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Research Article

Urinary IgM in patients with Lupus Nephritis: A marker or a bystander?

Ahmed Aziz[1], Dalia Fayez[2], Hayam Aref[1], Haitham Ezzat[1*], Rania El-Kabarity[3], Salah Said

[1]Department of Internal Medicine-Nephrology Division-Ain Shams University, Cairo, Egypt.
[2]Department of Internal Medicine-Rheumatology Division-Ain Shams University, Cairo, Egypt.
[3]Department of Clinical Pathology- Ain Shams University, Cairo, Egypt.
*Corresponding author: *haitham_ezzat@hotmail.com*

Abstract

Objective: There is a critical need to identify novel biomarkers for Systemic Lupus Erythematosus (SLE) which is usually associated with lupus nephritis. Urinary IgM has been investigated both in diabetic and non-diabetic glomerular disease. We therefore investigated the diagnostic value of u.IgM in patients with SLE with and without nephritis. **Patients and methods:** This is a cross-sectional observational study in which uIgM levels and the standard markers of SLE and LN activity were measured. **Results:** Ninety patients were recruited: thirty patients with SLE without nephritis, thirty patients with biopsy-proven lupus nephritis and thirty healthy volunteer subjects as a control group. uIgM was elevated in both groups of SLE being higher in those without nephritis (307.83 + 132.572ng/ml) than those with nephritis (284.83 + 133.487ng/mL).In the nephritis group, urinary IgM showed a weak inverse correlation with global SLEDAI (r = - 0.22, p=0.18). Also, it showed an inverse correlation with GFR (r = - 0.33, p=0.02) which was statistically significant, and with renal domain SLEDAI (r = - 0.36, p=0.01) which was also significant. Regarding urinary IgM, statistically significant difference was found between different pathological stages of lupus nephritis being highest in grade V lupus nephritis (f = 2.904, p=0.027). Binary logistic regression showed that urinary IgM>150 ng/mL is a significant independent predictor of LN (Beta-coeff. = 0.87 ,p=0.002 and 0dd's(95%CI)= 1.3). ROC curves have shown that, at a cut off level of 90ng/mL , the sensitivity of urinary IGM for early diagnosis of active LN was 91.5 % with a specificity of 95%. The area under the curve (AUC) for urinary IGM was .972 (95% CI: 0.95-1.00: p < 0.001) ,AUC for GFR was   .132 (95% CI: 0.60-0.205: p < 0.001), AUC for WBCs was 0.661(95% CI: 0.548-0.774: p =.016) , The AUC for RBCs was 0.559 (95% CI: 0.435-0.684: p   = .373) , and the AUC for presence of patholigal casts in urine was 0.556 (95% CI: 0.429-0.682: p   = .403). **Conclusion:** Thus although uIgM might not be useful in differentiating SLE patients with and without nephritis being elevated in both groups, yet, it might be useful to facilitate improved grading of lupus nephritis activity being notably increased with higher pathological grades (class IV and V)and being inversely correlated with GFR.

Keywords: SLE, nephritis, IgM

Background

Immunoglobulin M (IgM), secreted by plasma cells, is the largest antibody in the human circulatory system. Due to its large molecular radius (120 A°), the appearance of IgM in the urine indicates an increased density of large, highly nonselective pores ("shunts") in the glomerular capillary wall, which implicates a severe size-selectivity defect (1).Urinary IgM and IgG (consequence of alterations of the size-selective properties of the glomerular capillary wall) seem to be better markers than albuminuria for detecting and predicting renal injury in patients with type 2 diabetes (2). Increased urinary IgM excretion in patients with nondiabetic glomerular disease is associated with high degree of fibrosis and global glomerulosclerosis. Furthermore, high urinary IgM excretion is a better predictor of decline in kidney function than albuminuria in these patients (3). For patients with ANCA-associated small vessel vasculitis, a high level of urine IgM excretion at time of diagnosis was strongly associated with the development of end stage renal disease, and in addition to old age, also predicted patient survival. IgM in the urine represents the degree of mechanical glomerular damage. IgM may thus be a better marker of glomerular damage (4).To the best of our knowledge, urinary IgM has not been studied in patients with lupus nephritis. This study was thus carried out to explore the possible role of the urinary IgM as a marker of lupus nephritis.

Patients and Methods

Ninty subjects were chosen including:

Sixty patients with SLE, selected from the in-patients and out-patients' clinic of the Rheumatology, Rehabilitation and Physical Medicine Department of Ain Shams university hospitals in the period from December 2013 to August 2014. Every case met at least 4 items of SLE diagnostic criteria revised by American Rheumatism Association in 1982(5,6).
Thirty apparently healthy volunteers matched for age and sex.

An informed consent was obtained from all participants in the study, and the study was approved by the ethical committees of Ain-Shams Faculty of Medicine. Individuals less than 18 years old, diabetic patients, patients with other kidney or autoimmune disease were excluded.

Clinical and laboratory measurements:

Disease activity was evaluated according to the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score (7) and (SLICC/ACR) Damage Index (8).

Laboratory parameters included: full blood count, BUN and serum creatinine, estimation of the GFR using MDRD equation, urine analysis by dipstick, urine microscopy, urine protein/creatinine ratio, ANA and anti-dsDNA antibody titres. Fresh urine samples obtained for uIgM testing were immediately centrifuged to remove sediments and then frozen in aliquots at -80°C for uIgM determination by ELISA.

For renal involvement, renal SLE Disease Activity Index (SLEDAI) was used to assess kidney disease activity. The score consists of the four kidney-related parameters: hematuria, pyuria, proteinuria, and urinary casts. Scores for the renal SLEDAI can range from 0 (inactive renal disease) to a maximum of 16(7) .Since urinary tract infection could also result in abnormal findings on urine microscopy or on a reagent strip test, all SLE patients enrolled in the present study were confirmed to be free of infection by negative urine bacterial culture and by the lack of any features of infection upon follow up in the absence of antibiotic treatment. For our inclusion criteria, any rSLEDAI score >0 was considered as active LN.

All LN patients underwent a kidney biopsy confirming their renal disease histologically. Renal biopsy specimens from LN patients were classified according to the World Health Organization (WHO) criteria: minimal changes (class I), mesangial alterations (class II), focal proliferative (class III), diffuse proliferative (class IV), membranous (class V) glomerulonephritis , advanced sclerosing glomerulonephritis (class VI).

Statistical analysis: Analysis of data was done by IBM computer using SPSS (statistical program for social science version 16).

Results

Thirty SLE patients fulfilled at least four of the 1982 revised American College of Rheumatology criteria for the diagnosis of SLE (28 patients were females and 2 were males, their age ranged from 21 to 48 years with age of (29.47 + 5.812), thirty SLE patients with renal biopsy-proven lupus nephritis (27 patients were females and 3 were males, their age ranged from 21 to 46 years with age of (29.07 + 5.644), and thirty

apparently healthy volunteers matched for age and sex with the SLE patients were recruited. There were two patients with less than 6 months disease duration. So, we were unable to perform global SDI or renal domain SDI for them. Detailed comparison between the studied groups as regards laboratory data and urinary IgM levels is shown in tables 1 and 2.The frequency distribution of renal biopsy results among LN group showed eleven patients were of **grade 4 LN (**the most frequent **36.6%), nine patients were grade 3(30%),five patients were grade 2(16.6%),and five patients were grade 5(16.6%).**

Table (1): Comparison between the studied groups as regards laboratory data by using one way ANOVA test

Variables	Controls n=30	LN n=30	SLE n=30	P	LSD(post hoc test)
Cr	0.92±0.3	1.7±0.3	1.16±0.4	**0.000HS**	-Cont –LN =0.00HS -Cont –SLE=0.00HS -LN-SLE = 0.22NS
BUN	23±5	36.6±11	20.9±8	**0.000HS**	-Cont –LN =0.00HS -Cont –SLE=0.00HS -LN-SLE = 0.00HS
Pr/cr	0.22±0.03	3.2±1.3	0.25±0.12	**0.000HS**	-Cont –LN =0.00HS -Cont –SLE=0.00HS -LN-SLE = 0.01S
Urinary red cells	1±0.2	4±2	1±0.3	**0.000HS**	-Cont –LN =0.00HS -Cont –SLE=0.32NS -LN-SLE = 0.00HS
Urinary pus cells	1±0.3	13±6	1±0.4	**0.000HS**	-Cont –LN =0.00HS -Cont –SLE=0.44NS -LN-SLE = 0.00HS
GFR	83±6	39±8	63.5±18	**0.000HS**	-Cont –LN =0.00HS -Cont –SLE=0.00HS -LN-SLE = 0.00HS
SLEDI global	0	14.6±3	3.9±1.7	**0.000HS**	-Cont –LN =0.00HS -Cont –SLE=0.00HS -LN-SLE = 0.00HS
SLEDI Renal domain	0	11.5±5	0	**0.000HS**	-Cont –LN =0.00HS -Cont –SLE=0.00HS -LN-SLE = 0.00HS
SDI global	0	1.9±0.6	0.6±0.3	**0.000HS**	-Cont –LN =0.00HS -Cont –SLE=0.00HS -LN-SLE = 0.00HS
SDI renal domain	0	0.26±0.06	0	**0.000HS**	-Cont –LN =0.00HS -Cont –SLE=0.00HS -LN-SLE = 0.00HS

Table (2): Comparison between the studied groups as regards urinary IgM level by using one way ANOVA test .

Variables	Controls	SLE	LN	P	LSD(post hoc test)
Mean±SD	34±44	307±138	284±133	**0.00 HS**	-Cont –LN =0.00HS -Cont –LE=0.00HS -LN-SLE = 0.00HS
Median (IQR)	20(6.9-60)	385(220-400)	240(170-400)		

As regards urinary IGM levels and correlation with clinical and laboratory parameters, the values of u.IgM in the study groups are shown in table 2 as mean ±SD, median, IQR. Focusing on the correlation between urinary IgM versus different variables among LN group: urinary IgM showed a weak inverse correlation with global SLEDAI (**r = - 0.22 , p=0.18**). Also, it showed an inverse correlation with GFR (**r = - 0.33, p=0.02) which was stastistically significant,** and with renal domain SLEDAI (**r = - 0.36, p=0.01)** which was also significant. No correlation was found with the extra-renal SLEDAI (**r = 0.06, p=0.70)**. Binary logistic regression was performed to assess the independent predictors for LN activity. I t showed the significant independent predictors of LN by using backward likelihood technique of logistic regression were urinary IgM>150 (Beta-coeff. = 0.87, p=0.002 and 0dd's(95%CI)= 1.3), protienuria Pr/cr>0.41(Beta-coeff. = 0.99, p=0.000 and 0dd's (95%CI)= 1.8), cr>1.35 (Beta-coeff. = 0.92, p=0.000 and 0dd's

(95%CI)= 1.2), BUN>20 (Beta-coeff. = 0.35, p=0.000 and 0dd's (95%CI) = 1.7), GFR<90 (Beta-coeff. = -0.78, p=0.000and 0dd's (95%CI)= 1.5) , renal domain SLEDAI >6 (Beta-coeff. = 0.50, p=0.000 and 0dd's (95%CI) = 1.3) and global SLEDAI >9.5 (Beta-coeff. = 0.55, p=0.000 and 0dd's (95%CI)= 1.2). To assess the diagnostic values of uIgM in discriminating nephropathy of SLE, ROC curves (receiver operating characteristic curves) were constructed. The results are shown in tables 6 and 7. **At a cut off level of 90ng/mL,** the sensitivity of urinary IGM for early diagnosis of active LN was **91.5 %** with a specificity of **95%**. The area under the curve (AUC) for urinary IGM was **.972 (95% CI: 0.95-1.00: p < 0.001)** ,AUC for GFR was **.132 (95% CI: 0.60-0.205: p < 0.001)**, AUC for pus cells **was 0.661(95% CI: 0.548-0.774: p =.016) ,** The AUC for red cells **was 0.559 (95% CI: 0.435-0.684: p = . 373)** and The AUC for pathologigal casts was **0.556 (95% CI: 0.429-0.682: p = .403) .**

Table (3): Urinary IGM levels among different grades of renal pathology in LN patients

Variable		Grade 2	Grade 3	Grade 4	Grade 5	P value (ANOVA F test)
urinary IGM	Mean ± SD	284.00 ± 160.717	251.11 ± 90.062	293.33 ± 149.081	368.00 ± 135.351	.027* (2.904)
	(minimum-maximum)	(80 – 500)	(160 – 400)	(80 – 500)	(140 – 500)	

Table (4): Correlation between urinary IgM versus different variables among LN group by using Spearman correlation.

Variables	Urinary IgM	
	r	P
Age	0.24	0.33
Cr	-0.12	0.50
BUN	-0.08	0.60
GFR	**-0.33**	**0.02S**
Global SLEDI	-0.22	0.18
Renal domain SDI	0.26	0.30
Renal domain SLEDAI	**-0.36**	**0.01S**
Non renal SLEDAI	0.06	0.70
Global SDI	-0.18	0.86
Urine RBCs	-0.19	0.35
Urine WBCs	-0.05	0.90
Pr/cr	-0.18	0.23

Table (5) : Correlation between nephropathy versus different predictors by binary logistic regression analysis

Variables	Beta-coefficient	P	0dd's(95%CI)
Urinary IgM≥150	0.87	0.002	1.3(0.5-11)
Pr/cr≥0.41	0.99	0.000	1.8(0.2-18)
Cr≥1.35	0.92	0.000	1.2(0.6-12.5)
BUN≥20	0.35	0.000	1.7(0.3-14)
GFR≤90	-0.78	0.000	1.5(0.3-20)
Renal domain SLEDI≥6	0.50	0.000	1.3(0.2-11)
Global SLEDI≥9.5	0.55	0.000	1.2(0.6-17)

Table (6): Receiver operating characteristic curves (ROC) of u.IGM , GFR for the diagnosis of LN activity

Test Result Variable(s)	Area	P value	95% Confidence Interval	
			Lower Bound	Upper Bound
Urinary IGM	.972	< .001 *	.943	1.000
GFR	.132	< .001 *	.060	.205

Table (7) : Receiver operating characteristic curves (ROC) of u.IGM , WBCs,RBCs and pathologigal casts for the diagnosis of LN activity

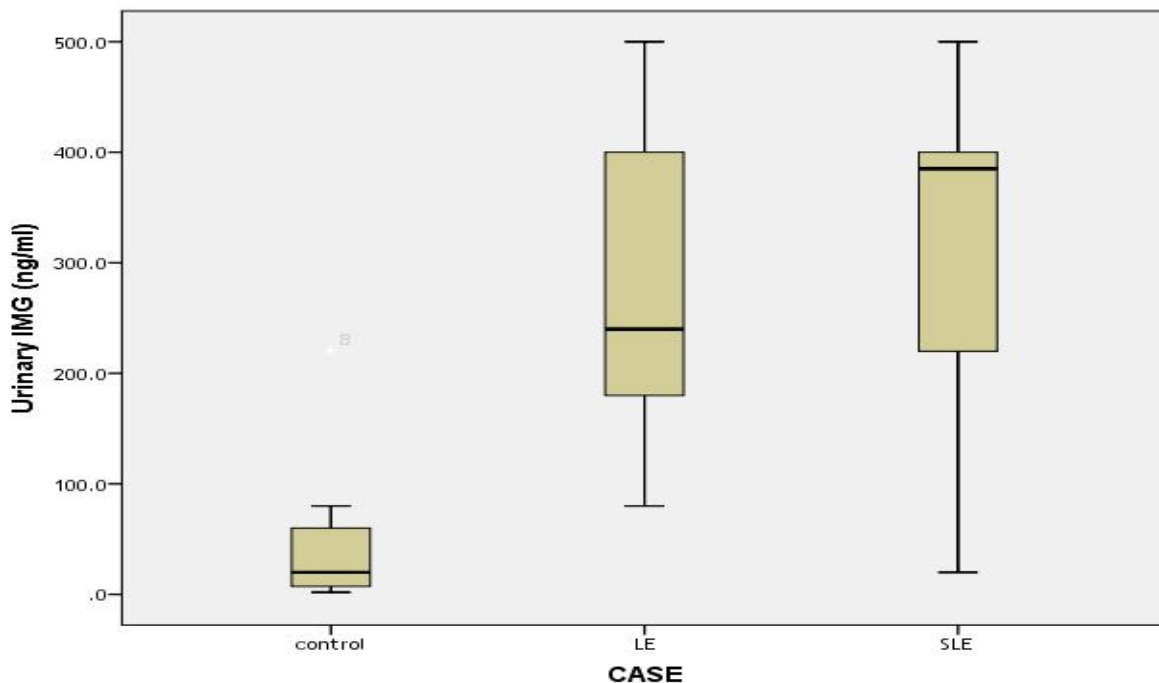| Test Result Variable(s)	Area	P value	95% Confidence Interval	
			Lower Bound	Upper Bound
Urinary IGM	.972	< .001 *	.943	1.000
WBCs	.661	.016*	.548	.774
RBCs	.559	.373	.435	.684
Presence of pathologigal casts	.556	.403	.429	.682

Fig.1: uIGM levels in all studied groups The horizontal line across the boxes represent the median value of uIGM levels among different groups: the areas between the upper and lower limits of boxes represent the interquartile range; the vertical lines protruding from the box represent the maximum and minimum values of uIGM levels respectively. Highly statistical significant difference was found (f = 51.743,p<0.001).
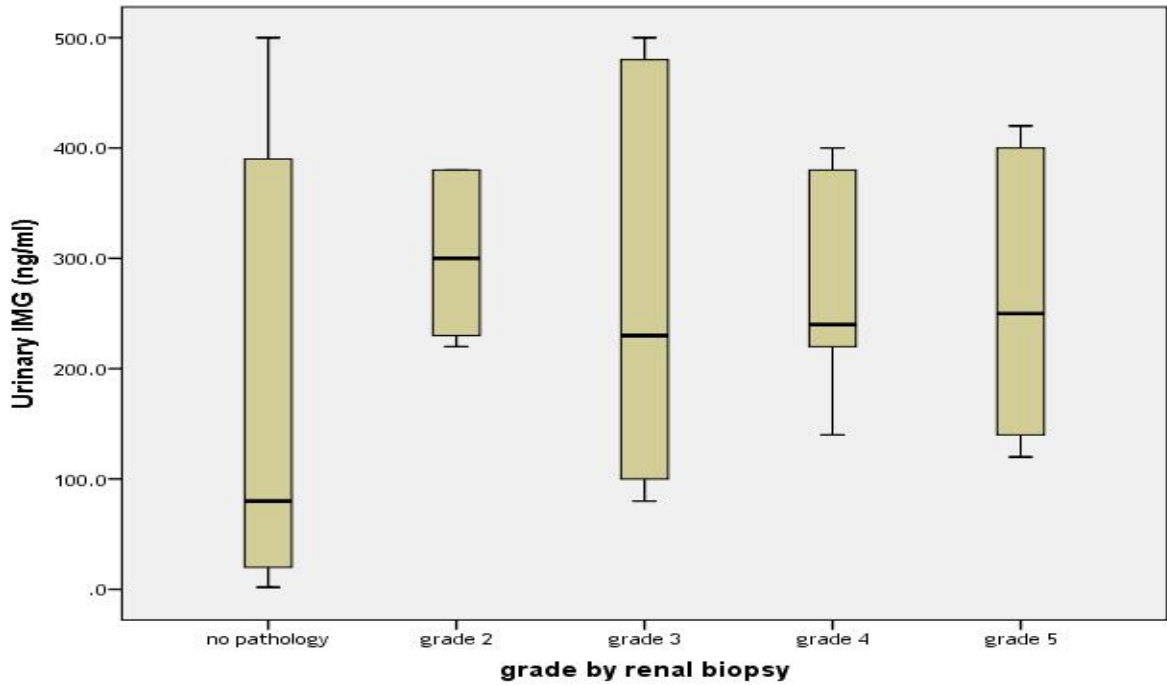
Fig.2: Comparison between different grades in renal biopsy regarding urinary IGM (ng/mL) The horizontal line across the boxes represent the median value of uIGM levels among different groups: the areas between the upper and lower limits of boxes represent the interquartile range; the vertical lines protruding from the box represent the maximum and minimum values of uIGM levels respectively. Highly statistical significant difference was found (f = 2.904 ,p=0.027).
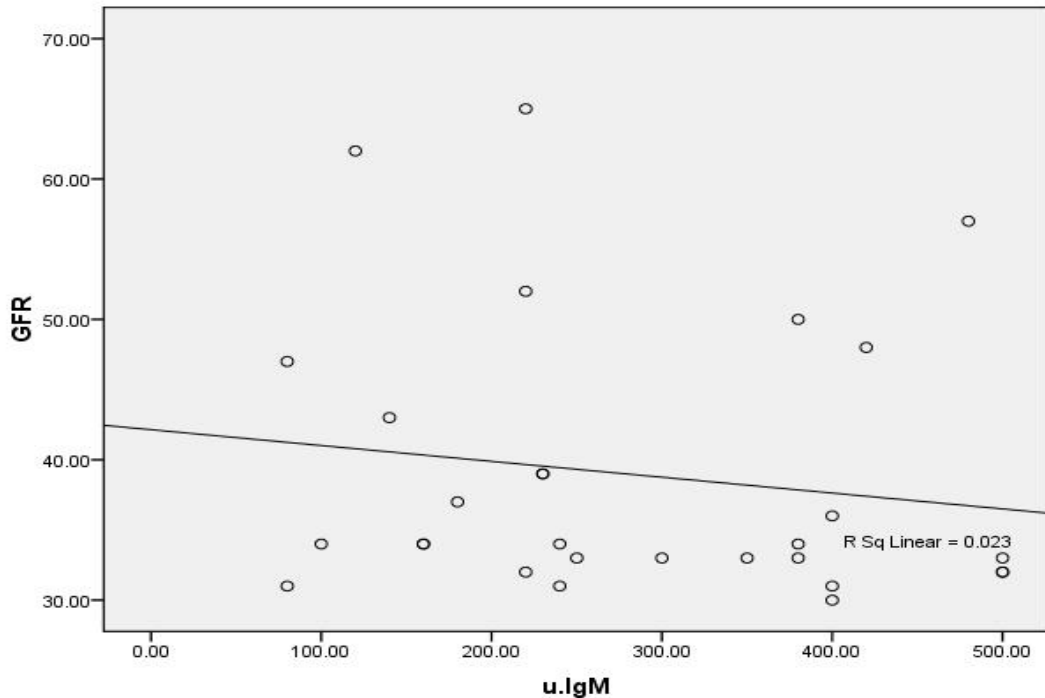

Figure 3: Correlation between urinary IgM versus GFR among LN group.
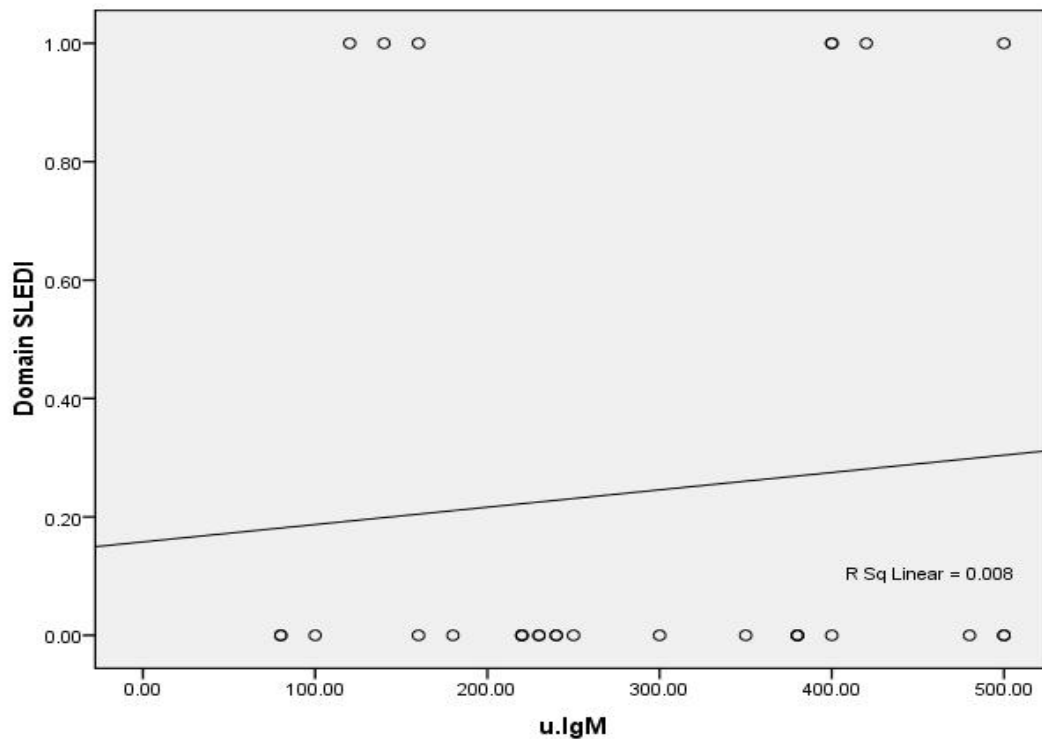Urinary IgM inversely correlated with GFR(R= - 0.33, P= 0.02).

Figure 4: Correlation between urinary IgM versus renal domain SLEDI among LN group.
Urinary IgM inversely correlated with renal domain SLEDI(R= - 0.36, P= 0.01).

Discussion

Renal involvement in SLE contributes significantly to patient morbidity and mortality (9).Renal biopsy is the gold standard for providing information on the histological classes of lupus nephritis and the relative degree of activity and chronicity in the glomeruli. However, it is invasive and serial biopsies are impractical in the monitoring of lupus nephritis. Thus, novel biomarkers that are able to discriminate lupus renal activity and its severity, predict renal flares, and monitor treatment response and disease progress are clearly necessary (10).Hence, it is essential to find a non-invasive biomarker that could be used for the monitoring of LN disease activity as well as early diagnosis of flares (11).In recent years, there have been several studies demonstrating association of urine biomarkers with lupus nephritis, including CSF-1(10), ICAM-1 (13); NGAL (14), TWEAK (15), OPN and MCP-1 (16), ET-1 (17), transferrin, ceruloplasmin (18,19), alpha1-acid-glycoprotein(19), lipocalin-type prostaglandin-D synthetase (L-PGDS(18,19), free light chain Ig (18,20), VCAM-1 (13,21), CXCL16 (21), haptoglobin (22), adiponectin (23), and IL-6(24).Urine biomarkers are attractive candidates as non-invasive alternatives in the diagnosis of lupus nephritis. Preferably, the selected urinary marker(s) must also accurately reflect underlying or ongoing renal pathology. In this cross-sectional study of 60 patients with SLE with and without nephritis as well as 30 healthy control subjects, we evaluated the role of urinary IgM levels as a non-invasive biomarker for LN activity and investigated its correlations with current standard laboratory markers and disease activity indices. We found that uIgM levels were higher in both patients' groups, it showed highest values in those with SLE without nephritis (307.83 + 132.572ng/ml) followed by those with nephritis (284.83 + 133.487ng/mL) while in the control subjects, levels were as low as (34.79 + 44.575ng/mL) with a highly significant statistical difference between the three groups (p<.001). In our results, regarding uIgM level, there was a statistically significant difference (f = 2.904, p=0.027) between the histopathological groups of lupus nephritis, being highest in WHO classes V and VI. This may lead us to the speculation that high uIgM may occur during deterioration of renal disease in SLE patients. In a correlation between urinary IgM versus different variables among LN group, urinary IgM was inversely correlated with global SLEDI (r = - 0.22, p=0.18). It also inversely correlated with GFR, which was statistically significant (r = - 0.33, p=0.02) and with renal domain SLEDI which was also statistically significant (r = - 0.36 , p=0.01) . No correlation was found with the extra - renal SLEDAI (r = 0.06,

p=0.70). It reflects that these correlations were due to renal damage in LN patients and were specific for the renal insult. In turn, it strongly suggests that urinary IgM levels could potentially serve as a biomarker of renal disease activity. Similarly, Pitashny M. et al who studied urinary lipocalin-2 as a biomarker in LN found that Levels of urinary lipocalin-2 showed a weak correlation with the total SLE Disease Activity Index (SLEDAI) score (r =0.254, P =0.034), while , stronger correlation was found between levels of urinary lipocalin-2 and the renal SLEDAI score(r =0.349, P =0.003). However, when only extra-renal manifestations (the extra-renal SLEDAI) were considered, the correlation with urinary lipocalin-2 was lost (r =0.066, P =0.586). They concluded that the association of urinary lipocalin-2 with active lupus was primarily dependent on the renal components of the score (25).In our results, urinary IgM did not significantly correlate with proteinuria among LN group (r = -0.18, p = 0.23), indicating that the presence of uIgM cannot be explained by renal protein excretion. One possible explanation could be similar to that presented by Bakoush O .et al who found that high urinary IgM excretion correlates with decreased GFR in primary glomerular diseases regardless of the degree of albuminuria. In parallel, low urinary IgM excretion indicates beneficial prognosis in these diseases. Since IgM passes the glomerular barrier entirely through large shunts or defects in the glomerular capillary wall, decreased urine content of IgM might be considered as a sign of recovery in the glomerular damage (26). Finally, it is recommended to perform other prospective studies focusing on serial measurements of uIgM in patients with known lupus nephritis to detect flares of renal disease and to study the effects of the different immunotherapies given. As uIgM was an independent predictor for clinically or overtly active LN, it is well known that patients with clinically active LN have a spectrum of renal involvement on renal biopsy which may range from histo-pathologically severe disease to minimal activity in response to treatment. Similarly, patients with clinically inactive LN also have varying grades of renal histopathologic findings. This further supports the inclusion of uIgM to the current clinical markers as a fine-tuning tool for following LN activity and urges to perform further studies correlating the levels of uIgM with the activity and chronicity indices in renal biopsy specimens which was not done in our study.

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