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Analysis of the relationship between disease activity and damage in patients with systemic lupus erythematosus—a 5-yr prospective study

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Objective. **To determine whether initial damage, disease duration, age, initial health status, average disease activity over the 5 yr or an average medication score covering the follow-up period would predict an increase in damage in patients with systemic lupus erythematosus (SLE) within the next 5 yr.**

Methods. **A 5-yr prospective longitudinal study of a cohort of 141 consecutive patients with SLE attending a specialist lupus out-patient clinic in London from their first assessment between July 1994 and February 1995. Disease activity was assessed using the BILAG system, initial health status by the Medical Outcome Survey Short Form 20 with an extra question about fatigue (SF-20+) and damage by the SLICC/ACR Damage Index (SDI). Damage was reassessed 5 yr later. Statistical analysis was carried out using multiple logistic regression analysis (logXact).**

Results. **One hundred and thirty-three female and eight male SLE patients (97 Caucasians, 16 Afro-Caribbeans, 22 Asians and 6 others) were included, their age at inclusion was 41.1 ± 12.5 yr and their disease duration 10.2 ± 6.3 yr. The mean measures at inclusion were: total BILAG 5.2 (range 0–17), total SDI 1.2 (0–7) and medication score 1.2 (0–3). Six patients were lost to follow-up because they had moved. Of the remaining 135 patients total damage had increased in 40 patients and 10 patients had died. At the end of the study, at 4.63 ± 0.19 yr, the total SDI had increased to 1.6 ± 1.7. Multiple logistic regression analysis revealed that death and increase in damage were strongly predicted by a high total disease activity over the entire study period ($P < 0.001$) as we had hypothesized. When the total BILAG score was replaced by the average number of A-flares the prediction of accrual of damage during the study period was again highly significant ($P = 0.004$).**

Conclusions. **In this first prospective study of its type a highly significant impact of total disease activity, as measured over 5 yr using the BILAG system, on the development of total damage was revealed. Moreover, these results provide further proof of the validity of the SDI and support the BILAG concept of the A-flares.**

KEY WORDS: SLE, Disease activity, BILAG, Damage, SLICC/ACR Damage Index, SF-20.

There is increasing agreement that in order to capture the totality of the effects of SLE upon a patient there is a need to ascertain the level of disease activity (those potentially reversible impairments that are amenable to therapy), damage (meaning irreversible, permanent problems) and the patient's own perception of their health status. Major international attempts have been undertaken in the past decade to demonstrate the reliability and validity of at least some of the available disease activity indices (reviewed in [1, 2]). In contrast a single instrument was developed to assess damage in patients with SLE [3], the SLICC Damage Index, which was shown to be valid at the same time (March 1996) in Europe and in Canada and the USA [4, 5]. Its reliability [6], as well as the validity of single-organ damage scores (its renal, pulmonary, neuropsychiatric, musculoskeletal, cardiovascular and peripheral vascular scores), has been demonstrated [4, 7]. Since its acceptance and approval by the American College of Rheumatology it has been renamed the SLICC/ACR Damage Index (SDI) and is now widely used. Although not disease specific the SF-36 has followed the SF-20 as a widely accepted health status instrument to be used in SLE patients [8–10].

In the main disease activity indices are of a global nature. The complexity of systemic lupus erythematosus (SLE), however, means that these indices can provide at best a relatively crude assessment of disease activity. Occasionally, paradoxical situations can be identified in which, for example, a patient in hospital with severe renal disease, but little else, could have a lower global activity score than a patient with mild to modest disease in several systems who was still able to work. In order to capture the subtleties of disease activity in patients with SLE the British Isles Lupus Assessment Group has established the BILAG index. This index is based upon the principle of the physician's intention to treat with disease-modifying therapy, such as high doses of corticosteroids or immunosuppressives [11]. The BILAG index distinguishes disease activity in eight organs or systems. The BILAG index is reliable and its total score as well as all its organ/system scores, even in numerical form, are valid [1, 12, 13]. The importance of using organ/system scores in addition to a total activity score has been demonstrated by the low internal consistency of the total BILAG score (Cronbach's

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$\alpha = 0.35$) also mirrored in a lack of statistically significant correlations among different organ/system activity scores [13].

Many groups have assessed SLE patients using the SLICC/ACR Damage Index (SDI) in cross-sectional studies, but rather sparse data are available on its longitudinal and long-term use in real patients. Gilboe *et al.* [14] found that disease activity and damage at baseline predicted increase in damage 2 yr later. To our knowledge no prospective 4- or 5-yr follow-up data have been published assessing disease activity over the study period and looking at its impact on the increase in damage. Therefore, in the present study we have determined prospectively over 5 yr the relationship between disease activity and the development of damage. Is there an obvious link between global disease activity and the development of permanent damage as expressed by the total damage score or between the disease activity in one organ/system and the accrual of the respective organ damage?

The aim of the present study was to investigate whether one of the dimensions of the assessment in SLE patients (initial damage, initial health status or disease activity during the whole follow-up period) or possible contributors to damage besides SLE disease activity such as age or drug side-effects (as assessed by a medication score during the whole observation period) would predict an increase in damage within the next 5 yr.

We hypothesized that an increase in total damage would be predicted by a high total disease activity during the follow-up period in accordance to a study in paper patients [5]. We expected the same to be true for the organ/system scores, e.g. musculoskeletal disease activity during the whole study period was expected to lead to more musculoskeletal damage after 5 yr as suggested by a cross-sectional study [7] and by Gilboe *et al.*'s investigation [14]. As damage is recorded following the diagnosis of SLE regardless of its attribution to the disease process itself, drug side-effects or even comorbidity, it cannot be ruled out that drug side-effects (as assessed by a medication score) over the follow-up or age at diagnosis (a crude parameter for comorbidity) would also contribute to an increase in damage.

Patients and methods

Study design

This was a prospective longitudinal study of a cohort of 141 consecutively attending British patients with SLE followed up in a specialist lupus out-patient clinic. Their first assessment in the study occurred between July 1994 and February 1995. Each patient met four or more of the revised classification criteria of the ACR for SLE [15]. These patients (representing approximately 70% of the patients with lupus under our care in 1995) were followed-up until June 1999. At every out-patient attendance a formal BILAG disease activity assessment was undertaken. Patients were usually followed at 3-monthly intervals. In those patients with quiescent SLE intervals could be prolonged up to 6 months or in very rare cases up to 12 months. Every patient was instructed to bring her/his appointment forward if she/he felt to be in any danger of flaring. At every out-patient visit a medication score was also determined. Damage was assessed at study entry and reassessed 5 yr later at a visit to the same out-patient clinic in the summer of 1999. Besides disease activity and damage further disease parameters were assessed (see below).

The assessments undertaken in this study were part of our normal clinical assessments and were performed at a time (1994–1999) when the hospital did not require us to seek ethical committee approval for this type of study. The patients involved were all informed about the study and all gave their verbal consent to a project that involved them in no additional time, inconvenience or venesection (altogether fulfilling the declaration of Helsinki).

Measures of assessment

Disease activity. BILAG [11–13] includes a total of 86 items in eight organs or systems (general, mucocutaneous, neurological, musculoskeletal, cardiovascular/respiratory, vasculitis, renal and haematological). Each item is scored as present or absent within the previous month. For an item to be recorded in any category the assumption is made that the problem is due to lupus (thus a patient with concomitant bronchial asthma would not have shortness of breath recorded if the clinician felt it was due to the coincident disease). To obtain a global score, BILAG component scores can be assigned numerical values: A = 9 (most active disease), B = 3 (intermediate activity), C = 1 (mild and stable disease activity), D = 0 (inactive disease) and E = 0 (no activity ever), resulting in a potential summed range from 0 to 72 points. This numerical score has been shown to be valid [13]. Validity has been demonstrated for the hypothesis that an organ/system score of 9 (A) represents a flare (A-flare) [16]. For the analyses either the average scores per visit to the out-patient clinic or the average number of flares per visit were used.

SLICC/ACR Damage Index (SDI). Damage, i.e. irreversible impairment since onset of SLE, is usually defined as a clinical feature that has to be continuously present for at least 6 months to score. In addition some irreversible events such as a myocardial infarction or a cerebrovascular accident score as damage on their occurrence. The components have been reported in detail elsewhere [4–7]. Briefly, damage is defined for 12 organ systems: ocular (range 0–2), neuropsychiatric (0–6), renal (0–3), pulmonary (0–5), cardiovascular (0–6), peripheral vascular (0–5), gastrointestinal (0–6), musculoskeletal (0–7), skin (0–3), endocrine (diabetes) (0–1), gonadal (0–1) and malignancies (0–2). Damage over time can only be stable or increase, theoretically to a maximum of 47 points.

MOS short form 20 with an additional question for fatigue (SF-20+). At the initial out-patient visit (i.e. on the same day) the patients completed the MOS short form 20 with an additional question for fatigue (SF-20+) [17, 18]. The 20 questions of SF-20 comprise six sections: physical, role, social functioning, mental health, health perception and pain. As explained elsewhere, a further question about fatigue was added and we multiplied the numerical rating scale (0–10) by 10 [7]. Most of the scale scores are scored so that higher scores mean better health (range 0–100). Only the scores for fatigue and pain have the opposite polarity so that 0 means not fatigued at all or no pain [13, 17, 18].

The medication score. A medication score was determined at each visit by the physician [19]. The medication score ranged from 0 to 3 (0 = neither prednisone nor immunosuppressants, 1 = prednisone 1–20 mg/day, 2 = prednisone > 20 mg/day, 3 = immunosuppressants, regardless of steroid dose). The average medication score per visit was used for the analyses.

Age at diagnosis, disease duration. The date at which a patient fulfilled the fourth of the revised classification criteria established by the American College of Rheumatology [15] was recorded as the date of diagnosis which allowed us to calculate the age at diagnosis. Disease duration (yr) was calculated by subtracting the date of entry into the study from the date of diagnosis.

Statistical analysis

Dependent variables. Outcome at 5 yr follow-up was divided into two groups: no increase in total damage score or increase in total damage score. Death was regarded as the worst outcome and therefore included in the latter group. The same was done for organ damage scores as outcome, but excluding patients who had died. Organ damage scores were analysed only if they had increased in more than nine patients (otherwise too low a sample size would not have allowed statistically significant conclusions).

Independent variables. All the variables assessed at study entry (initial damage, disease duration, age at diagnosis, initial health status) and those being derived over the whole study period (the average BILAG or the average number of A-flares and an average medication score) were used to predict outcome. To predict increase in damage only the corresponding disease activity score was used, e.g. total BILAG to predict total damage or musculoskeletal disease activity to predict musculoskeletal damage.

Analysis. The bivariate relationship between disease activity and increase in damage was investigated in an explorative analysis using Spearman's rank correlation coefficient. To determine the impact of each independent variable on the dependent outcome variables multiple logistic regression analysis was used (program logXact for Windows). For group comparisons the Mann–Whitney *U*-test was used.

Results

One hundred and thirty-three female and eight male SLE patients (97 Caucasians, 16 Afro-Caribbeans, 22 Asians and 6 others) were included, their age at inclusion was 41.1 ± 12.5 yr and their disease duration 10.2 ± 6.3 yr (range 0.1 to 32 yr). Their initial disease characteristics at the first assessment and their damage indices at the end of the study are shown in Table 1. At the assessment 5 yr after inclusion six patients were lost to follow-up because they had moved. Table 2 gives the disease activity characteristics assessed over the entire study period, i.e. the average BILAG disease activity scores, the average number of A-flares and the medication score per encounter of the remaining 135 SLE patients. The number of encounters over the 5 yr was on average 22 ± 8 (ranging from 1 to 56). Average disease activity was slightly lower than the initial one.

In 40 patients total SDI had increased and the mean damage score was now 1.6 (range 0–8) ($n = 125$, see Tables 1 and 2: damage scores at 5 yr are given in brackets). The damage score had increased in 28 patients by 1, in eight patients by 2 and in two patients by 3 and 4. Ten patients had suffered the maximum 'damage' as they had died during the follow-up period. Death was caused by a cerebrovascular accident in three patients, by cancer in two and by heart problems, bowel perforation, 'old age', alcohol intoxication and CNS lupus followed by septicaemia in one patient each. The mean study duration in the 125 surviving patients was 4.63 ± 0.19 yr (range 4.02 to 4.94 yr).

Tables 3 and 4 show which variables predicted a negative outcome, i.e. death within the study period or an increase in damage until the end of the study. Table 3 demonstrates the results of the multiple logistic regression analysis when disease activity was expressed as the average total BILAG score (per visit). Table 4 shows the results of the multiple logistic regression analysis when the average total number of BILAG A-flares (per visit) was entered instead as disease activity marker. Average total BILAG score ($P < 0.001$) (and the total number of flares per encounter, respectively, $P = 0.004$) were the strongest predictors of an increase in total damage and death. Initial mental health was the third significant predictor of an increase in total damage and death, although to a relatively weak extent ($P = 0.03$).

Table 1. Disease characteristics of the 141 SLE patients at the first assessment and, in brackets, damage scores 5 yr later ($n = 125$). The organ damage score is only given if the number of patients with an increase in damage score was >7

SDI/BILAG/SF-20+/ medication scores	Mean ± S.D.	Median; range
Total damage	1.27 ± 1.62 (1.6 ± 1.7)	1; 0–7 (1; 0–8)
Musculoskeletal damage	0.27 ± 0.56 (0.36 ± 0.74)	0; 0–3 (0; 0–3)
Total BILAG score	5.2 ± 3.8	4; 0–17
General BILAG	1 ± 1.1	1; 0–9
Mucocutaneous BILAG	0.7 ± 1.2	0; 0–9
Neurological BILAG	0.3 ± 0.9	0; 0–9
Musculoskeletal BILAG	1.2 ± 2	1; 0–9
Cardiovascular/respiratory BILAG	0.3 ± 0.6	0; 0–3
Vasculitis BILAG	0.4 ± 0.7	0; 0–3
Renal BILAG	0.3 ± 0.9	0; 0–3
Haematological BILAG	1 ± 1.2	0; 0–9
SF-20+: physical functioning*	59 ± 34	67; 0–100
SF-20+: role functioning*	54 ± 42	50; 0–100
SF-20+: social functioning*	71 ± 29	80; 0–100
SF-20+: mental health*	64 ± 22	68; 16–100
SF-20+: health perception*	45 ± 25	43; 0–100
SF-20+: pain	53 ± 35	50; 0–100
SF-20+: fatigue	59 ± 29	70; 0–100
Medication score	1.2 ± 1.3	1; 0–3

*Lower scores always mean better health except for the SF-20+ scores marked with an asterisk.

Musculoskeletal damage increased in 12 patients (for details see Table 6), neuropsychiatric damage in nine, ocular and skin damage each in seven, renal, peripheral vascular and gastrointestinal damage each in three, pulmonary, cardiovascular damage, premature gonadal failure and malignancy each in two patients. An increase in neuropsychiatric damage meant cranial or peripheral neuropathy in three patients, seizures/psychosis, cognitive impairment and cerebral vascular accident each in two patients. Ocular damage in six patients was cataract and in one retinal changes. Skin damage consisted of scarring chronic alopecia in six patients and extensive scarring in one patient.

Table 2. Disease activity characteristics and medication score per encounter over the whole study period ($n = 135$)

SDI/BILAG/SF-20+/ medication scores	Mean ± S.D.	Median; range
Total BILAG score	4.5 ± 2.3	4.2; 0.4–13
General BILAG	1 ± 0.6	0.9; 0–3.9
Mucocutaneous BILAG	0.4 ± 0.4	0.3; 0–1.9
Neurological BILAG	0.3 ± 0.3	0.2; 0–2.1
Musculoskeletal BILAG	0.9 ± 1	0.8; 0–9
Cardiovascular/respiratory BILAG	0.3 ± 0.5	0.1; 0–2.1
Vasculitis BILAG	0.4 ± 0.4	0.4; 0–1.5
Renal BILAG	0.2 ± 0.5	0; 0–2.4
Haematological BILAG	0.9 ± 0.8	0.9; 0–3.1
Total A-flares	0.16 ± 0.27	0; 0–1.6
General A-flares	0.05 ± 0.13	0; 0–0.8
Mucocutaneous A-flares	0.02 ± 0.09	0; 0–1
Neurological A-flares	0.02 ± 0.09	0: 0–0.8
Musculoskeletal A-flares	0.02 ± 0.07	0; 0–0.5
Cardiovascular/respiratory A-flares	0.04 ± 0.12	0; 0–0.6
Vasculitis A-flares	0.006 ± 0.03	0; 0–0.2
Renal A-flares	0.001 ± 0.02	0; 0–0.2
Haematological A-flares	0.007 ± 0.05	0; 0–0.4
Medication score	1.2 ± 1.2	1; 0–3

The number of encounters over the 5 yr was on average 22 ± 8 (ranging from 1 to 56).

Table 3. Prediction of death or increase in total damage score 5 yr after inclusion ($n = 135$) when disease activity was described using the average of the total BILAG scores (per visit)

Disease variable	Odds ratio	95% C.I.	*P*
Total BILAG score (average per encounter)	1.623	1.219–2.161	0.001***
Initial mental health (SF-20+)	1.029	1.003–1.056	0.029*
Disease duration	1.063	0.988–1.144	0.104
Physical functioning (SF-20+)	0.987	0.968–1.006	0.167

Only variables at a *P* level <0.2 are given. Variables entered into the analysis were all the variables assessed at study entry (total damage, disease duration, age at diagnosis, all the seven domains of SF-20+) and the average total BILAG and medication scores over the duration of the study.

Exploratory analysis with statistically significant bivariate correlations between disease activity and increase in total damage over the 5 yr duration of the study, $n = 135$ (Spearman's rank correlation coefficients are given): total BILAG 0.38**, haematological BILAG 0.33**, cardiovascular/respiratory BILAG 0.27* (* = $P < 0.05$; ** = $P < 0.01$; *** = $P < 0.001$).

Table 4. Prediction of death or increase in total damage score 5 yr after inclusion ($n = 135$) when the average total number of BILAG A-flares (per visit) was entered as disease activity marker

Disease variable	Odds ratio	95% C.I.	*P*
Total number of A-flares (average per encounter)	18.588	2.5–138.2	0.004**
Initial mental health (SF-20+)	1.03	1.003–1.058	0.028*
Initial physical functioning	0.985	0.966–1.003	0.107
Disease duration	1.058	0.985–1.136	0.124

Only variables at a *P* level <0.2 are given. Variables entered into the analysis were all the variables assessed at study entry (total damage, disease duration, age at diagnosis, all the seven domains of SF-20+) and the average number of A-flares and medication scores over the duration of the study.

Exploratory analysis with statistically significant bivariate correlations between disease activity and increase in total damage over the 5 yr duration of the study, $n = 135$ (Spearman's rank correlation coefficients are given): total number of A-flares 0.27**; total number of constitutional A-flares 0.25* (* = $P < 0.05$; ** = $P < 0.01$).

Table 5. Disease characteristics of the 50 patients with an increase in total damage or death and of those 85 with a stable damage score at follow-up

SDI/BILAG/SF-20+/ medication scores	Patients with increase in damage, mean ± S.D. (median; range)	*P* value	Patients with stable damage, mean ± S.D. (median; range)
Age at diagnosis (yr)	32 ± 13	NS	31 ± 9
Disease duration (yr)	12 ± 7	*	9 ± 6
Initial total damage score	1.7 ± 2.0 (1; 0–10)	*	1.0 ± 1.3 (0; 0–5)
Initial musculoskeletal damage score	0.44 ± 0.58 (0; 0–2)	***	0.16 ± 0.53 (0; 0–3)
SF-20+: physical functioning†	50 ± 36 (50; 0–100)	*	63 ± 32 (67; 0–100)
SF-20+: role functioning†	45 ± 44 (38; 0–100)	NS	58 ± 41 (63; 0–100)
SF-20+: social functioning†	69 ± 30 (60; 0–100)	NS	72 ± 29 (80; 0–100)
SF-20+: mental health†	66 ± 22 (68; 16–100)	NS	64 ± 22 (64; 20–100)
SF-20+: health perception†	39 ± 24 (39; 0–87)	NS	48 ± 25 (47; 0–100)
SF-20+: pain	55 ± 36 (75; 0–100)	NS	52 ± 36 (50; 0–100)
SF-20+: fatigue	62 ± 29 (70; 0–100)	NS	58 ± 30 (70; 0–100)
BILAG total score (average per encounter)	5.6 ± 2.6 (5.3; 1.2–13)	***	3.9 ± 1.8 (3.6; 0.4–8.1)
General BILAG (average per encounter)	1.2 ± 0.8 (1.1; 0–3.9)	*	0.9 ± 0.5 (0.9; 0–2.5)
Mucocutaneous BILAG (average per encounter)	0.5 ± 0.5 (0.3; 0–1.9)	NS	0.4 ± 0.4 (0.4; 0–1.9)
Neurological BILAG (average per encounter)	0.3 ± 0.3 (0.2; 0–1.3)	NS	0.3 ± 0.3 (0.1; 0–9)
Musculoskeletal BILAG (average per encounter)	1.2 ± 1.4 (0.9; 0–9)	*	0.8 ± 0.7 (0.7; 0–3.2)
Cardiovascular/respiratory BILAG (average per encounter)	0.5 ± 0.6 (0.3; 0–2.1)	*	0.2 ± 0.4 (0.1; 0–2)
Vasculitis BILAG (average per encounter)	0.4 ± 0.4 (0.4; 0–1.3)	NS	0.4 ± 0.3 (0.3; 0–1.5)
Renal BILAG (average per encounter)	0.3 ± 0.5 (0; 0–2.4)	NS	0.2 ± 0.4 (0; 0–2.3)
Haematological BILAG (average per encounter)	1.3 ± 0.8 (1; 0–3)	***	0.7 ± 0.7 (0.7; 0–3.1)
Total number of A-flares (average per encounter)	0.26 ± 0.31	***	0.11 ± 0.22
General A-flares (average per encounter)	0.1 ± 0.19	**	0.03 ± 0.08
Mucocutaneous A-flares (average per encounter)	0.03 ± 0.15	NS	0.007 ± 0.04
Neurological A-flares (average per encounter)	0.03 ± 0.07	NS	0.02 ± 0.1
Musculoskeletal A-flares (average per encounter)	0.03 ± 0.1	NS	0.01 ± 0.05
Cardiovascular/respiratory A-flares (average per encounter)	0.05 ± 0.12	NS	0.03 ± 0.12
Vasculitis A-flares (average per encounter)	0.008 ± 0.04	NS	0.005 ± 0.03
Renal A-flares (average per encounter)	0.004 ± 0.03	NS	0 ± 0
Haematological A-flares (average per encounter)	0.01 ± 0.06	NS	0.005 ± 0.04
Medication score (average per encounter)	1.5 ± 1.8 (1.1; 0–3)	*	1.1 ± 1.2 (0.5; 0–3)

†Lower scores always mean better health except for the SF-20+ scores marked with a dagger.
* = $P < 0.05$; ** = $P < 0.01$; *** = $P < 0.001$; NS = not significant.

Table 5 shows the disease activity characteristics of the 50 patients with an increase in total damage or death at 5 yr and of those 85 with a stable damage score at follow-up. The strongest differences between these two groups were found in disease activity markers over the entire study period, i.e. in higher total BILAG scores, higher haematological BILAG scores and a higher total number of A-flares in the patients with increasing damage (*P* always <0.001). Moreover, higher initial musculoskeletal damage scores were observed in the patients with increasing total damage ($P < 0.001$). After Bonferroni's correction all the other disease characteristics shown in Table 5 no longer show any significant statistical difference.

The only organ damage score with an increase in more than seven patients was the musculoskeletal damage score which increased in 13 lupus patients. Increases in other organ damage scores were observed in ≤7 patients. Table 6 shows that no variable predicted an increase in musculoskeletal damage score in a statistically significant way.

TABLE 6. Prediction of increase in musculoskeletal damage score 5 yr after inclusion ($n = 125$) when musculoskeletal disease activity was described using the average musculoskeletal BILAG scores (per visit)

Disease variable	Odds ratio	95% C.I.	P
Age at diagnosis	0.885	0.781–1.002	0.054
Initial musculoskeletal damage	2.596	0.653–10.324	0.12
Musculoskeletal BILAG score (average per encounter)	4.255	0.768–23.580	0.18
Physical functioning (SF-20+)	0.98	0.950–1.011	0.19

Increase in musculoskeletal damage meant in six patients avascular necrosis, in four patients osteoporosis with fracture and in one each either deforming/erosive arthritis or muscle atrophy/weakness.

Only variables at a P level <0.2 are given. Variables entered into the analysis were all the variables assessed at study entry (musculoskeletal damage, disease duration, age at diagnosis, all the seven domains of SF-20+) and the average musculoskeletal BILAG scores and medication scores over the duration of the study.

Exploratory analysis with statistically significant bivariate correlations between disease activity and increase in musculoskeletal damage over the 5 yr duration of the study, $n = 125$ (Spearman's rank correlation coefficients are given): musculoskeletal BILAG 0.22*; total BILAG 0.20*; haematological BILAG 0.18* (* = $P < 0.05$).

Discussion

The present study examined prospectively the relationship between disease activity and the development of damage in a cohort of 141 British SLE patients attending a specialist lupus out-patient clinic. The patients had suffered from SLE for over 10 yr with a mean age of 41 yr at study entry. Over the study period six patients had moved away and were lost to follow-up. Of the remaining 135 patients total damage increased in 40 (29.6%). Ten patients had died.

In this study activity was assessed by the BILAG activity index and damage by the SLICC/ACR damage index; both are established and validated measures. Although most current studies use the SF-36 to assess patient perception of disease, its primacy was not established in 1994 when we started our study. Furthermore we have shown a closer correlation between the SF-20+ (used in this study) and the SF-36 [8].

Multiple logistic regression analysis revealed that death and increase in damage were strongly predicted by a high total disease activity over the entire study period ($P < 0.001$) as we had hypothesized. When total BILAG score was replaced by the average number of A-flares the prediction of accrual of damage during the study period was again highly significant ($P = 0.004$). Also, when omitting the patients who died the analysis revealed unchanged results as total BILAG scores ($P < 0.001$) and the number of A-flares still strongly predicted ($P = 0.008$) increases in total damage. Accordingly the patients with an increase in damage during the study had higher total BILAG scores and a higher number of A-flares ($P < 0.001$). Moreover, our findings, the first in adult patients with SLE, are in accordance with those revealed in a shorter longitudinal study in childhood-onset SLE which used the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) to assess disease activity [20]. This paediatric SLE study found cumulative disease activity over time to be the best predictor of damage [20]. These findings reinforce the need to lower disease activity in every single lupus patient and to support efforts to find new and more potent therapeutics and treatment strategies in SLE to achieve this goal.

Initial mental health scores as assessed by SF-20+ predicted to a statistically significant extent an increase in total damage, but unexpectedly, higher mental health scores (indicating better health) predicted worse outcome. However, when comparing the group with stable total damage to that with an increase in total damage a significant difference in initial mental health scores was no longer present. Moreover, a previous study [21] had shown 'health perception' and not 'mental health' scores to predict increase in damage. Further studies are needed to clarify the relationship between mental health scores and increase in total damage.

Interestingly neither the average medication score over the whole study period nor the age at diagnosis had predictive value. As damage by definition is scored regardless of its attribution to the disease process, comorbidity or drug side-effects, these findings may indicate that SLE disease activity has a far bigger impact on development of total damage than the other two variables. However, age and the medication score used in the present study are rather coarse substitutes for comorbidity and drug side-effects, respectively. More detailed studies are warranted to corroborate our results. However, undertaking such studies will be very challenging, as for example, a patient suffering from myocardial infarction may demonstrate: it can be hard to attribute coronary artery disease solely to disease activity (vasculitis), atherosclerosis caused by the traditional cardiovascular risk factors or drug side-effects (e.g. by steroids).

The present study found no predictor of an increase in musculoskeletal damage. There was a trend for age at diagnosis to predict an increase in musculoskeletal damage. This may be a hint that comorbidity has a stronger impact on musculoskeletal damage than on total damage. Musculoskeletal disease activity was not significantly correlated with the increase in musculoskeletal damage ($P = 0.18$, Table 6). As we cannot exclude a type 2 error (too small sample size), studies with much bigger cohorts than the present one are warranted to shed more light on damage accrual in each organ score. From a cross-sectional study [7] we would expect a significant correlation between organ-specific disease activity over time and the corresponding organ-specific damage accrual.

In the present prospective study the initial prevalence of damage in at least one organ system in 56% of our SLE patients is similar to that reported by Gorgos *et al.* [22] (59.8%) and the mean initial damage score (1.2) is also similar to that of the Montreal cohort of 1.3 with a mean disease duration of 15 yr [9].

In summary this prospective study revealed the highly significant impact of total disease activity, as measured over 5 yr using the BILAG system, on the development of total damage. Moreover, these results provide further proof of the validity of the SLICC/ACR Damage Index and support the BILAG concept of the A-flares.

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Key messages

- This 5-yr prospective study shows a highly significant impact of disease activity over time on the development of future damage in SLE patients.
- The BILAG concept of A-flares is corroborated.

The authors have declared no conflicts of interest.

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