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Research Article

# Correlation Between Serological Makers and Immunofluorescence Deposits i n Kidney Tissue of Patients with Lupus Nephritis

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**ABSTRACT**

Background: Systemic lupus erythematosus (SLE) is an autoimmune disease. Few biomarkers for SLE have been validated and widely accepted for the laboratory follow-up of inflammatory activity. In SLE patients, with lupus nephritis (LN), complement activation leads to fluctuation of serum C3 and C4 that are frequently used as clinical biomarker of disease activity in SLE. Patients and Methods: In this study the number of patients were 37, seven patients were excluded for incomplete data collection, 28 were females ,2 were males. The duration of the study is two years from 2015 to 2017. Patients were considered to have SLE and LN according to American College of Rheumatology (ACR) criteria, and International Society of Nephrology/ Renal Pathology Society (ISN/RPS). All patients were evaluated with clinical presentation, laboratory investigations. Our patients underwent kidney biopsy according to standard procedure by Kerstin Amann, and their tissue specimens were studied in the laboratory with light microscope (LM) and immunofluorescence microscope reagents. The relationship between the serological markers and immunofluorescence deposits in kidney biopsy of all patients were studied using the statistical analysis of Pearson correlation and single table student's T test. A P value <0.05 was considered statistically significant. Results: The granular pattern of IF deposits was present in all LN patients, and in more than two third of patients these IF deposits presented in glomerular, tubular, and mesangium sites. While less than one third of patients had IF deposits in the mesangium only. There was no statistically significant correlation between serum ANA, anti-dsDNA, and IF deposits of different types. There was significant correlation between serum C3 and C4 hypocomplementemia and IgG immune deposits in kidney biopsy, and there was significant relationship between serum C3 hypocomplementemia and full house immunofluorescence (FHIF) deposits in kidney biopsy.Conclusions:Immunofluorescence deposits is mainly granular pattern in LN patients. There was no significant association between serum ANA, anti-dsDNA, and immune deposits in kidney tissue. Immunofluorescence deposits of IgG type correlates significantly with serum C3 and C4 hypocomplemetemia, and these immune deposits in association with low complement levels correlates with LN flare. There was significant correlation between C3 hypocomplementemia and FHIF.

**Keywords:** lupus nephritis, serological makers, immunofluorescence.

## INTRODUCTION

Systemic lupus erythematosus (SLE) is an immune disorder with a lot of clinical manifestations. Lupus nephritis (LN) is an important and most serious finding of SLE that leads increase of morbidity and mortality among patients with SLE[1-3]. To rise the prognosis of LN we need to advance newer strategies which are further specific for the onset and relapse of activity in renal disease, which allow earlier beginning of management strategies[2]. The pathological processes causing LN may arise before renal function becomes reduced and can be discovered by laboratory parameters[2]. Although the renal biopsy is still the gold standard for diagnosing and classifying the grade of renal inflammation and scarring, its invasiveness as a technique with risk of complications makes it inappropriate for serial checking[3-7]. For these causes, new biomarkers are clearly necessary. A biomarker is a biological, biochemical, or molecular material that can be identified qualitatively and quantitatively by laboratory procedures, that show a relationship with disease pathogenesis or activity at different times. Regarding LN, a perfect biomarker should have the following features: Specific for renal involvement in SLE patients, has proven correlation with renal involvement, Capable for serial monitoring of disease status, superior to classical clinical or laboratory parameters in early predicting renal flares in order to start prompt treatment and inhibit renal damage, capable to gauge severity of renal involvement, so that clinicians can recognize which patients that might benefit from more forceful treatments, has been confirmed in two or more different cohorts. Simple to perform, using minimal infrastructure, and above all, low-cost[2].

Anti-dsDNA antibodies institute an important diagnostic tool for SLE and have been involved in the pathogenesis of renal disease as well as other manifestations of SLE.

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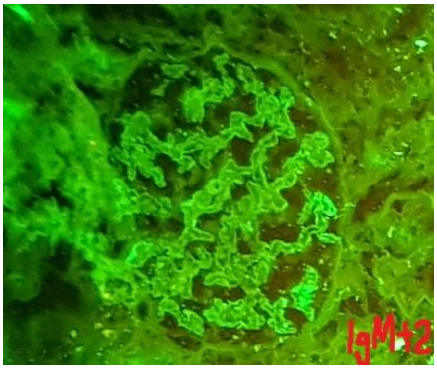


Figure 1

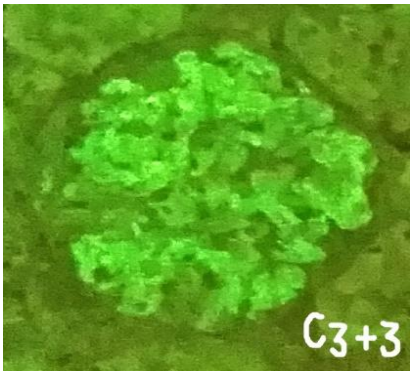


Figure 2

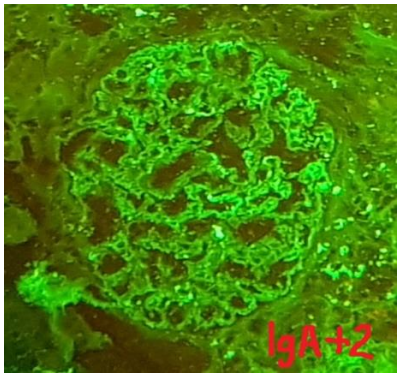


Figure 3

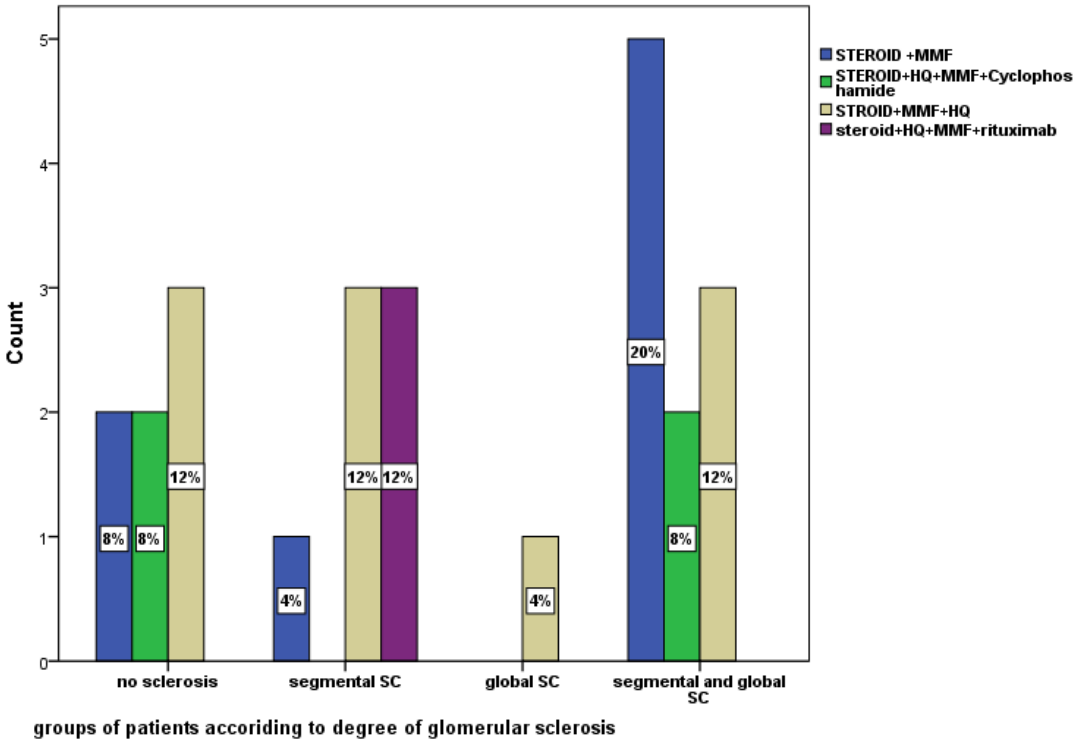


Figure 4: Percentage of treated SEL patients and have glomerular sclerosis.

Antibodies for -dsDNA are existing in renal tissue in higher concentrations compared to systemic circulation[8]. It has been established that before lupus flares the level of anti-dsDNA antibodies in serum often increased. additionally, prophylactic treatment of these patients after rises in anti-dsDNA antibody levels leads to reduction in the occurrence of successive flare up of disease[9-12]. also high levels of anti-dsDNA antibody are linked to more rise of flare up of renal disease in those patients with past history of renal involvment[13]. anti-dsDNA antibodies with different features appear to be linked to different disease expressions. It has been identified, that the Farr assay primarily identifies high-avidity anti-dsDNA antibodies that accompanying renal involvement[14].

The patients with the two autoantibodies; anti-C1q and anti-dsDNA antibodies simultaneously positive presented with the most severe renal histopathological disease activity, such as end capillary hyper cellularity, karyorrhexis/fibrinoid necrosis, sub endothelial hyaline deposits, leukocyte infiltration[15]. High level of anti-dsDNA antibody often precedes an exacerbation by weeks[13]. the ELISA exhibits a sensitivity and specificity of 56–67% and 91–96%, respectively where as in Farr radioimmunoassay the sensitivity 42-85% and specificity of 95-99%[16].

At initial diagnosis Decline of serum C3 and C4 is associated with poor outcome[17]. It has been familiar that low level of circulating C3 and C4 usually seen in LN patients as opposed to patients without renal involvement[18], and throughout LN flares versus non renal flare up[19-21], and more likely to detect lupus patients susceptible to progress to end-stage renal disease. This is clarified by excessive consumption of complement by

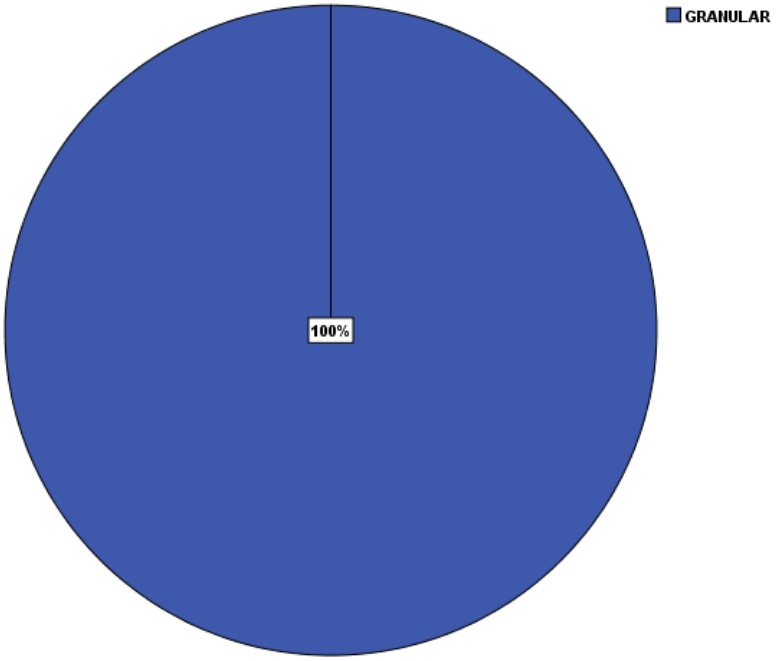


Figure 5: Percentage of the pattern of IF deposits in kidney tissue of LN patients.

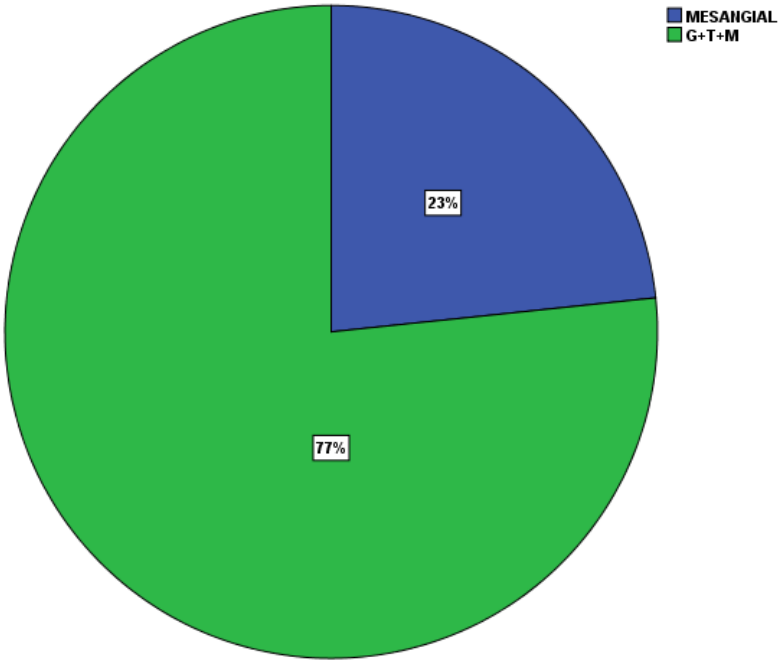


Figure 6: Percentage of IF deposits in glomerular, tubular and mesangial sites.

more activation , also noted that patients with LN not always have low level of C3 and C4, and these complements are not always decreased throughout flare up of LN.

In lupus nephritis immune deposits can be identified in all renal compartments, including the blood vessels, interstitium, tubules and glomeruli . the IF staining pattern in renal biopsy of patient suspected SLE or in doubt is very useful in confirming a diagnosis of LN[22]

It has been estimated that immune deposit of all renal biopsies of patients with progressive LN present in 99% of glomeruli ,50% of tubules and 20% vasculer[23]

The occurrence of renal immune deposits, particularly in the full-house pattern, make the diagnosis of SLE more strong[24], Hill et al[25] found a good association between the severity of proliferative lesions and the amount of immune deposits and even suggested to include in the classification of LN the quantity of immune deposits[26].

In renal biopsy of patient with LN IgM deposit were associated with high level of anti-dsDNA in serum and

Table 1: Correlation between ANA, anti-dsDNA, and different IF deposits in kidney tissue.

| | | GIgG | GIgM | GIgA | GC3 | C1Q | FHIF |
|---|---|---|---|---|---|---|---|
| ANA | pearson correlation | .266 | .086 | .128 | .029 | .138 | .279 |
| | P value | .220 | .697 | .560 | .894 | .529 | .197 |
| anti-dsDNA | pearson correlation | .230 | .125 | .098 | .119 | .132 | .128 |
| | P value | .291 | .570 | .657 | .589 | .548 | .559 |

also considered as nonpathogenic and has protective role as suggestion[27] and new experimental evidence that IgM auto antibodies help in reduction of severity of IgG mediated inflammation support this concept[28,29].

In glomeruli IgG is usually dominant in intensity with lesser quantities of IgA and IgM.[30]Using full house immunofluorescence staining denotes to the presence of all three immunoglobulin and both complements (C3and C1q).[30]C1q is less frequent complement component than C3[31,32]. Glomerular immune deposits are frequently in the mesangium and in some cases possibly the only location for renal deposits[33].

Patients and methods: Over a period of two years started from 2015 to 2017, we collected kidney biopsy specimens from thirty seven SLE patients, 28 were females and 2 were males, who were referred to AL-kafeel center of nephrology and kidney transplantation,kerbala hole,Iraq.All patients were diagnosed as SLE if fulfilled ≥4 ACR[34] criteria for SLE. Seven patients were excluded from the study due to the following reasons: two of them did not complete the investigations required for the study, three patients the biopsy not stained by the immunofluorescence required for the study, and two Patients did not agree to do the kidney biopsy. For all patients detailed history and physical examination were done. All patients underwent routine and specific investigations for LN. The values of serological markers were categories as the following: ANA levels are considered negative if value less than 1.0 IU, weakly positive if value 1.1-2.9 IU, positive if value 3.0-5.9 IU, strongly positive if greater than 6.0 IU[35]. Anti-dsDNA normal value less than 30.0 IU/ml, positive if >75.0 IU/ml, strongly positive if >100 IU/ml. [35]Serum C3 normal value more than 80 mg/dl, low level if 20-60 mg/dl strongly low < 20 mg/dl[35].Serum C4 level considered normal if more than 12mg/dl, low level if 5-12 mg/dl, strongly low level if < 5 mg/dl[35]. After completing the investigations each SLE patient in this study was considered as a case of LN if have one of the following ACR criteria[36]:Proteinuria persistent 0.5 gm. Per day or greater than 3+by dipstick, And /or cellular casts comprising red blood cells casts, granular, tubular or mixed casts. Active urinary sediment ≥5 RBCs/high-power field [HPF], ≥5 white blood cells [WBC]/HPF in the absence of infection.

In this study LN patients were divided into three groups according to the duration of SLE: < two years, two to four years, >four years.

All patients were informed about the indications, method used and possible complications of kidney biopsy procedure beforehand, and signed informed consents were taken. The procedure were done according to the standard guideline by Kerstin Amann[37]. Three cores were taken from either the right or left kidney under ultrasound guidance, with assistance of trained interventional radiologist.1 core was kept in 5% formalin contained test tube, 2 cores were kept in 0.9% isotonic saline contained tube, and all the specimens were sent immediately after the procedure to the laboratory for Immunofluorescence and light microscopic study. The following reagents were applied for all the biopsies:Hematoxylin and eosin stain, Periodic acid–Schiff (PAS) stain, Trichrome stain, Methenamine silver stain, Congo red stain, IF protein stains which includes: anti-IgG antisera, anti-IgA antisera, anti-Ig M antisera, anti-complement C3 antisera, anti-complement C4 antisera, anti-complement C1q antisera. Each specimen was studied by 2 different pathologists and specimen should contain more than or equal to 10 glomeruli for LM study, and >5 glomeruli for IF study[37].

For IF study, a semi quantitative scale was used. This scale is calibrated by the pathologist is considered: 0= negative Immunofluorescence, 1+= mild intensity.2+ = moderate intensity, 3+ = severe or high intensity according to: Severity of deposits, Site of the deposits:glomerular, tubular, mesangial, Pattern of deposits :granular, linear. Type of the deposits:IgG,IgA,IgM,C1q,C3,C4

After IF staining each SLE patient was defined as FHIF according to the presence in renal tissue of both complements(C3and C1q) and all Ig classes(IgG, IgM,IgA)[38]. We use Statistical package for social sciences (SPSS) version 24 computer program by choosing chi square test, Pearson correlation, and single table student "T" test. P values <0.05 was considered statistically significant.

Results: The granular pattern of IF deposits predominated in all LN patients (figures1,2,5). About two thirds of patients had their IF deposits in glomerular, tubular, and mesangial sites. While about one third of patients had their IF deposits in the mesangium only (figures 3,6).

G= glomerular, T= tubular, M= mesangium

The total percentage of treated LN patients who have variable degree of glomerular sclerosis in kidney biopsy is 83.3%, the Incidence of glomerular sclerosis (segmental and global) in patients taking Hydroxy Chloroquine was less than 12%, the incidence of glomerular sclerosis in patients taking MMF combined with steroid was the highest (20%), the incidence of glomerular sclerosis was less than 12% in patients taking MMF combined with steroid and Hydroxy Chloroquine and Rituximab, while patients taking Cyclophosphamide in combination with steroid and Hydroxy Chloroquine and MMF have less than 8% glomerular sclerosis. (Figure 4).

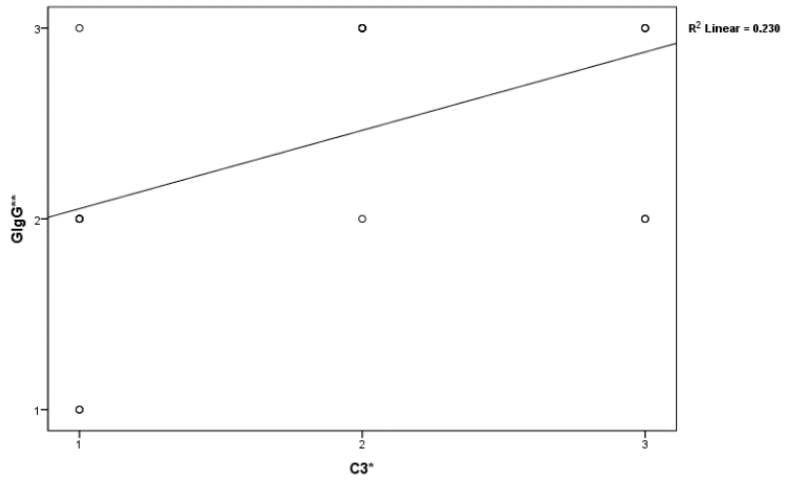


Figure 7: correlation between C3 hypocomplementemai and glomerular IgG deposit P value=0.038.
* 1= normal serum C3 level more than 80 mg/dl, 2= low serum C3 level 20-60mg/dl, 3= strongly low serum C3 level less than 20 mg/dl
** 1= 1+ IF intensity, 2= 2+ IF intensity, 3= 3+ IF intensity.

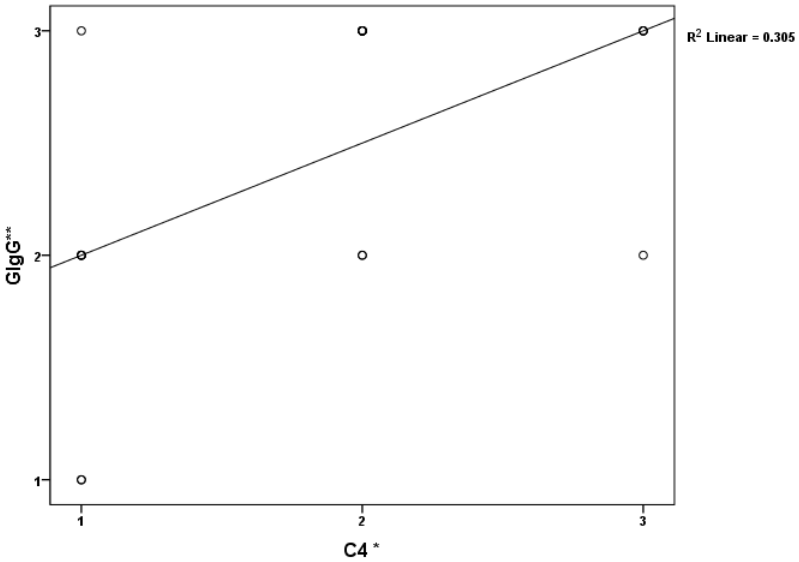


Figure 8: correlation between C4 hypocomplementemai and glowerular IgG deposit P value=0.014.
* 1= normal serum C4 level more than 12 mg/dl, 2= low serum C4 level 5-12 mg/dl, 3= strongly low serum C4 level less than 5 mg/dl
** 1= 1+ IF intensity, 2= 2+ IF intensity, 3= 3+ IF intensity

HQ= Hydroxy Chloroquine, SC= sclerosis, MMF= Mycophenolate mofetil

There was no statistically significant correlation between serum ANA, anti-dsDNA, and IF deposits of different types. P value >0.05 see table 1.

Patients with low levels of C3 and C4 were associated with significantly higher intensity of glomerular IgG deposits, for C3 and IgG correlation coefficient= 0.48, P value= 0.038. For C4 and IgG Correlation coefficient= 0.55, P value= 0.014 was statistically significant see figure 7 and 8.

There is one quarter of patients who have strongly low serum C3 level and FHIF deposits while there is 1/3 of patients who have normal serum C3 and have FHIF deposits. (Figure 9)

## DISCUSSION

In this study we detected granular IF deposits in all patients. This pattern is often seen in focal and diffuse PLN that is mentioned in the atlas of renal pathology[39,40]. In this study we found that almost two third of patients have IF deposits distributed in glomerular, tubular, and mesangial areas. This may indicate these patients had high grade of proliferative lesions that was distributed over different areas,in the glomerular tuft the distribution of immune deposits will determines the proliferative

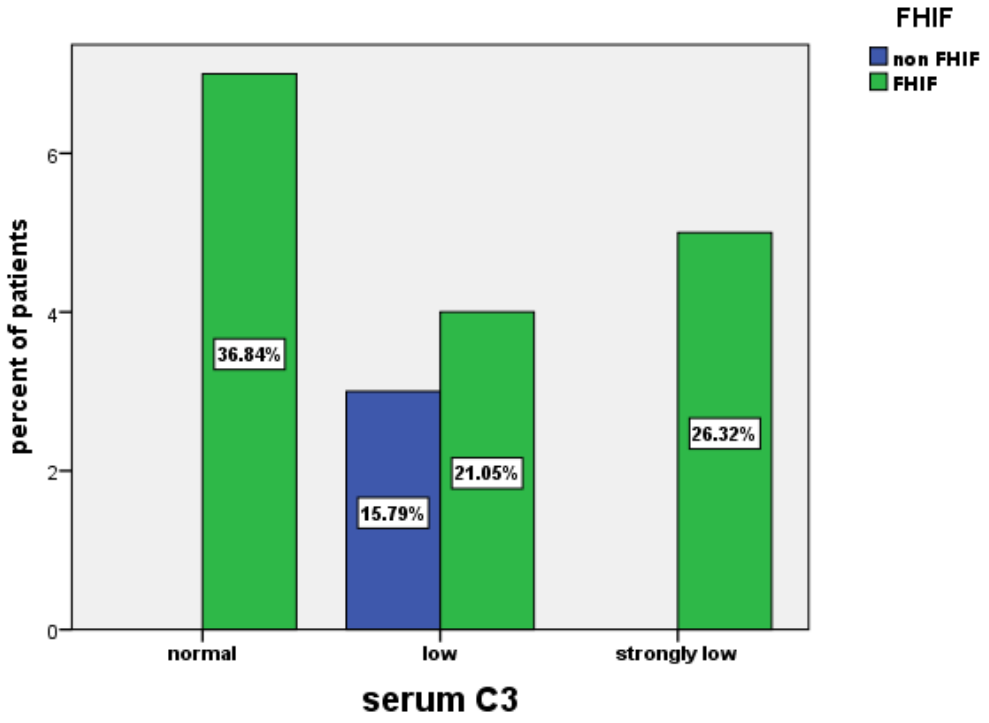


Figure 9: Correlation between C3 hypocomplementemai and FHIF P value <0.05.
Normal serum C3 level more than 80 mg/dl, 2= low serum C3 level 20-60mg/dl, 3= strongly low serum C3 level less than 20 mg/dl

response and the pattern of immune deposition serving in interpretation of glomerular lesion that result[28,41]. So further studies is recommended to determine the relationship between the distribution of IF deposits and the histopathological grade.

In this study no significant association between serum ANA, anti-dsDNA, and immune deposits in kidney tissue. It has been proven in different studies that lupus flares often preceded by increase in serum anti-dsDNA antibodies moreover using prophylactic treatment of patients After rises in anti-dsDNA antibodies levels lead to reduction in incidence of consequent flares of disease[12-15]. Furthermore, serum levels may be a weak reflection of changes at tissue levels and this was mentioned in a study done by Nossent JC[42]. This study showed no association between serum levels of ANA, and anti-dsDNA with IF deposits and this may possibly duo to a lack of current IFM to specific antisera, so it's not possible to decide directly if for example, these immune complexes contain anti-dsDNA. In addition this could mean that deposit of IF in LN denotes other autoantibodies such as antiC1q antibodies or anti-nucleasome antibodies and this is mentioned in a study done by Berden JH[43]. We recommend further studies to determine the association between serum levels of other autoantibody such as anti-NCS and anti-C1q with IF in kidney tissue. Also we recommend further researches to identify specific IF anti-sera to dsDNA in this case we can exactly correlate serum levels of anti-dsDNA with IF deposits. In this study there was significant relationship especially between serum C3, C4 hypocomplementemia and IgG deposit, P value=0.03, and P value= 0.04 respectively. Also documented that levels of circulating C3and C4 are lower in patients with LN as opposed to patients without renal[25], also throughout LN flares as opposed to non renal flares[27-29], and further to recognize which patient with lupus susceptible to develop end stage renal disease .

In a study done by Hill et al[34] found strong correlation between severity of proliferative lesions and the amount of immune deposits and recommended to include in the classification of LN the quantity of immune deposits .

In a study done by Esdaile et al[35] on repeat renal biopsies in LN patients and established good correlation between preservation of renal function and decrease in the amount of deposits . Despite all those above-mentioned studies there is significant records that existence of renal immune deposits not always lead to clinical signs and /or inflammation of renal system ,and this making the association between inflammation in PLN and the amount of immune deposits remote from straight forward. This is approved in the newest revision of the WHO classification for renal biopsies in LN ,where class1B with deposits present by IFM is categorized under normal results[35].

We conclude that IF deposits of IgG type correlates significantly with serum C3 and C4 hypocomplemetemia. We conclude these immune deposits in association with low complement levels correlates with LN flare, and we recommend further studies to determine the association between the immune deposits and the histopathological grade in kidney biopsy and comparing it with the serological markers of SLE.

In this study we found a significant correlation between serum C3 and FHIF deposit, P value (0.04).FHIF deposits is recognized as distinguishing feature of LN[17,44], but not pathognomonic for LN as it can occasionally be found in other glomerular diseases such as in IgA nephropathy, membrano-proliferative GN, and post-infectious GN[35,45,46]. A number of studies revealed appearance of nephropathy with FHIF pattern in SLE patient several years before other clinical and serological
Features and recommended that FHIF nephropathy could be the first symptom of lupus patients[47,48]. We conclude that a significant correlation is present between C3 hypocomplementemia and FHIF and we recommends further studies for those patients initially non –lupus FHIF nephropathy looking for clinical features and /or auto antibodies indicative of SLE .

## CONCLUSIONS

IF deposits is mainly granular pattern in LN patients.
High percentage of LN Patients have IF deposits distributed in glomerular, tubular, and mesangial areas.
No significant association between serum ANA, anti-dsDNA, and immune deposits in kidney tissue. IF deposits of IgG type correlates significantly with serum C3 and C4 hypocomplemetemia, and these immune deposits in association with low complement levels correlates with LN flare. Significant correlation is present between C3 hypocomplementemia and FHIF. Further studies to determine the association between the histopathological grade in kidney biopsy and comparing it with the serological markers of SLE.

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