Acta Med. Okayama, 2020
Vol. 74, No. 3, pp. 191–198

Acta Medica Okayama
http://escholarship.lib.okayama-u.ac.jp/amo/

Original Article

Risk Factors for Chronic Damage Accumulation Across Different Onset Eras in Systemic Lupus Erythematosus: A Cross-sectional Analysis of a Lupus Registry of Nationwide Institutions (LUNA)

Keiji Ohashi[a], Ken-Ei Sada[a]*, Yosuke Asano[a], Keigo Hayashi[a], Yuriko Yamamura[a], Sumie Hiramatsu Asano[a], Yoshia Miyawaki[a], Michiko Morishita[a], Eri Katsuyama[a], Haruki Watanabe[a], Noriko Tatebe[a], Mariko Narazaki[a], Yoshinori Matsumoto[a], Katsue Sunahori-Watanabe[a], Tomoko Kawabata[a], Nobuyuki Yajima[b,c,d], and Jun Wada[a]

[a]Department of Nephrology, Rheumatology, Endocrinology, and Metabolism, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama 700-8558, Japan, [b]Division of Rheumatology, Department of Medicine, Showa University School of Medicine, Tokyo 142-8666, Japan, [c]Department of Healthcare Epidemiology, Kyoto University Graduate School of Medicine and Public Health, Kyoto 606-8501, Japan, [d]Center for Innovative Research for Communities and Clinical Excellence, Fukushima Medical University, Fukushima 960-1295, Japan

Chronic damage accumulation affects not only mortality but also quality of life in patients with systemic lupus erythematosus (SLE). Risk factors for chronic damage were explored in SLE through different onset eras. Two hundred forty-five patients at Okayama University Hospital and Showa University Hospital were divided into three groups based on the onset era: a past-onset group (onset before 1995; n = 83), middle-onset group (1996-2009; n = 88), and recent-onset group (after 2010; n = 74). The mean Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) score as an index of chronic damage was 1.93, 1.24, and 0.53 in the past-, middle-, and recent-onset groups, respectively. In the past-onset group, the total SDI score was significantly associated with glucocorticoid monotherapy by linear regression analysis (β-coefficient [β] = 0.63; 95% confidence interval [CI], 0.21-1.05) and C-reactive protein levels (β = 0.67; 95% CI, 0.27-1.07). In the middle-onset group, the total SDI score was significantly associated with the SLE Disease Activity Index at registration (β = 0.09; 95% CI, 0.03-0.12). Reducing the accumulation of chronic damage in SLE patients might be possible with the concomitant use of immunosuppressants and tight control of disease activity.

Key words: systemic lupus erythematosus, chronic damage, glucocorticoids, disease activity, disease duration

The prognosis of systemic lupus erythematosus (SLE) has been dramatically improved by the progression of immunosuppressive therapy [1]. The initiation of glucocorticoids (GCs) and hydroxychloroquine (HCQ) in the 1950s was the first innovation in the management of SLE [2, 3]. Subsequently, in the 1970s, combination treatment with GCs and several immunosuppressants, including azathioprine and cyclophosphamide, was started [4-7]. In the 1990s, concomitant use of mycophenolate mofetil (MMF) and/or a calcineurin inhibitor with GCs emerged as new treatment

Received September 2, 2019; accepted December 17, 2019.
*Corresponding author. Phone: +81-86-235-7235; Fax: +81-86-222-5214
E-mail: sadakenn@okayama-u.ac.jp (K. Sada)

Conflict of Interest Disclosures: No potential conflict of interest relevant to this article was reported.

options [8-11]. More recently, several biological agents, including belimumab, known as a B-cell activating factor inhibitor, have become available for the treatment of SLE.

Followed by the improvement of prognosis, the accumulation of chronic damage has become a major concern in the clinical course of patients with SLE [12, 13]. The accumulation of chronic damage is associated not only with mortality, but also with a reduced quality of life [14-17]. During a mean 5-year disease duration, disease activity was reported as the main risk factor for chronic damage [18, 19]. In studies that included patients with a mean 10-year disease duration, the accumulation of chronic damage was related to disease activity, demographic factors, treatment status, and complications [20-22]. However, only older age and use of GCs were risk factors in the studies that included patients with a mean disease duration of over 10 years [23-25]. The factors related to chronic damage have been speculated to change with the onset era due to the staggered emergence of different treatment options.

In the present study, we explored the risk factors for chronic damage in patients with SLE across different onset eras.

Methods and Patients

Study design and patients. This study had a cross-sectional design, using enrollment data from our registry of patients with SLE (Lupus Registry of the Nationwide Institution [LUNA]). We commenced registration for the LUNA registry in February 2016. All patients were older than 20 years, and they fulfilled ≥4 of the American College of Rheumatology criteria for the classification of SLE [26]. For the present study, we analyzed the LUNA data for patients registered at Okayama University and Showa University between February 2016 and September 2016.

The data for each patient in the LUNA registry included demographic information, date of onset, underlying comorbidity, smoking and drinking habits, past medical history, reproductive history, and blood pressure. Laboratory data at registration were also included, and consisted of complete blood count, biochemical examination, urinalysis, complement levels, anti-double-stranded DNA antibody titer, and anti-phospholipid antibody. Disease activity and damage were evaluated using the SLE Disease Activity Index (SLEDAI) and the Systemic Lupus International Collaborating Clinics /American College of Rheumatology Damage Index (SDI), respectively [27, 28]. Information about current and previous treatment, such as prednisolone dosage, concomitant use of immunosuppressants, and treatments for comorbidity (*e.g.*, diabetes mellitus, dyslipidemia, hypertension, osteoporosis, and infections), was also collected. All data for LUNA were collected from electronic medical records and patient-reported information.

This study was conducted in accordance with the Declaration of Helsinki and the ethical guidelines for epidemiological research in Japan. This study was approved by the Ethics Committee of Okayama University Hospital and Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences (Ken1807-002). Patient consents for participation in this study were obtained by an opt-out consent form.

Statistical analysis. We initially described the characteristics of all enrolled patients, and then explored the factors related to the total SDI score. The patients were divided into three groups based on the onset era: a past-, middle- and recent-onset group with onset before 1995, between 1996 and 2009, and after 2010, respectively. We explored the factors related to total SDI score using uni- and multivariate linear regression analyses in each group. Candidate factors for multivariate analyses were selected based on the univariate analysis results.

Clinical characteristics were presented as the mean ±standard deviation (SD). Continuous variables were compared using the Mann–Whitney *U* test, whereas categorical variables were compared between the 2 groups using the Fisher's exact probability test. A p-value of <0.05 was considered significant. When comparing three categories, statistical significance was determined by using the Bonferroni correction to adjust for multiple testing ($p<0.05/3$). All statistical analyses were performed using the JMP 11.2.0 software package (SAS Institute Inc., Cary, NC, USA).

Results

Baseline characteristics and treatment status. Two hundred and forty-five patients with SLE were included in the present study. The mean (±SD) disease onset age of the enrolled patients was 28 (±14) years;

222 patients (91%) were female. The mean disease duration was 13 (±10) years. The mean (±SD) SLEDAI and total SDI score at the registration were 5.0 (±5.1) and 1.3 (±1.7), respectively. Treatments at the registration were as follows: GC monotherapy in 78 (32%) patients, immunosuppressant monotherapy in 4 (2%), and concomitant immunosuppressants with GCs in 144 (58%). Nineteen (8%) patients had no immunosuppressive treatments.

On univariate analysis, the total SDI score was significantly associated with sex, age at disease onset, disease duration, SLEDAI at registration, GC monotherapy, C3, C4, CH50, white blood cell (WBC) count, C-reactive protein (CRP), and glycated hemoglobin (HbA1c). Multivariate analysis using the above variables (WBC count, C3, C4, and CH50 were excluded because SLEDAI at registration included those variables) showed that age at disease onset (β-coefficient [β] = 0.083; 95% confidence interval [CI], 0.02 to 0.05), disease duration (β = 0.08; 95% CI, 0.05 to 0.11), SLEDAI at registration (β = 0.08; 95% CI, 0.03 to 0.12), and CRP (β = 0.47; 95% CI, 0.21 to 0.73) were the factors significantly related to the total SDI score (Table 1).

Comparison of patient characteristics across different onset eras. Patient characteristics across the three different onset eras are shown in Table 2. Patients in the past-onset group had a significantly younger age onset than those in the other 2 groups (the past-onset vs the middle-onset group, $p = 0.0031$; and the past-onset vs the recent-onset group, $p = 0.0005$). The patients in the recent-onset group were taller than those in the past-onset group ($p = 0.016$). With regard to the laboratory data, CH50 levels in the past-onset group were significantly higher than those in the other 2 groups (the past-onset vs the middle-onset group, $p = 0.0077$; the past-onset vs the recent-onset group, $p = 0.0049$). The middle-onset group had lower C4 levels than the past-onset group ($p = 0.011$). The WBC count of the recent-onset group was significantly lower than that of the past-onset group ($p = 0.0016$).

Comparisons of total SDI score and each component score across the three different onset eras are shown in Fig. 1. The mean (±SD) total SDI scores were 1.94 (2.00), 1.24 (1.75), and 0.53 (0.81) in the past-, middle-, and recent-onset groups, respectively. Significant differences in total SDI score were found across the 3 groups (the past-onset vs the middle-onset group, $p = 0.0081$; the past-onset vs the recent-onset group, $p < 0.0001$; the middle-onset vs the recent-onset group, $p = 0.0092$). The peripheral vascular score of the recent-onset group was significantly lower than that of the past- and middle-onset groups (the past-onset vs the

Table 1 Linear regression analysis of total SDI

	Univariate			Multivariate		
	Coefficient	95% CI	*p*-value	Coefficient	95% CI	*p*-value
Sex	0.41	0.04, 0.78	0.03	0.30	−0.09, 0.69	0.13
Age of disease onset	0.03	0.01, 0.04	0.0003	0.03	0.02, 0.05	0.0002
Disease duration	0.06	0.04, 0.08	<0.0001	0.08	0.05, 0.11	<0.0001
Weight	0.006	−0.01, 0.03	0.55			
BMI	0.03	−0.02, 0.09	0.22			
SLEDAI	0.07	0.02, 0.11	0.002	0.08	0.03, 0.12	0.0009
Dosage of PSL	−0.003	−0.04, 0.04	0.88			
GC monotherapy	0.36	0.14, 0.59	0.002	0.18	−0.11, 0.46	0.23
WBC count	0.0001	0.00003, 0.0002	0.009			
Lymphocyte count	−0.0003	−0.02, 0.02	0.97			
Plt	−0.011	−0.04, 0.02	0.45			
CRP	0.64	0.35, 0.92	<0.0001	0.47	0.21, 0.73	0.0005
C3	0.009	0.002, 0.02	0.008			
C4	0.07	0.04, 0.09	<0.0001			
CH50	0.03	0.01, 0.06	0.003			
Anti-ds-DNA antibody	−0.002	−0.008, 0.004	0.52			
HbA1c	0.86	0.41, 1.32	0.0002	0.40	−0.04, 0.83	0.07

SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; CI, confidence interval; BMI, body mass index; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; PSL, prednisolone; GC, glucocorticoid; WBC, white blood cell; Plt, platelet; CRP, C-reactive protein; ds-DNA, double strand-deoxyribonucleic acid; HbA1c, glycated hemoglobin.

Table 2 Patient characteristics at enrollment

	Past-onset group: Onset before 1995 (n=83)	Middle-onset group: Onset between 1996 and 2009 (n=88)	Recent-onset group: Onset after 2010 (n=74)
Female, n (%)	77 (93)	79 (90)	66 (89)
SLEDAI	4.3 ± 4.7	6.0 ± 6.1	4.5 ± 4.1
Height, cm†	155 ± 7	158 ± 7	158 ± 6
Weight, kg	53 ± 10	55 ± 12	55 ± 12
BMI	21.7 ± 4.1	21.8 ± 3.7	22.0 ± 4.4
Age of disease onset, years*,†	29 ± 14	35 ± 16	36 ± 15
Duration of disease, years*,#,†	24.5 ± 6.8	10.9 ± 2.6	3.4 ± 1.7
Dosage of PSL, mg/day	5.8 ± 3.7	7.0 ± 5.1	7.3 ± 8.1
GC monotherapy, n (%)	35 (42)	23 (26)	20 (27)
Laboratory data			
Serum C3, mg/dL	86.3 ± 21.3	82.1 ± 21.8	85.8 ± 49.7
Serum C4, mg/dL*	17.9 ± 7.9	15.1 ± 6.9	15.4 ± 8.4
CH50, U/mL*,†	37.2 ± 9.5	33.5 ± 9.5	32.3 ± 10.0
Anti-ds-DNA antibody, IU/mL	17.6 ± 34.2	23.4 ± 45.2	20.3 ± 28.3
WBC count, /μL†	6,304 ± 2,257	5,693 ± 2,003	5,232 ± 2,090
Lymphocyte count, /μL	1,152 ± 619	1,107 ± 652	1,190 ± 709
Hb, g/dL	12.3 ± 1.5	12.5 ± 1.4	12.3 ± 1.4
Plt, $\times 10^4/\mu L$	22.5 ± 8.0	23.7 ± 8.1	23.8 ± 7.1
CRP, mg/dL	0.37 ± 1.07	0.29 ± 0.50	0.31 ± 0.80
HbA1c, %	5.8 ± 0.8	5.8 ± 0.5	5.6 ± 0.4

Comparisons between the past-onset, middle-onset, and recent-onset groups were made using the Mann–Whitney *U* test or Fisher's exact probability test. Statistical significance was determined by using the Bonferroni correction ($p<0.05/3$): *Past-onset vs middle-onset group; #Middle-onset vs recent-onset group; †Past-onset vs recent-onset group.

SLEDAI, systemic lupus erythematosus disease activity index; BMI, body mass index; PSL, prednisolone; GC, glucocorticoid; ds-DNA, double strand-deoxyribonucleic acid; WBC, white blood cell; Hb, hemoglobin; Plt, platelet; CRP, C-reactive protein; HbA1c, glycated hemoglobin.

recent-onset group, $p=0.0021$; the middle-onset vs the recent-onset group, $p=0.014$), while the ocular, renal, cardiovascular, and musculoskeletal scores of the past-onset group were significantly higher than those of the recent-onset group ($p<0.0001$, $p=0.0043$, $p=0.0088$, and $p=0.0085$, respectively).

Risk factors for chronic damage in each onset era. Subsequently, we explored the factors for the total SDI score using uni- and multivariate linear regression analysis in each onset era.

Table 3 shows the linear regression analysis results in the past-onset group. On univariate analysis, the total SDI score was significantly associated with the proportion of GC monotherapy, CRP level, and C4 level. Multivariate analysis using these three variables revealed that GC monotherapy (β=0.63; 95% CI, 0.21 to 1.05) and CRP level (β=0.67; 95% CI, 0.27 to 1.07) were the independent risk factors for total SDI score.

The linear regression analysis results of the middle-onset group are shown in Table 4. Univariate analysis revealed that total SDI score had significant correlations with sex; age at disease onset; SLEDAI at registration; HbA1c; C3; and C4 levels. On multivariate analysis using these variables (C3 and C4 were not included because SLEDAI included them), SLEDAI at registration (β=0.09; 95% CI, 0.03 to 0.12) and age at disease onset (β=0.05; 95% CI, 0.02 to 0.08) were independently related with total SDI score in the middle-onset group.

In the recent-onset group, total SDI score was associated with sex, age at disease onset, and C3 level on univariate analysis (Table 5). On multivariate analysis, age at disease onset was the only independent factor related to the total SDI score (β=0.02; 95% CI, 0.01 to 0.04).

Discussion

In the present study, we focused on the factors related to chronic damage in patients with SLE across different onset eras. Because clinical practice has changed dramatically over the past 20 years, evaluating

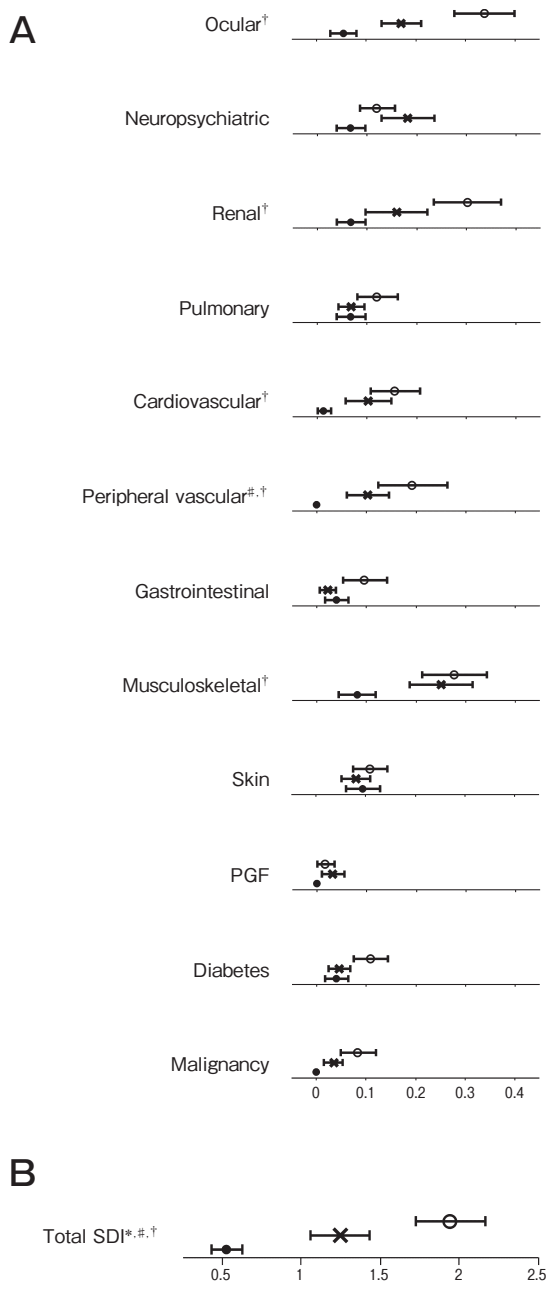

Fig. 1 Comparison of total SDI score and SDI score by organ. Open circle, X-mark, and closed circle show the mean SDI score of the past-, middle-, and recent-onset groups, respectively. Bars show the standard error. Comparisons between the past-, middle-, and recent-onset groups were performed using the Mann–Whitney *U* test or Fisher's exact probability test. Statistical significance was determined by using the Bonferroni correction ($p<0.05/3$): *Past-onset vs middle-onset group; #Middle-onset vs recent-onset group; †Past-onset vs recent-onset group.
SDI, the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; PGF, premature gonadal failure.

the risk factors for chronic damage was difficult in a single population that included patients with both recent and past onset of disease. Evaluation in each onset era provided different factors related to the accumulation of damage as represented by the SDI score.

Patients in the past-onset group had a significantly younger disease onset, were treated with GC monotherapy more frequently, and tended to be treated with a lower dosage of GC than those in the middle- and recent-onset groups. The components of SDI also differed significantly among groups. Previous reports in patients with a mean disease duration of over 10 years identified only older age at onset and GC use as risk factors for the accumulation of chronic damage [23-25]. However, it is necessary to evaluate the risk factors for the accumulation of chronic damage separately by disease onset era, because patient characteristics and treatment status, such as age at disease onset and immunosuppressant usage, vary among eras.

In the past-onset group, GC monotherapy and CRP level were significantly associated with total SDI score. GC use is a strong, well-known risk factor for the accumulation of chronic damage, and the CRP level is associated with disease activity and organ damage in SLE patients [25,29,30]. Although we could not evaluate the cumulative GC dose, GC monotherapy in the present study might reflect a portion of the cumulative GC dose, because GC monotherapy requires a greater GC dose for disease control. Considering that the dosage of GC was lower in the past-onset group, the CRP levels in this study may reflect atherosclerosis caused by long-term GC monotherapy rather than current disease activity [31-35]. The higher WBC counts and CH50 levels in the past-onset group also suggest that patients in the past-onset group exhibited lower disease activity than the other groups. In the present study, patients in the recent-onset group received GC monotherapy less frequently, so the rate of GC-related damage accumulation may decline in the future.

In the middle-onset group, the total SDI score was significantly related to current SLEDAI. Previous reports also revealed that disease activity itself is a risk factor for SDI score accumulation [18,19]. Therefore, tight maintenance of remission may be important in the middle-onset group. In contrast, total SDI score in the recent-onset group was not associated with current disease activity and was only related to age at disease onset. Because the increase rate of the SDI score is reportedly

Table 3 Linear regression analysis of total SDI: Past-onset group

	Univariate			Multivariate		
	Coefficient	95% CI	*p*-value	Coefficient	95% CI	*p*-value
Sex	0.30	−0.55, 1.15	0.48			
Age of disease onset	0.03	−0.003, 0.06	0.08			
Disease duration	0.05	−0.01, 0.12	0.11			
Weight	−0.004	−0.05, 0.04	0.86			
BMI	0.04	−0.07, 0.15	0.50			
SLEDAI	0.05	−0.04, 0.15	0.26			
Dosage of PSL	0.09	−0.03, 0.21	0.15			
GC monotherapy	0.69	0.28, 1.11	0.001	0.63	0.21, 1.05	0.004
WBC count	0.0001	−0.00005, 0.0003	0.13			
Lymphocyte count	0.01	−0.03, 0.06	0.60			
Plt,	0.008	−0.05, 0.06	0.78			
CRP	0.85	0.46, 1.24	<0.0001	0.67	0.27, 1.07	0.002
C3	0.02	−0.004, 0.04	0.11			
C4	0.08	0.02, 0.13	0.008	0.002	−0.03, 0.08	0.40
CH50	0.03	−0.02, 0.08	0.24			
Anti-ds-DNA antibody	0.007	−0.007, 0.02	0.32			
HbA1c	0.71	−0.01, 1.43	0.05			

SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; CI, confidence interval; BMI, body mass index; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; PSL, prednisolone; GC, glucocorticoid; WBC, white blood cell; Plt, platelet; CRP, C-reactive protein; ds-DNA, double strand-deoxyribonucleic acid.

Table 4 Linear regression analysis of total SDI: Middle-onset group

	Univariate			Multivariate		
	Coefficient	95% CI	*p*-value	Coefficient	95% CI	*p*-value
Sex	0.67	0.07, 1.27	0.03	0.47	−0.17, 1.11	0.15
Age of disease onset	0.05	0.03, 0.07	<0.0001	0.05	0.02, 0.08	0.002
Disease duration	0.03	−0.11, 0.18	0.66			
Weight	0.03	−0.004, 0.06	0.09			
BMI	0.08	−0.03, 0.18	0.14			
SLEDAI	0.09	0.03, 0.15	0.004	0.09	0.03, 0.12	0.006
Dosage of PSL	−0.02	−0.09, 0.06	0.62			
GC monotherapy	0.04	−0.38, 0.47	0.84			
WBC count	8.46e−5	−0.0001, 0.0002	0.37			
Lymphocyte count	0.007	−0.03, 0.04	0.71			
Plt	−0.010	−0.06, 0.04	0.68			
CRP	0.78	−0.02, 1.57	0.06			
C3	0.02	0.007, 0.04	0.006			
C4	0.09	0.04, 0.14	0.0005			
CH50	0.04	−0.001, 0.08	0.06			
Anti-ds-DNA antibody	−0.005	−0.01, 0.004	0.25			
HbA1c	1.02	0.08, 1.97	0.03	0.01	−0.95, 0.98	0.98

SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; CI, confidence interval; BMI, body mass index; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; PSL, prednisolone; GC, glucocorticoid; WBC, white blood cell; Plt, platelet; CRP, C-reactive protein; ds-DNA, double strand-deoxyribonucleic acid.

about 1 point per 10 years [12], the observation period of the recent-onset group might have been too short to evaluate factors related to the SDI score.

There are several limitations to this study. First, we could not assess disease relapses in the present study. Relapses may have affected the chronic damage, particularly in the group with long disease duration. However, patients in the past-onset group were fre-

Table 5 Linear regression analysis of total SDI: Recent-onset group

	Univariate			Multivariate		
	Coefficient	95% CI	*p*-value	Coefficient	95% CI	*p*-value
Sex	0.34	0.04, 0.63	0.03	0.14	−0.15, 0.43	0.34
Age of disease onset	0.03	0.01, 0.04	<0.0001	0.02	0.01, 0.04	0.0006
Disease duration	−0.04	−0.15, 0.07	0.46			
Weight	0.002	−0.01, 0.02	0.82			
BMI	−0.004	−0.005, 0.04	0.87			
SLEDAI	0.04	−0.007, 0.09	0.10			
Dosage of PSL	0.0007	−0.02, 0.02	0.96			
GC monotherapy	0.02	−0.20, 0.23	0.88			
WBC count	7.04e−6	−8.56e−5, 9.96e−5	0.88			
Lymphocyte count	0.007	−0.01, 0.02	0.40			
Plt,	−0.02	−0.05, 0.006	0.14			
CRP	−0.03	−0.31, 0.25	0.82			
C3	0.004	0.00005, 0.008	0.047	0.003	−0.001, 0.006	0.16
C4	0.009	−0.02, 0.03	0.46			
CH50	0.003	−0.02, 0.02	0.79			
Anti-ds-DNA antibody	−0.005	−0.01, 0.002	0.16			
HbA1c	0.44	−0.21, 1.10	0.18			

SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; CI, confidence interval; BMI, body mass index; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; PSL, prednisolone; GC, glucocorticoid; WBC, white blood cell; Plt, platelet; CRP, C-reactive protein; ds-DNA, double strand-deoxyribonucleic acid.

quently treated with GC monotherapy and lower GC dosage, and therefore additional immunosuppressants might not be needed due to the less frequent relapses. Second, the beneficial effects of HCQ could not be considered, because HCQ was not available for SLE treatment in Japan until 2015. However, this situation could make it possible to elucidate the risk factors for chronic damage more clearly.

In conclusion, the present study showed that reducing the accumulation of chronic damage in SLE patients would be possible, depending on the concomitant use of immunosuppressants and rapid and tight control of disease activity.

Acknowledgments. The authors thank all medical staff members in our department.

References

1. Mak A, Cheung MW, Chiew HJ, Liu Y and Ho RC: Global trend of survival and damage of systemic lupus erythematosus: meta-analysis and meta-regression of observational studies from the 1950s to 2000s. Semin Arthritis Rheum (2012) 41: 830–839.
2. Soffer LJ, Levitt MF and Baehr G: Use of cortisone and adrenocorticotropic hormone in acute disseminated lupus erythematosus. AMA Arch Intern Med (1950) 86: 558–573.
3. Page F: Treatment of lupus erythematosus with mepacrine. Lancet (1951) 2: 755–758.
4. Hadidi T: Cyclophosphamide in systemic lupus erythematosus. Ann Rheum Dis (1970) 29: 673–676.
5. Austin HA 3rd, Klippel JH, Balow JE, le Riche NG, Steinberg AD, Plotz PH and Decker JL: Therapy of lupus nephritis. Controlled trial of prednisone and cytotoxic drugs. N Engl J Med (1986) 314: 614–619.
6. Steinberg AD and Steinberg SC: Long-term preservation of renal function in patients with lupus nephritis receiving treatment that includes cyclophosphamide versus those treated with prednisone only. Arthritis Rheum (1991) 34: 945–950.
7. Schur PH and Christian CL: Controlled study of azathioprine in lupus. N Engl J Med (1968) 278: 1019–1020.
8. Dooley MA, Cosio FG, Nachman PH, Falkenhain ME, Hogan SL, Falk RJ and Hebert LA: Mycophenolate mofetil therapy in lupus nephritis: clinical observations. J Am Soc Nephrol (1999) 10: 833–839.
9. Gaubitz M, Schorat A, Schotte H, Kern P and Domschke W: Mycophenolate mofetil for the treatment of systemic lupus erythematosus: an open pilot trial. Lupus (1999) 8: 731–736.
10. Tokuda M, Kurata N, Mizoguchi A, Inoh M, Seto K, Kinashi M and Takahara J: Effect of low-dose cyclosporin A on systemic lupus erythematosus disease activity. Arthritis Rheum (1994) 37: 551–558.
11. Caccavo D, Lagana B, Mitterhofer AP, Ferri GM, Afeltra A, Amoroso A and Bonomo L: Long-term treatment of systemic lupus erythematosus with cyclosporin A. Arthritis Rheum (1997) 40: 27–35.
12. Petri M, Purvey S, Fang H and Magder LS: Predictors of organ damage in systemic lupus erythematosus: the Hopkins Lupus Cohort. Arthritis Rheum (2012) 64: 4021–4028.
13. Watson P, Brennan A, Birch H, Fang H and Petri M: An integrated extrapolation of long-term outcomes in systemic lupus erythematosus: analysis and simulation of the Hopkins lupus

cohort. Rheumatology (Oxford) (2015) 54: 623–632.
14. Bruce IN, O'Keeffe AG, Farewell V, Hanly JG, Manzi S, Su L, Gladman DD, Bae SC, Sanchez-Guerrero J, Romero-Diaz J, Gordon C, Wallace DJ, Clarke AE, Bernatsky S, Ginzler EM, Isenberg DA, Rahman A, Merrill JT, Alarcon GS, Fessler BJ, Fortin PR, Petri M, Steinsson K, Dooley MA, Khamashta MA, Ramsey-Goldman R, Zoma AA, Sturfelt GK, Nived O, Aranow C, Mackay M, Ramos-Casals M, van Vollenhoven RF, Kalunian KC, Ruiz-Irastorza G, Lim S, Kamen DL, Peschken CA, Inanc M and Urowitz MB: Factors associated with damage accrual in patients with systemic lupus erythematosus: results from the Systemic Lupus International Collaborating Clinics (SLICC) Inception Cohort. Ann Rheum Dis (2015) 74: 1706–1713.
15. Rahman P, Gladman DD, Urowitz MB, Hallett D and Tam LS: Early damage as measured by the SLICC/ACR damage index is a predictor of mortality in systemic lupus erythematosus. Lupus (2001) 10: 93–96.
16. Conti F, Perricone C, Reboldi G, Gawlicki M, Bartosiewicz I, Pacucci VA, Massaro L, Miranda F, Truglia S, Alessandri C, Spinelli FR, Teh LS, Ceccarelli F and Valesini G: Validation of a disease-specific health-related quality of life measure in adult Italian patients with systemic lupus erythematosus: LupusQoL-IT. Lupus (2014) 23: 743–751.
17. Jolly M, Pickard AS, Wilke C, Mikolaitis RA, Teh LS, McElhone K, Fogg L and Block J: Lupus-specific health outcome measure for US patients: the LupusQoL-US version. Ann Rheum Dis (2010) 69: 29–33.
18. Shariati-Sarabi Z, Monzavi SM, Ranjbar A, Esmaily H and Etemadrezaie H: High disease activity is associated with high disease damage in an Iranian inception cohort of patients with lupus nephritis. Clin Exp Rheumatol (2013) 31: 69–75.
19. Ugarte-Gil MF, Acevedo-Vasquez E, Alarcon GS, Pastor-Asurza CA, Alfaro-Lozano JL, Cucho-Venegas JM, Segami MI, Wojdyla D, Soriano ER, Drenkard C, Brenol JC, de Oliveira e Silva Montandon AC, Costallat LT, Massardo L, Molina-Restrepo JF, Guibert-Toledano M, Silveira LH, Amigo MC, Barile-Fabris LA, Chacon-Diaz R, Esteva-Spinetti MH, Pons-Estel GJ, McGwin G, Jr. and Pons-Estel BA: The number of flares patients experience impacts on damage accrual in systemic lupus erythematosus: data from a multiethnic Latin American cohort. Ann Rheum Dis (2015) 74: 1019–1023.
20. Mok CC, Ho CT, Wong RW and Lau CS: Damage accrual in southern Chinese patients with systemic lupus erythematosus. J Rheumatol (2003) 30: 1513–1519.
21. Shaharir SS, Hussein H, Rajalingham S, Mohamed Said MS, Abdul Gafor AH, Mohd R and Mustafar R: Damage in the Multiethnic Malaysian Systemic Lupus Erythematosus (SLE) Cohort: Comparison with Other Cohorts Worldwide. PLoS One (2016) 11: e0166270.
22. Demir S, Artim-Esen B, Sahinkaya Y, Pehlivan O, Alpay-Kanitez N, Omma A, Erer B, Kamali S, Gul A, Aral O, Ocal L and Inanc M: Metabolic syndrome is not only a risk factor for cardiovascular diseases in systemic lupus erythematosus but is also associated with cumulative organ damage: a cross-sectional analysis of 311 patients. Lupus (2016) 25: 177–184.
23. Goncalves MJ, Sousa S, Ines LS, Duarte C, Borges J, Silva C, Romao VC, Terroso G, Bernardes M, Cerqueira M, Raposo A, Sequeira G, Barcelos A, Macieira C, Canas da Silva J, Costa L, Pereira da Silva JA, Cunha-Miranda L, Da Silva JA, Canhao H and Santos MJ: Characterization of damage in Portuguese lupus patients: analysis of a national lupus registry. Lupus (2015) 24: 256–262.
24. Conti F, Ceccarelli F, Perricone C, Leccese I, Massaro L, Pacucci VA, Truglia S, Miranda F, Spinelli FR, Alessandri C and Valesini G: The chronic damage in systemic lupus erythematosus is driven by flares, glucocorticoids and antiphospholipid antibodies: results from a monocentric cohort. Lupus (2016) 25: 719–726.
25. Tarr T, Papp G, Nagy N, Cserep E and Zeher M: Chronic high-dose glucocorticoid therapy triggers the development of chronic organ damage and worsens disease outcome in systemic lupus erythematosus. Clin Rheumatol (2017) 36: 327–333.
26. Hochberg MC: Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum (1997) 40: 1725.
27. Bombardier C, Gladman DD, Urowitz MB, Caron D and Chang CH: Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. Arthritis Rheum (1992) 35: 630–640.
28. Gladman D, Ginzler E, Goldsmith C, Fortin P, Liang M, Urowitz M, Bacon P, Bombardieri S, Hanly J, Hay E, Isenberg D, Jones J, Kalunian K, Maddison P, Nived O, Petri M, Richter M, Sanchez-Guerrero J, Snaith M, Sturfelt G, Symmons D and Zoma A: The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. Arthritis Rheum (1996) 39: 363–369.
29. Lee SS, Singh S, Link K and Petri M: High-sensitivity C-reactive protein as an associate of clinical subsets and organ damage in systemic lupus erythematosus. Semin Arthritis Rheum (2008) 38: 41–54.
30. Bertoli AM, Vila LM, Reveille JD and Alarcon GS: Systemic lupus erythematosus in a multiethnic US cohort (LUMINA): LXI. Value of C-reactive protein as a marker of disease activity and damage. J Rheumatol (2008) 35: 2355–2358.
31. Abou-Raya A and Abou-Raya S: Inflammation: a pivotal link between autoimmune diseases and atherosclerosis. Autoimmun Rev (2006) 5: 331–337.
32. Nikpour M, Gladman DD, Ibanez D and Urowitz MB: Variability and correlates of high sensitivity C-reactive protein in systemic lupus erythematosus. Lupus (2009) 18: 966–973.
33. Doria A, Shoenfeld Y, Wu R, Gambari PF, Puato M, Ghirardello A, Gilburd B, Corbanese S, Patnaik M, Zampieri S, Peter JB, Favaretto E, Iaccarino L, Sherer Y, Todesco S and Pauletto P: Risk factors for subclinical atherosclerosis in a prospective cohort of patients with systemic lupus erythematosus. Ann Rheum Dis (2003) 62: 1071–1077.
34. Ross IL and Marais AD: The influence of glucocorticoids on lipid and lipoprotein metabolism and atherosclerosis. S Afr Med J (2014) 104: 671–674.
35. Sacre K, Escoubet B, Pasquet B, Chauveheid MP, Zennaro MC, Tubach F and Papo T: Increased arterial stiffness in systemic lupus erythematosus (SLE) patients at low risk for cardiovascular disease: a cross-sectional controlled study. PLoS One (2014) 9: e94511.