance values against concentrations of Standards, and concentrations of unknown samples were determined using this standard curve. Disease activity was assessed according to the SLE Disease Activity Index (SLEDAI).

Results:

Table 1: Comparison between SLE patients and control group regards demographic data.

Variables	**SLE patients (No.=30) Mean± SD**		**Control (No.=15) Mean± SD**		**P value**	**Sig.**
Age (years)	31.13 ± 8.41		29±5.44		0.249	(NS)
Sex:	Number	Percent	Number	Percent		
females	28	(93.3%)	14	(93.3%)	0.827	NS
Males	2	(6.7%)	1	(6.7%)		

Table 2: Clinical menifestation of SLE patients:

Variables	**Number**	**Percent**
Skin rash	24	80%
Mucosal ulcer	17	57%
Alopecia	11	37%
Arithritis	9	30%
Visual disturibance	4	13%
Headache	14	46.7%
Fever	11	37%
Pericardial effusion	2	7%
Seizure	3	10%
Psychosis	1	3%
Pleural effusion	2	7%

Table 3: Disease activity scores and the laboratory parameters of SLE patients:

Variables	**Range**	**Mean±SD**
Total SLEDAI score	10-34	22.97±5.77
Renal SLEDAI	0-16	7.60±5.97
Extra renal SLEDAI	10-24	15.70±4.17
C3 (mg/dl)	44-119.5	87.63±16.69
C4 (mg/dl)	8.1-55.2	21.90±10.07
BUN (mg/dl)	16-112	45.60±25.72
WBC (103/mL)	2.4-14.4	7.98±3.58
RBC (million/mm3)	3.2-11.4	4.87±1.56
Platelet (103mL)	135-483	247.63±80.36
ESR (mm/hr)	10-80	40.37±18.53
BUN (mg/dl)	16-112	45.60±25.72
S.craetinine (mg/dl)	0.2-3.7	1.37±0.84
24 hr/urine protein (g/day)	0.11-5.5	1.41±1.50

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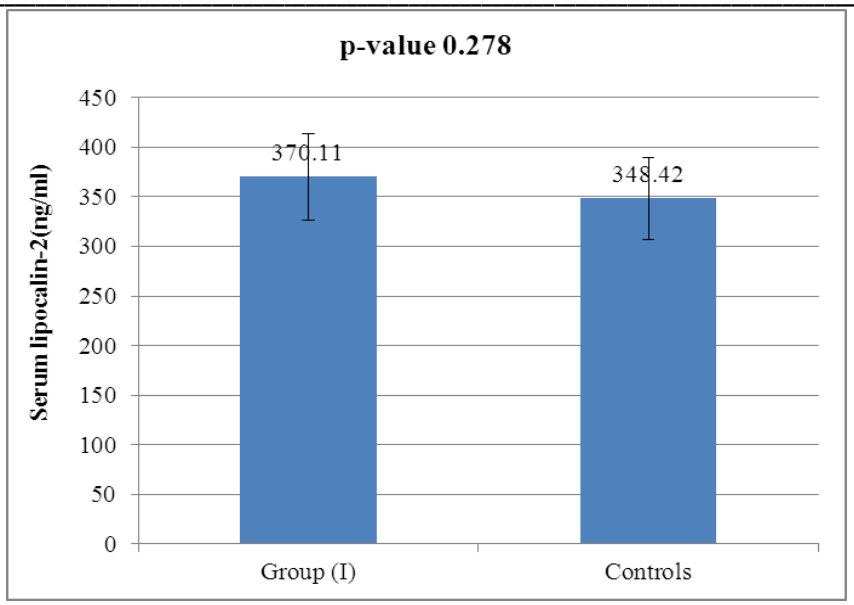

Fig. 1: Comparison between group (I) and control as regards serum lipocalin 2 (ng/ml).

Table 4: Demographic data of SLE patients without lupus nephritis group (II):

Variables	**Range** No.=15	**Mean± SD**
Age (years)	16-40	29.46±7.36
Disease Duration (years)	1-5	2.66±1.11
Sex:	**Number**	**Percent**
females	14	93.3%
Males	1	6.7%

Table 5: Disease activity scores and the laboratory parameters of group II:

Variable	**Range (No.=15)**	**Mean±SD**
Total SLEDAI	10-28	19.133±4.03
Renal SLEDAI	0-4	2.133±2.065
Extra renal SLEDAI	10-24	17.00±4.07
C3 (mg/dl)	44-119.5	89.02±19.66
C4 (mg/dl)	8.2-55.2	23.126±12.025
Hb (gm/dl)	9.7-14-4	11.71±1.50
WBCs (10^3/µL)	2.4-14	7.92±3.98
RBC (million/mm3)	3.2-5.92	4.50±0.833
Platelets (10^3/µL)	161-483	259.86-±89.66
ESR mM/hr	10-70	36.33±15.37
BUN (mg/dl)	16-42	29.33±9.15
Serum Creatinine (mg/dl)	0.2-1.3	0.79±0.27
24 hours urinary proteins (gm/dl)	0.11-042	0.28±0.1007

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Table 6: Comparison of the mean levels of urinary lipocalin-2 and serum lipocalin-2 in group II patients and the control group.

Variables	Group (II) No.=15 Mean ±SD	Controls No.=15 Mean ±SD	p-value	Sig.
Urinary lipocalin2 (ng/ml)	7.933±2.918	3.68±0.526	<0.001	HS
Serum lipocalin-2 (ng/ml)	362.80±55.40	348.42±41.09	0.120	NS

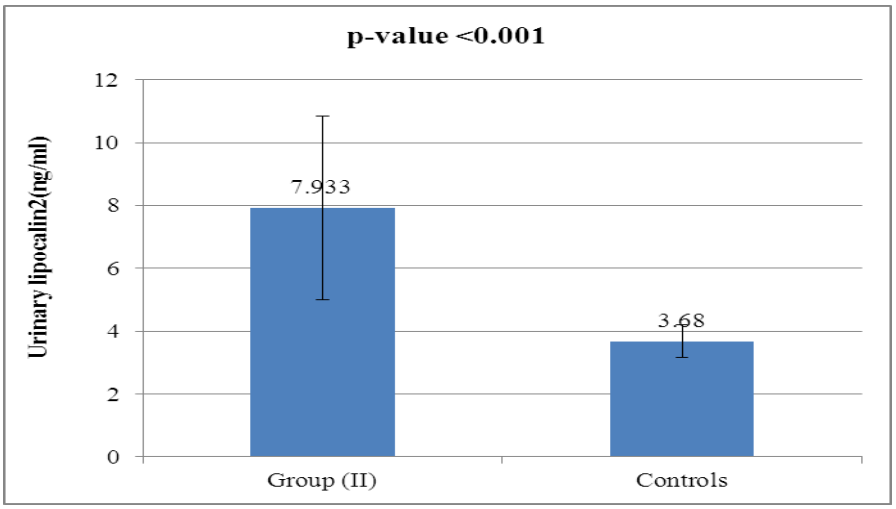

Fig. 2: Comparison between group (II) and control as regards urinary lipocalin 2 (ng/ml).

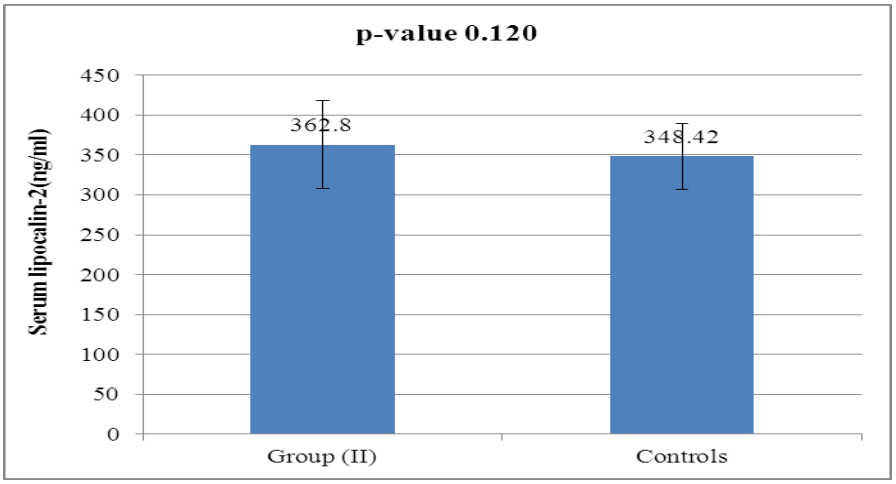

Fig. 3: Comparison between group (II) and control as regards serum lipocalin 2 (ng/ml).

Table 7: Comparison between Group I and Group II as regards demographic data.

Variables	Group (I) (No.=15) Mean ±SD	Group (II) (No.=15) Mean ±SD	P value.	Sig.
Age (years)	32.80±9.29	29.46± 7.36	0.284	NS

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Disease Duration (years)	4.01±2.35		2.66± 1.11		0.054	NS
Sex:	Number	Percent	Number	Percent		
females	14	(93.3%)	14	(93.3%)	1.000	NS
Males	1	(6.7%)	1	(6.7%)		

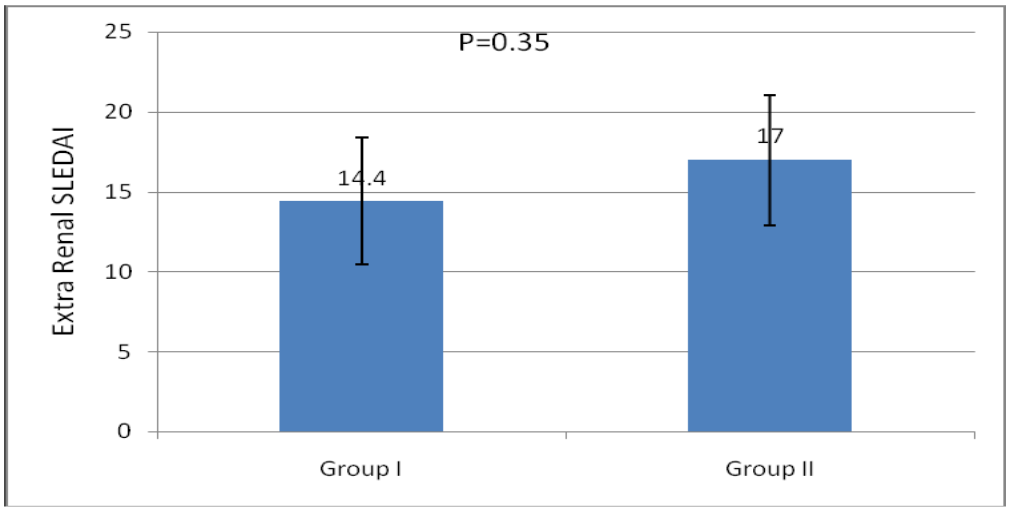

Fig. 4: Comparison between both groups as regards extra-renal SLEDAI score.

Table 8: Comparison between group I and group II as regards the levels of urinary and serum lipocalin-2:

Variables	**Group I No.=15**	**Group II No.=15**	***p*-value**	***Sig.***
	Mean ±SD	**Mean ±SD**		
Urinary lipocalin-2 (ng/ml)	14.417±3.226	7.933±2.918	<0.001	**S**
Serum lipocalin-2 (ng/ml)	370.11±43.81	362.80±55.40	0.752	NS

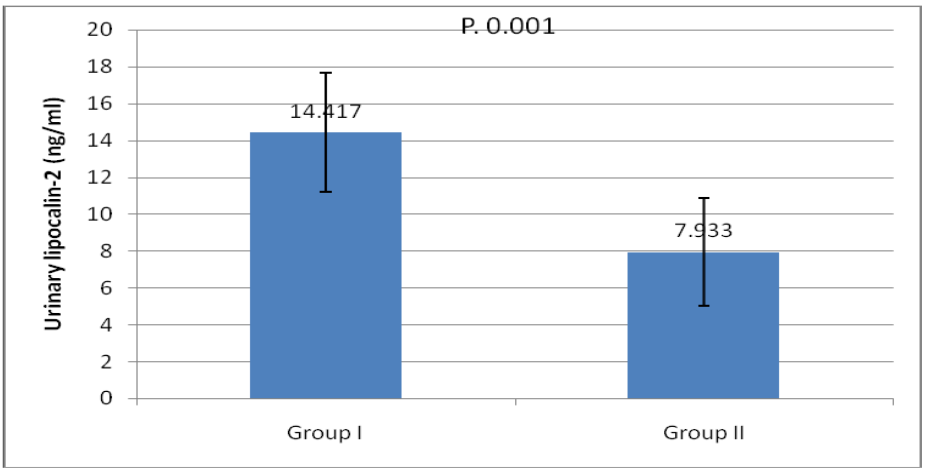

Fig. 5: Comparison between the mean levels of urinary lipocalin-2 in group I and group II.

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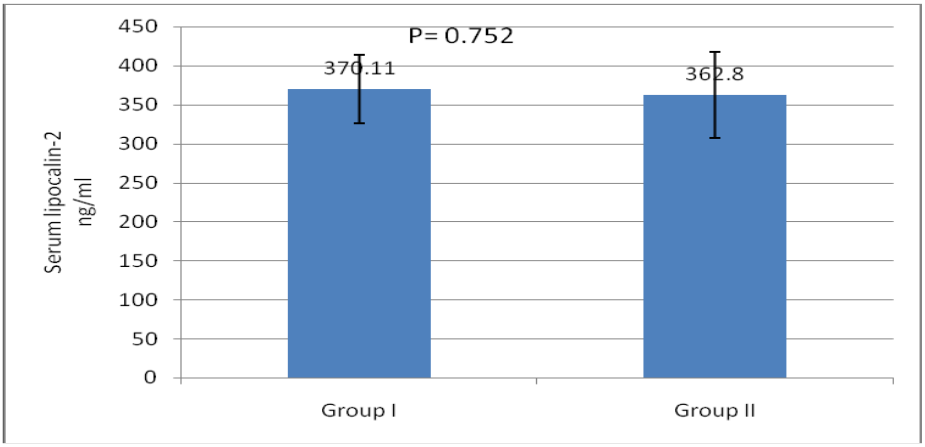

Table 9: Correlations of serum lipocalin-2 with disease activity scores and other labrotory parameters in group I:

Variables	serum lipocalin-2		Sig.
	R	***P***	
Renal SLEDAI	0. 206	0.461	NS
Total SLEDAI score	0.163	0.561	NS
Extra Renal SLEDAI	0.222	0.426	NS
BUN	0.375	0.169	NS
Serum creatinine	0.436	0.104	NS
Disease duration	0.262	0.725	NS
Anti-ds DNA	0.225	0.359	NS
C3	0.235	0.363	NS
C4	0.259	0.352	NS
ESR	0.112	0.691	NS
RBCs	0.006	0.984	NS
WBCs	0.436	0.104	NS
HB	0.582	0.223	NS
Platelets	0.169	0.546	NS
24 hr/urine protein	0.375	0.169	NS

Table 10: Correlations of urinary lipocalin-2 with disease activity score and other labrotory parameters in group II.

Variables	Urinary lipocalin-2		Sig.
	R	***P***	
Renal SLEDAI	0. 335	0.222	NS
Total SLEDAI score	0.054	0.850	NS
Extra Renal SLEDAI	0.223	0.424	NS
BUN	0.224	0.422	NS
Serum creatinine	0.404	0.135	NS
Disease duration	0.177	0.527	NS
C3	0.153	0.587	NS
C4	0.435	0.105	NS
ESR	0.319	0.247	NS
RBCs	0.067	0. 811	NS

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WBCs	0.252	0.365	NS
HB	0.191	0.496	NS
Platelets	0.134	0.634	NS
serum lipocalin-2	0.067	0.813	NS
24 hr/urine protein	0.300	0.277	NS

Discussion:

Systemic lupus erythematosus (SLE) is an immune-complex mediated autoimmune disease characterized by clinical manifestations and fluctuating disease course. Systemic lupus erythematosus (SLE) is an autoimmune disorder which has multi-organ involvements. The pathogenesis of SLE, which involves the various facets of the immune system, is complex and mazed [11,12]. The understanding of this disease includes autoantibodies production and immune complex deposition, which will give rise to the subsequent autoimmune phenomenon. Renal involvement in systemic lupus erythematosus (SLE) is common, with 50% of patients developing lupus nephitis (LN) in the first two years of diagnosis [13]. Lupus nephritis (LN) is one of the most severe manifestations of systemic lupus erythematosus (SLE), which is associated with significant morbidity and mortality of SLE patients. Up to 25% of these patients still develop end-stage renal disease (ESRD) 10 years after the onset of renal compromise [14]. The pathogenesis of LN is a complex process involving the deposition of autoantibodies in the glomerulus, activation of complement and macrophages, cell proliferation, production of extracellular matrix proteins, pro-inflammatory cytokines, and chemokines [15,16], which are then linked through multiple mechanisms to cause tubular damage, tubulointerstitial inflammation, and fibrosis. Different pathological conditions may be involved in the production of this molecule. Lipocalin-2 is a protein that plays an important role in iron transport [17,18]. The protein is produced in the immature neutrophil precursors in the bone marrow and stored in specific granules for subsequent release. In renal injury, lipocalin-2 is highly accumulated in the human kidney cortical tubules, blood, and urine, after nephrotoxic or ischemic injuries. Thus lipocalin-2 might represent an early, sensitive, non-invasive biomarker for acute renal injury.

In the present study, urinary lipocalin-2 levels were significantly higher in all SLE patients when compared to controls ($p =<0.001$) [19]; this comes in agreement with Pitashny and His Co-Workers in 2007, who studied 70 patients with SLE and reported also a highly statistically significant difference in the levels of urinary lipocalin-2 in all SLE patients compared to the control group. Suzuki and his colleagues in 2008 found results that matches with our current one as regards lipocalin-2 levels in SLE patients. Our results come in agreement with the study done by Farzaneh and his colleagues in 2013, who studied fifty-two lupus patients; urinary lipocalin-2 levels in LN patients were significantly higher than those in non-LN patients [20,21]. Also, our results were in accordance with the study done by Hammad, who studied 33 children with active SLE (22 with and 11 without LN) and compared them with 15 matched controls. Levels of urinary NGAL were higher in patients with LN than those without LN [22]. These findings come in consistent with previous work done by Youssef and his co-worker in 2015, who studied 44 SLE patients and divided them into two groups, group I (twenty-two patients with LN) and group II (twenty-two patients without LN), the urinary lipocalin-2 had the highest mean levels in LN patients (group I) compared to group II and controls with a statistically significant difference. Also, between SLE patients without nephritis (group II) and controls.

Conclusion:

In this study, urinary lipocalin-2 was significantly higher in the SLE patients compared to the control group, and the lupus nephritis patients, when compared to the patients with SLE without nephritis, showed significantly higher levels of urinary lipocalin-2. The significant association of the urinary lipocalin-2 with the renal SLEDAI shows that urinary lipocalin-2 can be an early biomarker to diagnose patients with lupus nephritis and to detect renal disease activity. In addition to its excellent diagnostic performance for discriminating patients with lupus nephritis from other SLE patients, even though the serum lipocalin-2 did not prove its usage in the assessment of the renal disease activity in SLE patients as was expected, indicating that renal epithelial cells were the major source of lipocalin-2. An important clinical conclusion is that adding measurement of urinary lipocalin-2 to the routine follow-up of LN patients may result in the earlier diagnostic marker for kidney function deterioration in SLE, provide additional clinically relevant information about disease activity to that given by the established marker and, therefore less delay in choice of appropriate treatment. Thus, our results are important as they suggest a novel approach to the clinical management of

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lupus patients. Possibly, the determination of urinary lipocalin-2 can be helpful in the evaluation of lupus nephritis in general.

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