High disease activity is associated with high disease damage in an Iranian inception cohort of patients with lupus nephritis

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Abstract

Objectives

This paper aims to determine disease activity and damage in patients with lupus nephritis (LN) and to evaluate the correlation among these domains and sociodemographic features.

Methods

This study was carried out on 71 lupus patients who were candidate for kidney biopsy due to their clinical renal manifestations. Clinical and sociodemographic data were collected and the Systemic Lupus Erythaematosus Disease Activity Index (SLEDAI-2K updated version), European Consensus Lupus Activity Measurement (ECLAM) and Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) were assessed after 10 days of admission, the day prior to performing renal biopsy.

Results

Sixty-five females (91.5%) and six males (8.5%) were studied. Their age was 24 (21–32) yr and disease duration was 1.5 (0.8–4) yr (median [IQR]). SLEDAI-2K, ECLAM and SDI scores were 25.5±12.3, 6.21±2.45, 2.0±2.3 (mean±SD) respectively. A great relationship between SLEDAI-2K and ECLAM ($r=0.827$, $p<0.001$) was found. SDI was significantly associated with SLEDAI-2K ($r=0.742$, $p<0.001$) and ECLAM ($r=0.699$, $p<0.001$). Age, gender and disease duration had no significant impact on SLEDAI-2K and ECLAM, while SDI was significantly higher in subjects with longer disease duration particularly in those of more than 3 years. Patients with lower education attainment had less medication adherence and higher disease activity and damage.

Conclusion

There is a highly significant correlation of high disease activity with cumulative damage in patients with LN, particularly in those with newly-onset disease. Considering that the first years of SLE are an active critical period which can lead to severe damage, this highlights the necessity of aggressive treatment, tight-organised follow-ups and more patient compliance with the physician orders.

Key words

SLEDAI, ECLAM, SDI, lupus nephritis, medication adherence

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Introduction

Systemic lupus erythaematosus (SLE) is a multi-organ autoimmune disease characterised by a wide array of clinical manifestations, from skin and mucosal lesions to severe inflammation that can lead to scarring of the kidneys or other organs (1). Among various organs affected in SLE, involvement of kidneys appears to be one of the most common, and concomitantly, the most life-threatening complication (1). In randomly-selected lupus patients, abnormalities in urine or renal function occur approximately in 30% through the disease duration (1). However, the prevalence of renal involvement in Iranian SLE patients was shown to be comparatively higher (48–64.5%) (2, 3).

Although SLE is basically characterised by a waxing and waning clinical course, some patients demonstrate a pattern of unremitting chronic activity. Therefore, patients may suffer from numerous complications involving any organs and this emphasises the need for careful and constant monitoring. In this respect, several valid and reliable measures of assessment of patients' clinical condition have been proposed (4). The Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and the European Consensus Lupus Activity Measurement (ECLAM) are instruments that assess lupus disease activity, those potentially reversible impairments which are amenable to therapy (4-6). These two most well-known indices have been shown to be valid, reliable and sensitive to change (7-9). The Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index (SLICC/ACR DI or SDI) is a validated unique instrument which was developed in 1996 to assess SLE disease damage, those irreversible events resulting from lupus disease activity, side effects of medications, or comorbid conditions (10, 11).

The objective of the present study was to assess disease activity and cumulative damage in Iranian lupus patients specifically those with nephritis. We also aimed to evaluate the correlation of disease activity and damage and to determine sociodemographic features and their effects on these two domains.

Patients and methods

Patients

In this inception cohort study which was directed through 2005 to 2011 at Mashhad Imam Reza Educational and Research Medical Centre (an affiliated hospital to Mashhad University of Medical Sciences), 71 consecutive SLE patients who had their first renal symptoms since their disease has been established were enrolled. They had at least 500 milligrams of 24-hour urine protein excretion to include as an eligible candidate for undergoing renal biopsy. All patients fulfilled four or more American College of Rheumatology (ACR) criteria (12), and were closely monitored for at least 10 days. Data comprised of sociodemographic status (gender, age, educational level), disease duration (calculated from the time patients first fulfilled the ACR criteria), patients medication history and level of their adherence, disease activity (assessed by the SLEDAI-2K and ECLAM), and end-organ failure scores (using the SDI) were obtained during a 10-day period monitoring and calculated in the day that patients were prepared for renal biopsy.

Medication adherence

Since the treatment of connective tissue disorders, especially SLE, is prolonged, and chronic use of drugs is the mainstay of therapy and somehow lifelong, adherence to prescribed medications is crucial to halter disease manifestations and lead to remission (13, 14). Medication adherence can be evaluated in different approaches, such as interviews, questionnaires, physician estimate, etc. (14). In the present study, we interviewed all patients and considered adherence to medications qualitatively in 3 levels. "Good" was determined for patients who perfectly complied with their treatment as they believed in the efficacy of treatment, and took their medicines precisely and punctually following the physician's orders. "Fair" was implied for patients who did believe in the efficacy of treatments, but occasionally did not take their medications because they forgot or could not afford the cost. "Poor" was defined for patients who neither

believed in their treatments nor accepted to take medications carefully due to social or economical reasons even for a short period of time.

Measures of assessment

– SLEDAI-2K

The SLEDAI is a disease activity instrument that is brief, easy to administer and with an objective scoring system. SLEDAI-2K is a valid updated version of SLEDAI which was published in 2002 (15). It is a weighted cumulative index, consisting of 24 items grouped into 9 organ systems (relative scores for each item in that organ system is shown in brackets) as follows: central nervous system (8), vascular (8), musculoskeletal (4), renal (4), serosal (2), dermal (2), immunologic (2), haematologic (1) and constitutional (1). All items present within 10 days prior to assessment contribute to the SLEDAI score. The final score, the sum of all weighted scores, ranges from 0 to 105. A higher score implies greater disease activity.

– ECLAM

The ECLAM was found to be one of the most reliable activity measures to classify lupus patients (16). It was developed in a group process and consists of 34 items grouped into 12 domains as follows (maximum relative scores for each item is in brackets) (6, 9, 16): constitutional (0.5), articular (1), mucocutaneous (0.5), myositis (2), pericarditis (1), intestinal (2), pulmonary (1), neuropsychiatric (2), renal (0.5), ha ematologic (1), erythrocyte sedimentation rate (ESR) (1), hypocomplementemia (1). Moreover, for evolving symptoms in mucocutaneous, renal and hypocomplementemia domains, other scores have been considered to be added. The final ECLAM disease activity score is always an integer number between 0 and 10. If the final total score is not an integer number, the sum should be rounded off to the lower integer for values less than 6 and to the higher integer for values over 6. And finally, if the total score is greater than 10, the sum should be rounded off to 10 (6, 9).

– SDI

This comprehensive index scores cumulative disease damage since the onset of SLE. The impairments in 12 organ systems including ocular (range 0–2), neuropsychiatric (0–6), renal (0–4), pulmonary (0–5), cardiovascular (0–6), peripheral vascular (0–5), gastrointestinal (0–5), musculoskeletal (0–6), skin (0–3), endocrine (diabetes) (0–1), gonadal (0–1) and malignancies (0–2), are considered only if present for at least six months. Damage over time can only be stable or increase, theoretically to a maximum of 46 points.

Statistical analysis

Results are shown as the median and interquartile range (IQR) for non-normal data and as mean±standard deviation for normally-distributed data. Data analysis was performed with the statistical package of social sciences (SPSS) for Windows version 11.5. Spearman's rank correlation coefficient test was done to investigate the relationship between two variables, of which one or both were not normally distributed. In order to compare the distributions of non-normal dependent variables in two independent categories, Mann-Whitney U-test and, in more than two categories, Kruskal-Wallis H-test were used. Correspondingly, the comparison of the means of normally distributed items in two and over two categories was done by Independent samples *t*-test and One-Way ANOVA, respectively. The value of the results was calculated at 95% CI. In all statistical analyses, *p*-values of less than 0.05 were interpreted as significant.

Table I. Sociodemographic characteristics of patients.

		n. (%)
Educational level		
	No formal education*	8 (11.2)
	Incomplete high school	32 (45.1)
	High School Graduate (Diploma)	22 (31.0)
	College/University Education	9 (12.7)
Medication adherence		
	Poor	21 (29.6)
	Fair	28 (39.4)
	Good	22 (31.0)

*Able to read and write but without any formal education certificate.

Results

This study includes 71 biopsy-proven lupus nephritis patients, comprised of 65 females (91.5%) and six males (8.5%). The mean age at presentation was 27.4±9.8 yr (median (IQR): 24 (21–32) yr). The majority of cases were under 35 years (80.3%). Disease duration of patients ranges from 1 month to 15 yr (median (IQR): 1.5 (0.8–4) yr).

Educational level and medication adherence of patients are shown in Table I. Eight patients (11.2%) had no formal education. Most patients had various levels of pre-college education (76.1%) and only 12.7 % of patients had college or university education.

The most common prescribed medications for our patients included prednisolone, hydroxychloroquine, azathioprine, anti-hypertensive and anti-osteoporotic drugs. Considering the fact that the glucocorticoids are a fundamental treatment of SLE which can rapidly control disease activity in mild to severe cases (17), nearly all of our patients were treated with moderate to high dose (25–100 mg per day) prednisolone and about two third of them were treated with hydroxychloroquine (200–400 mg per day). The most frequent anti-hypertensive drugs prescribed for patients were diuretics and ACE inhibitors and the most frequent antiosteoporotic drugs were calcium-D and alendronate. Only 31% of patients was found to adhere to medications perfectly, while the majority of patients had fair medication adherence (39.4%).

The mean SLEDAI-2K and SDI scores were 25.5±12.3 (range: 10–83; median [IQR]: 24 [17–30]), and 2.0±2.3 (range: 0–9; median [IQR]: 0 [0–3]), respectively. ECLAM as an all-inclusive tool in measuring lupus disease activity was employed to verify the accuracy and validity of our patients' disease activity scores determined with SLEDAI-2K. The mean ECLAM was 6.21±2.45 (range: 1–10).

At presentation, the most common active features were protein excretion over 500 milligrams in 24-hour urine (91.5%), haematuria (84.5%), arthritis (77.5%), positive anti-dsDNA antibody (74.6%) and malar rash (62%), while CVA (2.8%), seizure (4.2%) and cranial nerve disorder (4.2%) were rare (Table II). The average of proteinuria over 24 hours was 1.8±1.3 g/24/h. Hypertension (systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg or being treated with anti-hypertensive drugs) was found in 38 patients (53.5%).

SDI score categories are shown in Table III. Twenty-four patients (33.8%) had no organ damage and patients with over 4 SDI scores were in minority (15.5%). Table IV shows the proportions of patients with organ damage in different domains of the SDI. Kidneys were the most common damaged organ (38%), followed by musculoskeletal system (29.8%) and CNS (26.8%). Malignancy and premature gonadal failure were not seen in our patients.

Univariate analyses of SLEDAI-2K, ECLAM and SDI scores showed no statistically significant difference in gender or age-groups, even though, SLEDAI-2K, ECLAM and SDI scores tended to be higher in females (Table V). The SDI scores were significantly different in 3 categories of disease duration (p=0.007). As shown in Table V, more damage scores was measured in longer disease duration categories. Also by using Spearman's coefficient test, a highly significant relationship between damage and disease duration was found (p<0.001).

Correlation analyses showed that disease activity scores as assessed with SLEDAI-2K are significantly associated with the results of ECLAM (r=0.827, p<0.001) (Fig. 1). Moreover, the total commulative damage as evaluated with SDI was significantly related to SLEDAI-2K (r=0.742, p<0.001) and ECLAM (r=0.699, p<0.001) (Fig. 1-2).

Among specific damage items in SDI, patients who experienced thrombotic events (defined as angina, myocardial infarction, stroke, peripheral arterial thrombosis, deep vein thrombosis (venous circulation in the extremities or an internal organ) or pulmonary infarction (due to emboli)) had significantly higher SLEDAI-2K (p=0.003) and SDI (p<0.001). Moreover, patients with at least one episode of myocardial infarction (MI) had higher amount of urine protein excretion (p=0.019). Likewise, a higher amount of proteinuria was seen in patients with more SLEDAI-2K and SDI scores (p=0.021, 0.002, respectively). In addition, patients with higher protein excretion in 24-hour urine had longer disease duration (p=0.001). Furthermore, the presence of hypertension was higher in patients who suffered from more cumulative end-organ damage (p=0.011).

Table II. Frequency of SLEDAI-2K descriptors in patients with lupus nephritis.

Descriptor	n (%)	Descriptor	n (%)
Seizure	3 (4.2)	Proteinuria	65 (91.5)
Psychosis	7 (9.9)	Pyuria	42 (59.2)
Organic brain syndrome	9 (12.7)	Rash	44 (62)
Visual disturbance	5 (7)	Alopecia	29 (40.8)
Cranial nerve disorder	3 (4.2)	Mucosal ulcers	22 (31)
Lupus headache	8 (11.3)	Pleurisy	9 (12.7)
CVA	2 (2.8)	Pericarditis	7 (9.9)
Vasculitis	13 (18.3)	Low complement	33 (46.5)
Arthritis	55 (77.5)	Increased DNA binding	53 (74.6)
Myositis	5 (7)	Fever	7 (9.9)
Urinary casts	19 (26.8)	Thrombocytopenia	10 (14.1)
Haematuria	60 (84.5)	Leukopenia	8 (11.3)

Table III. Damage categories (SDI).

Total damage	n. patients (%)
0	24 (33.8)
1	15 (21.2)
2	12 (16.9)
3	4 (5.6)
4	5 (7)
5	4 (5.6)
≥6	7 (9.9)

Table IV. Frequency of end-organ damage in patients with lupus nephritis.

Organ damage	n (%)
Ocular	4 (5.6)
Neuropsychiatric	19 (26.8)
Renal	27 (38)
Pulmonary	4 (5.6)
Cardiovascular	8 (11.3)
Peripheral vascular	9 (12.7)
Gastrointestinal	1 (1.4)
Musculoskeletal	21 (29.6)
Skin	6 (8.5)
Diabetes	1 (1.4)
Premature gonadal failure	0 (0)
Malignancy	0 (0)

Patient's educational level was correlated to medication adherence positively (p=0.007). On the other hand, educational level was inversely associated with SLEDAI-2K and SDI scores (p=0.007, 0.033, respectively). Medication adherence was also inversely correlated with SDI scores (p=0.011; r=-0.301), but not with SLEDAI-2K and ECLAM.

Discussion

The main objective of this study was to describe the disease activity (as measured by the SLEDAI-2K and ECLAM) and disease damage (as scored by the SDI) in SLE patients with biopsy-proven nephritis and who present with very high disease activity in an Iranian population. In keeping with the study of Vitali *et al*., a great relationship between SLEDAI-2K and ECLAM scores was found in our study, suggesting further validation and realiablity of these two indices (18).

Correlation analyses revealed that greater SLEDAI-2K and ECLAM scores were strongly associated with higher total SDI scores. The link between SLE disease activity and damage has been reported in several articles (19-26), however, Gladman *et al*. and Freire *et al*. did not find such relationship in their studies (27, 28). The reasons of this discrepancy could be the following: firstly, there is a considerable difference in baseline disease activity scores among the mentioned studies and our study (mean SLEDAI in Gladman's study was 4.2 and in Freire's study was 2.5, while our mean score is 25.5), and secondly, the design of these studies was different, as

Table V. SLEDAI-2K, SDI, ECLAM scores according to age groups, disease duration and gender.

		n. of patients (%)	SLEDAI-2K (median [IQR])	ECLAM (mean±Std)	SDI (median [IQR])
Age groups	<20	14 (19.7)	24.0 (19.7–26.5)	6.21 ± 2.25	1.0 (0.0–1.2)
	21–25	25 (35.2)	26.0 (18.5–32.0)	6.56 ± 2.21	2.0 (0.0–4.5)
	26–35	18 (25.4)	20.5 (16.0–33.2)	6.05 ± 2.94	1.0 (0.0–3.2)
	>35	14 (19.7)	22.0 (15.0–25.7)	5.78 ± 2.54	2.0 (0.0–2.5)
	p-value		0.60[a]	0.80[c]	0.52[a]
Disease duration	<1 yr	21 (29.6)	20.0 (16.5–27.0)	5.47 ± 2.06	0.0 (0.0–2.0)
	1–3 yr	30 (42.3)	24.0 (17.7–34.0)	6.36 ± 2.49	1.0 (0.0–3.0)
	>3 yr	20 (28.1)	24.0 (17.0–32.5)	6.75 ± 2.69	2.0 (1.0–5.7)
	p-value		0.27[a]	0.22[c]	0.007[a]
Gender	Male	6 (8.5)	19.5 (16.2–25.7)	5.33 ± 3.07	0.0 (0.0–3.2)
	Female	65 (91.5)	24.0 (17.0–30.5)	6.29 ± 2.40	1.0 (0.0–3.0)
	p-value		0.31[b]	0.36[d]	0.28[b]

a. Kruskal-Wallis H-test was used
b. Mann-Whitney U-test was used
c. One-Way ANOVA was used
d. Independent samples *t*-test was used

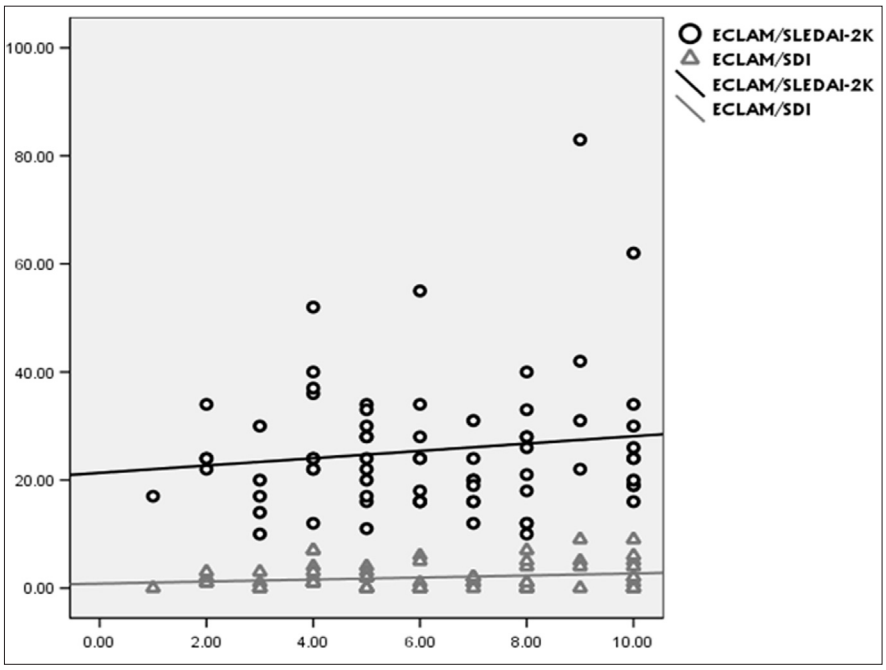

Fig. 1. Correlation of ECLAM with SLEDAI-2K and SDI.

we have evaluated lupus patients with very active disease pre-kidney biopsy and with uniformly having biopsy-proven lupus nephritis, while the other two studies included all of their SLE patients. On the other hand, the majority of our patients were at first years of their disease onset – 71.9% of subjects had SLE less than 3 years – which can justify this great correlation of disease activity and damage, since the increase in disease duration of rheumatic diseases may lead to decrease of the disease activity by the effect of treatments and more compliance of the patients.

In our study, disease activity and damage were higher in patients who had thrombotic events, replicating earlier findings (29). In addition, higher proteinuria, which implies more severe nephritis, was associated with MI. This finding supports the study of Wells *et al*., which ascertained nephritis as a great risk factor of acute myocardial infarction in patients with SLE (30). Patients with higher urine protein excretion also had significantly higher SLEDAI-2K and SDI scores, which is similar to the study by Falaschi *et al*. (31). This reflects that in higher overall SLE disease activity and damage, rising of the amount of protein excretion in urine is highly probable as kidneys may become more involved. In addition, we found that cumulative damage was related to the presence of hypertension, which was similar to the study of Swaak *et al*. (26).

As expected, increasing disease duration was associated with more disease damage, which is in accordance with the results of other previous studies (21-23, 32-35). Surprisingly, we found the highest damage scores as early as 3 years post-diagnosis in our patients. Since we know that lupus patients with early damage are most probably at risk for higher mortality and morbidity (36), we should make meticulous efforts to diagnose the disease early and to control tightly disease activity in severe lupus patients as they develop damage early in their course, especially in those with nephritis. In our study, the prevalence of damage in at least one organ system was higher (66.2%) than those reported by Gorgos *et al*. (59.8%) (37), Stoll *et al*. (56%) (24), and Mok *et al*. (31%) (38). Our mean damage score (2.0) was also higher than the one reported in the study by Fortin *et al*. (1.3) (39) and Stoll *et al*. (1.2) (24). These discrepancies may similarly be due to different study designs or the population studied. In other words, we demonstrated more damage than what has been described in other cohorts – *i.e*. only 3 years on average after diagnosis. This may be due to nephritis as an overwhelming complication or as a marker of severe disease that warrants early aggressive treatment.

In the present study, only 31% of patients was found to be completely adherent to their treatments, which resembles the study of Garcia-Gonzalez *et al*., focused on RA and SLE patients (40). This low medication adherence suggests that our lupus patients were

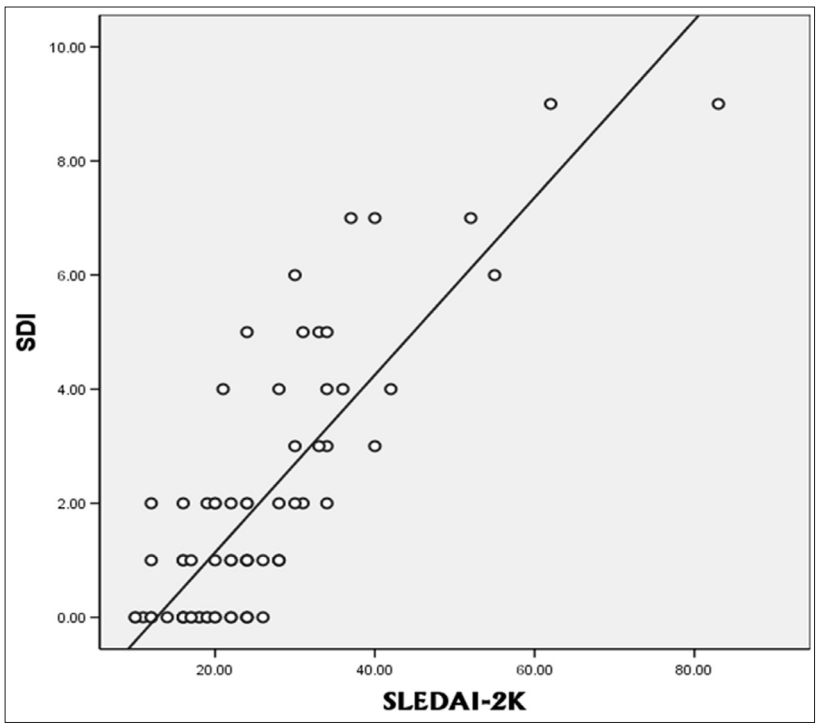

Fig. 2. Correlation of SLEDAI-2K and SDI.

not sufficiently informed about their diease acute and chronic complications and the necessity to fully comply with their physician orders. Importantly, we found that level of education was a strong determinant of medication adherence. This is in accordance with the studies of Koneru *et al*. and Garcia-Gonzalez *et al*., as they concluded that lower education can be associated with poor adherence (40, 41). We further showed that poor adherence to medications may be an additional factor associated with poor prognosis, as our patients with lower education had more disease damage. This finding is similar to the study by Sutcliffe *et al*. (19). Similarly, in the studies of Petri *et al*., Bruce *et al*. and Alder *et al*., it was shown that most of SLE patients with renal dysfunction were non-adherent to their treatments (42-44).

In conclusion, this advance disease activity and damage in our patients, apart from the possibility of being due to Iranian ethnicity or the nature of nephritis as an overwhelming complication, should bring our concern to detect our assessment pitfalls, monitor patients with tight-organised follow-ups, and also design further clinical trials to improve the treatment plans.

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