Renal Biopsy Findings in Lupus Patient with Insignificant Proteinuria: Relation To Disease Activity and Clinical Manifestations

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Abstract: Aim of the work: Lupus nephritis (LN) remains one of the commonest and most serious manifestations of systemic lupus erythematosus (SLE) and is associated with significant morbidity and mortality. Early and accurate detection of kidney involvement in SLE improves outcomes. Although renal biopsy is required for proper diagnosis of the histopathological subtype of LN and direction of proper treatment, the decision to recommend renal biopsy can be complex. We aimed to investigate whether SLE patients with insignificant proteinuria have significant renal involvement and need to be biopsied. Also, if there is a relation between severity of nephritis and the overall disease activity and other lupus manifestations. **Patients & Methods:** Forty lupus patients with proteinuria <500 mg/24 hrs were recruited from Ain Shams University Hospitals. Patients were diagnosed according to the 1997 updated American College of Rheumatology revised Criteria for diagnosis of lupus. Assessment of disease activity according to SLE disease activity index (SLEDAI). Renal biopsy was done to all patients and assessed by light microscopy, immunofluorescent and electron microscopy for identification of different pathological classes according to WHO classification. Patients were classified into two groups: Group A: with mild renal affection which was defined as class I or II according to WHO-histopathological classification of renal biopsy and Group B: with moderate to severe renal affection which was defined as class III, or more according to WHO classification. **Results:** All patients (100%) had lupus nephritis by histo-pathological examination according to the WHO classification. About 32.5% of SLE patients with insignificant proteinuria had mild lupus nephritis and 67.5% had moderate to severe nephritis. In Group A: 2 patients (5 %) had class I LN and 11 patients (27.5 %) had class II LN, while in Group B: 13 patients (32.5%) had class III LN, 10 patients (25 %) with class IV LN and 4 patients (10%) with class V LN. Comparing clinical characteristics of both groups; patients with severe LN (Group B) had more disease activity by SLEDAI (P= 0.049), higher ESR levels, higher Anti-dsDNA positivity (P= 0.020) and prevalence of low C3 and C4 levels (P= 0.028 and <0.001 respectively). As well, they were more anemic, leucopenic, lymphopenic and thrombocytopenic than patients with mild LN (group A) {P= 0.020, P = 0.005, P = <0.001and P = 0.050 respectively}. Urinary abnormalities; especially proteinuria and hematuria were significantly higher in patients with severe LN than those with milder LN (P = 0.009 and 0.047 respectively). Furthermore, patients with severe LN (group B) had significant polyarthralgia and history of recurrent thrombosis than those with mild LN (group A) { P =0.011 and 0.035 respectively}. **Conclusion:** We found significant renal involvement (Class III, IV, or V LN) in SLE patients with insignificant proteinuria (< 0.5 gm/24 hrs). Our data suggest that in order to achieve better outcome in SLE patients, renal biopsy should be justified in lupus patients with low proteinuria and without clinical sign(s) of renal affection, especially when they have one or more of the following: polyarthlralgia, recurrent thrombosis, Anti-dsDNA positivity, consumed C3 &/or C4, high ESR, high SLEDAI scores, anemia, leukopenia, lymphopenia, thrombocytopenia, and finally active urinary sediment; especially hematuria.
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1. Introduction

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease that can affect several organs and systems. It is characterized by high production of autoantibodies against nuclear compounds. Immunologic abnormalities, especially the production of a number of antinuclear antibodies, are another prominent feature of the disease; the clinical course of SLE is variable and may be characterized by periods of remissions and chronic or acute relapses. Women, especially in their 20s and 30s, are affected more frequently than men **[1].**

SLE may present with renal manifestations that frequently are difficult to categorize and lupus nephritis (LN) is an important predictor of poor outcome. The type and spectrum of renal injury may remain undiagnosed until full-blown nephritic and/or nephrotic syndrome appear with increased risk of end-

stage renal disease (ESRD). These abnormalities occur within the first few years after the diagnosis of lupus is made on clinical grounds and with the support of laboratory tests in high risk patients. Histological evidence of lupus nephritis is present in most patients with SLE, even if they do not have clinical manifestations of renal disease. An early renal biopsy is helpful in patients with an abnormal urinalysis and/or reduced glomerular filtration rate and the results form the basis for therapeutic decisions **[2].**

The biopsy also provides vital prognostic information based on histological categorization of different types of lupus nephritis, the degree of activity, chronicity and the immunopathogenesis. The use of cyclophosphamide and azathioprine and recently mycophenolate mofetil, reduce morbidity and maintenance therapies reduce the risk of ESRD. Clinical trials underway promise new, effective and safe immunosuppressive regimens for the treatment of proliferative lupus nephritis. With the advent of more aggressive immunosuppressive and supportive therapy, patient survival rates are improving **[2].**

Because early intervention is crucial to prevent poor outcomes, it's imperative that renal biopsy be performed for definitive diagnosis of histopathological subtypes and direction to proper treatment **[3].**

Most patients with SLE develop kidney disease related to this systemic underlying disease process. Renal biopsy plays a crucial role in the diagnosis of the specific form of lupus nephritis in any patient **[4]**. There is significant renal involvement (Classes III, IV, or V Lupus Nephritis) in SLE patients with < 1000 mg proteinuria including patients with proteinuria < 500 mg with or without hematuria. These findings suggest that biopsy be strongly considered in this patient population **[3].**

The aim of the present study was to investigate whether SLE patients with insignificant proteinuria (<0.5gram/24h) have significant renal involvement and need to be biopsied. Also, if there is a relation between severity of nephritis and the overall disease activity and other lupus manifestations.

2. Patients and Methods

Forty lupus patients randomly recruited in the internal medicine department and SLE specialized clinic at Ain Shams University hospitals participated in the present cross-sectional study. All patients were diagnosed according to the updating of the American College for Rheumatology (ACR) revised criteria for classification of SLE **[5]** at time of diagnosis with 24 hours urinary protein less than 0.5gm.

The nature of the present study and a written informative consent was obtained from all patients, which was approved by Ain Shams Medical Ethics Committee.

2.1 Exclusion criteria

Patients with proteinuria >500mg/24hrs were excluded from the study.

2.2 Clinical assessment

All patients were subjected to the following procedures: full medical history; thorough clinical examination including general, systemic and musculoskeletal examination with special emphasis on symptoms and sign of lupus; assessment of disease activity with Systemic lupus erythematosus disease activity index (SLEDAI), where patients with SLEDAI score less than 6 were considered clinically inactive, patients with score 6-11 were considered to have mild to moderate disease activity,while patients with score 12 or more were considered to have severe disease activity **[6].**

2.3 Laboratory and radiologic assessment

Venous blood (8mL) was withdrawn from each subject and 5 mL was placed in EDTA for a complete blood count measurement and the determination of erythrocyte sedimentation rate (ESR). Complete blood count by coulter counter, ESR by the Westergren method and C-reactive protein (CRP) by Avitex (Omega Diagnostics, Ltd., UK) were performed. Kidney function tests (serum creatinine, blood urea nitrogen) were done by calorimetric method. Liver enzymes (ALT, AST, total & direct bilirubin, total proteins and serum albumin) were done by kinetic method. Prothrombin time (PT), International Normalization Ratio (INR) and Partial Thromboplastin Time (PTT). Complete urine analysis, twenty-four hours urinary proteins and corrected creatinine clearance were also performed. Antinuclear antibody (ANA), Anti ds DNA antibody were done using immunofluoresence technique. Serum complement level: soluble antigen concentration was determined by a nephelometric method that involved a reaction with specific antisera (MININEPH HUMAN C3, C4 ANTISERA). It was Considered to be consumed if C3 <89 mg/dl (normally 89-126 mg/dl), C4 <15.5 mg/dl normally (15.5 – 23) mg/dl. Investigations also included Chest X-ray, ECG, echocardiography, abdominal ultrasonography and limb Doppler (when needed).

2.4 Renal Biopsy

Renal biopsy was carried out at the Radiodiagnosis department and histopathological analysis was done at the pathology department of Ain Shams university hospitals.

Using a microtome, sections 5 μm thick were cut from formalin-fixed paraffin embedded tissue blocks and subjected for H&E staining as follows: sections were placed in a 60°C oven for 60 minutes before staining to allow for fixation of tissue on the slide.

Slides were deparaffinized in xylene (2 changes, 10 minutes each). Rehydration was performed by placing the slides in descending grades of alcohol (absolute ethanol for 5 minutes, 90% ethanol for 5 minutes and 70% ethanol for 5 minutes). The slides were then rinsed in distilled water for 2 minutes. Staining with hematoxylin was done for 2 minutes followed by washing in running tap water until the sections were blue. Staining with eosin was then done for 1 minute. Slides were then dipped in 90% ethanol once, and then transferred to absolute alcohol (2 changes 2 minutes each). Finally, the sections were cleared in 2 changes of xylene (5 minutes each), mounted using Canada balsam and covered with clean glass slide covers.

The renal tissue obtained was evaluated by light microscopy. The biopsies were graded according to the classification of lupus nephritis by International Society of Nephrology/Renal Pathology Society (ISN/RPS) **[7]** in which normal glomeruli are designated as Class I lupus nephritis while mesangial hypercellularity represents Class II and a state of lupus nephritis showing focal or diffuse segmental or global endo- or extracapillary glomerulonephritis, with or without mesangial alterations is classified as Class III (focal lupus nephritis) and class IV (Diffuse lupus nephritis) respectively. Membranous nephritis is categorized as Class V, however Class VI is characterized by advanced sclerosis and activity and chronicity scores are used according to **Austin *et al.*[8].**

SLE patients in our work were divided into 2 groups: Group A (mild LN) included Class II LN and Group B (moderate to severe LN) included Classes III, IV & V LN.

Statistical analysis

Data were analyzed statistically using the Statistical program for social science (SPSS) version 12 software as follows : description of quantitative variables as mean, standard deviation (SD) and range, description of qualitative variables as number (N) and percentages. Chi-square test was used to compare qualitative variables and Unpaired t-test was used to compare two independent groups as regard quantitative variables. Mann Whitney test was used instead of t- test in non parametric data (SD more than 50%). Spearman correlation co-efficient rank test was used to correlate categorical parameters. A probability < 0.05 was considered to be significant **(9).**

3. Results:

3.1. Demographic, Clinical and laboratory data of SLE patients

This study included 40 SLE patients with 24 hrs urinary protein below 0.5 gm, 36 patients (90%) were females and 4 patients (10 %) were males. Their age ranged from 16-52 years with mean ± SD of age was 25.975 ± 8.466 and their disease duration ranged from 7-12 months with mean ± SD 9.648 ± 1.584. Other data of these patients are shown in Table 1 when further subdivided into two groups according to renal biopsy.

Table 1: Demographic, laboratory data and disease activity index of the SLE patients included in the study

Classification of kidney biopsies	Group A Classes I & II LN N=13	Group B Classes III, IV & V LN N=27	*P*
Age, yrs mean (±SD)	31.370 (±10.503)	23.923(±5.951)	0.023(S)
Female, N (%)	10 (76.9)	26 (96.3)	0.189(NS)
DD, month, mean (±SD)	8.028 (±1.14)	9.648 (±1.584)	0.002(S)
Serum creatinine, mean (±SD)	0.569 (±0.221)	0.681 (±0.218)	0.138(NS)
Anemia, hematocrit < 33% N(%)	11 (84.6)	25 (92.6)	0.020(S)
Leukopenia, N (%)	4 (30.8)	17 (63.0)	0.005(S)
Neutropenia, N (%)	4 (30.8)	13 (48.1)	0.029(S)
Lymphopenia, N (%)	4 (30.8)	24 (88.9)	<0.001(HS)
Thrombocytopenia, N (%)	6 (46.2)	15 (55.6)	0.050 (S)
ESR, mean (±SD)	72.154(±42.204)	98.963(±32.455)	0.033(S)
CRP positivity, N (%)	8(61.5)	17(63)	0.072 (NS)
SLEDAI score, mean (±SD)	12.692(±3.924)	15.519(±4.210)	0.049 (S)
Low C3, N (%)	9 (69.2)	21 (77.8)	0.028(S)
Low C4, N (%)	2 (15.4)	19 (70.4)	<0.001(HS)
Anti-dsDNA N (%)	11 (84.6)	25 (92.6)	0.020(S)
Antiphospholipid antibody, N(%)	0 (0.0)	6 (22.2)	0.035(S)
24 h urinary protein, mean (±SD)	0.202(±0.087)	0.269(±0.096)	0.039(S)
Hematuria N (%)	0 (0.0)	6 (22.2)	0.035(S)
Red blood cell casts N (%)	1 (7.7)	2 (7.4)	0.564(NS)
PYURIA (%)	4 (30.8)	9 (33.3)	0.166(NS)

DD= disease duration, ESR= erythrocyte sedimentation rate, CRP= C reactive protein, SLEDAI= SLE disease activity index,C3= complement 3, C4= complement 4, Anti-dsDNA= anti-double-stranded DNA.

3.2. Renal biopsy of SLE patients included in the study

The patients in our study were divided into two groups according to the WHO histopathological classification of renal biopsy: Group A: Thirteen patients (32.5%) with mild renal affection class I or II, two patients (5 %) and 11 patients (27.5%) respectively. Group B: Twenty seven patients (67.5%) with moderate to severe renal affection (class III or more), 13 patients (32%) had class III LN, 10 patients (25 %) had class IV LN and 4 patients (10 %) had class V LN.

3.3 Comparison between the two groups of SLE patients

Comparing both groups; patients with Group B were significantly younger in age (P = 0.023), had more disease activity by SLEDAI (P= 0.049), higher ESR levels (P = 0.033), higher Anti-dsDNA titer (P = 0.020) and lower C3 and C4 levels (P = 0.028 and <0.001 respectively). In addition, they were more anemic, leucopenic, lymphopenic and thrombocytopenic than patients with group A (P = 0.020, P = 0.005, P = <0.001 and P = 0.050 respectively). Other demographic, clinical and laboratory data compared in Table 1.

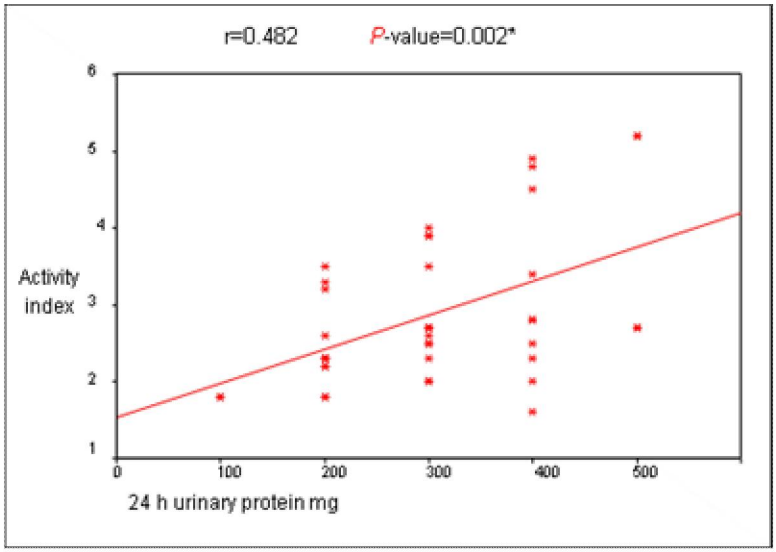

Figure 1: Correlation study between activity Index of renal biopsy and 24 hrs urinary protein.

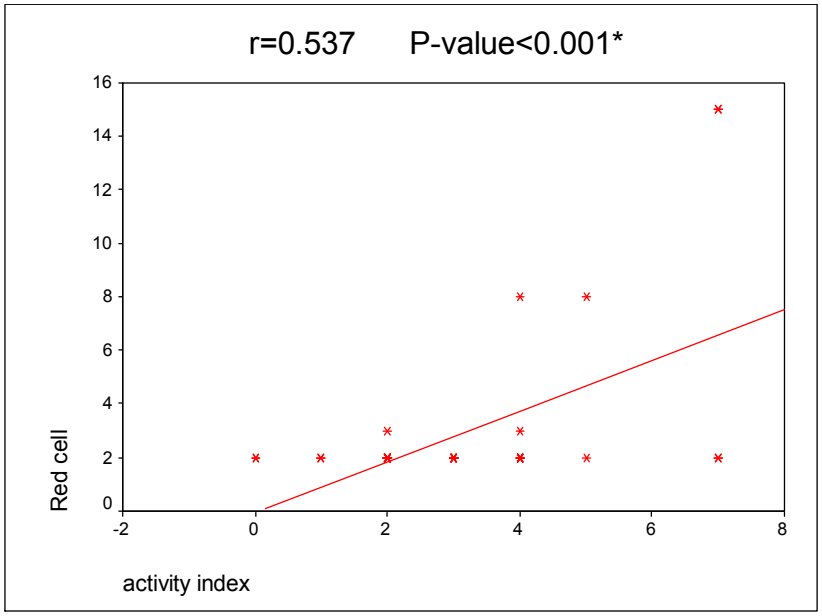

Figure 2: Correlation study between activity Index of renal biopsy and red cells

3.4 Correlation between renal biopsy findings and both proteinuria and haematuria.

There were significant positive correlations between the activity index of renal biopsy and both the 24 hrs urinary protein levels (r = 0.482, P = 0.002; Figure 1) and the presence of microscopic hematuria (r = 0.537, P < 0.001; Figure 2). There were significant positive correlations between the chronicity index of renal biopsy and the 24 hrs urinary protein levels (r = 0.449, *P* = 0.004; Figure 3).

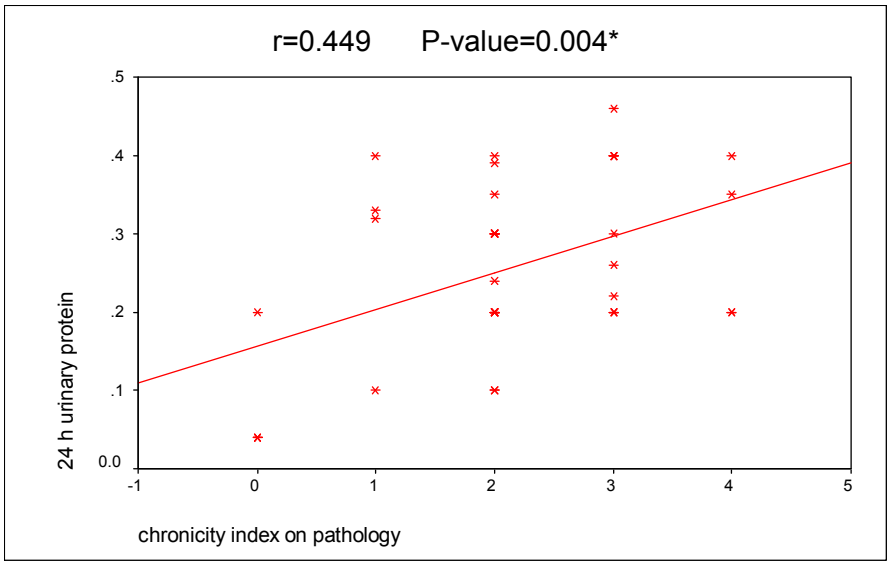

Figure 3: Correlation study between chronicity index of renal biopsy and 24hrs urinary protein.

4. Discussion

Lupus nephritis is one of the most serious complications of SLE leading to significant morbidity and mortality. The clinical presentations of LN are diverse as are the kidney pathologic lesions in SLE. They range variably from asymptomatic proteinuria and/or hematuria to rapidly progressive glomerulonephritis and renal failure. Missing subclinical nephropathy is not uncommon and more accurate screening for those patients at risk of serious renal disorder is important [10].

The incidence of LN varies according to the diagnostic methods used. It is about 60 – 80% if diagnosis is established solely on clinicobiological criteria (e.g. proteinuria, haematuria). On the other hand, it reaches from 95 to 100% when the diagnosis is based on the histo-pathological exam of the kidney biopsy [11].

All SLE patients included in our study (with proteinuria < 500 mg/24hrs) were diagnosed to have lupus nephritis by histopathological examinations according to the WHO classification. Our result agree with that of **Zabaleta-Lanz *et al.***, who found that forty-one (97.5%) out of 42 renal asymptomatic patients had silent lupus nephritis according to histo-pathological findings [12].

In our work, a considerable prevalence of various grades of LN was detected. We divided the SLE patients in our study into two groups according to the WHO histopathological classification of renal biopsy: Group A: Thirteen patients (32.5%) with mild renal affection class I or II, two patients (5 %) and 11 patients (27.5%) respectively. Group B: Twenty seven patients (67.5%) with moderate to severe renal affection (class III or more), 13 patients (32%) had class III LN, 10 patients (25 %) had class IV LN and 4 patients (10 %) had class V LN. This in agreement with **Christopher-Stine** *et al.,* who demonstrated that, in patients with low level of proteinuria, 14% had LN class II, 47% had class III, 9.5% had class IV and 5 % had class V. That suggested renal biopsy is essential to detect early renal involvement and in SLE even in patients with absence of clinical renal affection [3].

On the other hand, some contrasting results were found by **Vargas-Arenas *et al.,*** who studied renal histopathological changes in lupus patients with proteinuria less than 0.3 gm and found that WHO Class II was present in 64% of patients with Lupus nephritis, while the prevalence of class IV was observed in only 7.7% of the cases [13].

In the present study, patients with severe lupus nephritis (group B) were found to have significantly longer disease duration, higher disease activity (SLEDAI score), and higher ESR levels, although no difference was found between both groups regarding CRP positivity. Similarly, a recent Iranian study reported a highly significant correlation between high

disease activity (both SLEDAI and ECLAM) with the cumulative damage in patients with lupus nephritis, in addition, they found significantly higher SDI in patients with longer disease duration [14]. Also, ESR values were found to be more elevated in class III and class IV lupus nephritis than in class II [15].

Anti-double-stranded DNA (dsDNA) antibody is the best serological correlate for lupus nephritis **[16 & 17]**. Anti-DNA antibodies are important diagnostic markers and are actively involved in the pathogenesis of lupus nephritis through their ability to bind to cell surface antigens or components of the glomerular basement membrane either directly via cross-reactivity or indirectly via chromatin material **[18]**. We found that prevalence of anti-DNA antibodies in our study was high (36 out of 40 patients i.e. 90%) and was significantly higher in patients with severe lupus nephritis (group B) (92.6%) than those with mild nephritis (group A) (84.6%). Our results come in agreement with **Manteanu *et al.,*** that revealed Anti- dsDNA antibodies were positive in 100% of the LN patients they studied, their titers being correlated with the disease activity and with the histological type involved **[11].** This is also in accordance with **Wen, 2011**, who found anti-double-stranded DNA to correlate with pathology of LN in new-onset SLE patients **[19]**. An interesting more recent study by **Wakasugi *et al.,*** demonstrated that class III or IV lupus nephritis could be hidden in patients with SLE who present both a high titer of anti-dsDNA antibody and a low concentration of C3, even when they have clinically normal urinary findings and renal function **[20]**.

Ho *et al.,* found that decreases in C3 and C4 were associated with a concurrent increase in renal disease activity **[21]**. **Franco *et al.,*** reported decreased complement levels in all patients with lupus nephritis especially in patients with classes III, IV, V and VI **[15]**. In a more recent study **Birmingham *et al.,*** studied the relationship between serum C3 and C4 levels and lupus renal flare and found that reduced levels of C4, but not C3, were independently associated with the two-month pre-flare period. Conversely, reduced levels of C3, but not C4, were independently associated with the flare visit **[22]**. They found that the main pro-flare effectors were lower C4 levels, higher ESR and younger age, they also identified lower C3 as a significant effector of renal flare. They suggested that C4 activation is critical for initiating renal flare while C3 activation is involved in the actual tissue damage **[22]**. Another study by **Franco *et al.,*** that was performed on 67 patients diagnosed to have lupus nephritis reported that complement levels were uniformly decreased in the population studied especially in patients with the proliferative forms and C4 was more significantly depressed in the proliferative forms of lupus nephritis (classes III and IV lupus nephritis) they found also that C3 levels were lower in the proliferative group, but the difference was not quite statistically significant **[23]**. Similarly **Wen, 2011** demonstrated that decreased C4 complement levels were more common in proliferative LN **[19]** similar also to **Hsieh *et al.,*** and both studies were in early onset renal involvement in SLE **[24]**. Our results were closely similar to the fore mentioned studies as we found that patients with severe lupus nephritis (group B) have significantly lower C3 and C4 levels prevalence than those with mild nephritis (group A).

In the current study, abnormalities of the hematological system were common in patients with severe lupus nephritis (group B) than those with mild nephritis (group A) as we found that anemia, leukopenia especially lymphopenia and thrombocytopenia found to be significantly higher in patients with more aggressive nephritis (group B) than those with mild nephritis. This was in agreement with **Beyan *et al.,*** who found positive correlation between anemia and nephritis **[25]**, also agreed with **Giannouli *et al.,*** who explained that by an inappropriately low level of erythropoietin production by the affected kidneys **[26]**. In addition, strong positive relation was previously reported between lymphopenia and renal involvement by **Vila *et al.,*** in a large SLE cohort study comprising 591 SLE patients **[27]**. Also our results were close to those of a previous Russian study done on 60 lupus nephritis patients as they found a strong relation between thrombocytopenia and activity of nephritis especially those with positive anticardiolipin antibodies, they reported that in active LN platelet activity and metabolism became enhanced **[28]**.

Among our studied patients, history of recurrent thrombosis and arthralgia were significantly higher in group B than group A which is in agreement with the results of **Franco *et al.,*** who found that classes IV and V lupus nephritis test positive for anticardiolipin antibodies more often **[15]**. On the other hand, our data differ from that of **Zaldívar-Alcántara *et al.,*** who found no difference in risk of thrombosis with the histological type of LN **[29]**.

Inspite of the fact that urine analysis is an effective method to diagnose and monitor the activity of lupus nephritis **[10 & 30]**, there is much debate about the correlation between urinary abnormalities and the biopsy findings in lupus nephritis. **Cross and Jayne,** mentioned that urinary abnormalities of hematuria and proteinuria are usually the first clinical indication of lupus nephritis **[31]**. In our study we found that proteinuria (inspite of being insignificant) and microscopic hematuria were found to be

significantly higher in group B (patients with severe nephritis) who also had a higher SLEDAI score than in group A (patients with mild nephritis). In addition, significant positive correlations were found in our study between the activity index of renal biopsy and both microscopic hematuria and 24 hours urinary protein levels, and between the chronicity index and 24 hours urinary protein levels. Similarly, **Hurtado *et al.,*** found that an elevated NIH activity index to be correlated with microhematuria, proteinuria, and impaired renal function **[32]**. Also, hematuria (usually microscopic, rarely macroscopic) with dysmorphic cells indicates inflammatory glomerular or tubulointerstitial disease **[30]**. In addition, **Rahman *et al.,*** found isolated hematuria and isolated pyuria to be associated with active renal (renal disease activity was assessed by scoring renal biopsies) and non-renal disease activity **[33]**. In contrast, other researchers found no significant correlation between the histological type of renal affection and neither haematuria nor proteinuria **[11]** and patients presenting with isolated hematuria were found to have inactive forms of nephritis upon biopsy **[24]**.

In another older study, no correlation was found between the degree of proteinuria and the underlying histology except for patients with class V membranous disease, who tended to have higher levels of proteinuria and they found also that, an elevated chronicity index correlated with renal function, hypertension and microhematuria but not with proteinuria [34].

Finally, we found significant renal involvement (Classes III, IV, or V LN) in SLE patients with insignificant proteinuria (< 0.5 gm/24 hrs). Our data suggest that in order to achieve better outcome in SLE patients, renal biopsy should be justified in lupus patients with low proteinuria and without clinical sign(s) of renal affection, especially when they have one or more of the following: polyarthralgia, recurrent thrombosis, Anti-dsDNA positivity, consumed C3 &/or C4, high ESR, high SLEDAI scores, anemia, leukopenia, lymphopenia, thrombocytopenia, and finally active urinary sediment; especially hematuria.

Our work concludes that the presence of low level proteinuria in SLE patients is strongly associated with significant renal involvement (proved by biopsy) even though without overt clinical signs. Performing renal biopsy for those patients might lead to early diagnosis of LN, early management and better prognosis.

5. Conflict of interest

There is no conflict of interest of the authors.

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