The Effect of Menopause on Disease Activity in Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** To determine the effect of menopause on disease activity and course of systemic lupus erythematosus (SLE).

Methods. Patients were identified from the University of Toronto lupus clinic database. Menopause was diagnosed on the basis of 12 months of amenorrhea. A 3 part study was carried out. Part 1 included an inception cohort of 190 women with SLE diagnosed in the premenopausal years (Group A) and an inception cohort of 55 women with SLE diagnosed in the postmenopausal years (Group B), both followed for a minimum of 3 years. Part 2 included 49 patients followed in the clinic for at least 3 years before and 3 years after their menopause (Group C). Part 3 included 193 patients followed for 6 years entirely in the premenopausal period (Group D) and 76 patients followed for 6 years entirely in the postmenopausal period (Group E). Disease activity was measured by the SLE Disease Activity Index 2000 (SLEDAI-2K) and the adjusted mean SLEDAI-2K (AMS). Damage was assessed by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) damage index. Comparisons were made using t-tests and chi-square and McNemar tests. A multivariate linear regression model was used to establish the impact of menopausal status on change in disease related features.

Results. In the first 3 years of disease, AMS was higher in Group A than Group B (6.6 ± 3.8 vs 5.0 ± 3.3, $p = 0.003$). Damage accrual was higher in Group B than in Group A both in the first year and at 3 years. For Group C, AMS and the number of flares per 3 year interval were lower in the postmenopausal period. SLICC/ACR damage index was greater during the 3 years in the postmenopausal period then in the premenopause ($p = 0.006$). SLEDAI-2K was higher among Group D than Group E at the start of the study (6.71 vs 4.86, $p = 0.04$). AMS for the 6 years was higher in the premenopausal than postmenopausal women (5.14 vs 3.54, $p < 0.0001$), however, the magnitude of change in the first and second 3 year periods was not different between Group D and E. The 3 year AMS of patients in Groups C, D, and E was plotted by age and menopausal status. The slopes of AMS in the pre- and postmenopausal periods were identical, indicating that time and not menopausal status is associated with the decrease in disease activity. On the other hand, SLICC damage index showed a greater damage in postmenopausal women at any of the time points of the study. To further delineate the effect of menopausal status on changes in disease activity and damage, multiple linear regressions were performed including age at diagnosis, disease duration, and SLEDAI-2K at presentation as independent variables. No changes in AMS, number of flares, or SLICC/ACR damage index score were associated with the menopausal status.

Conclusion. Although premenopausal women with SLE have more disease activity than postmenopausal women with SLE, we have shown that there is a constant rate of improvement over time, be it in the premenopause, across the menopause, or postmenopause. This improvement is not due to change in menopausal status. Thus clinicians should not be anticipating the postmenopausal era in a patient's course as a period of natural disease improvement. (First Release Sept 15 2006; J Rheumatol 2006;33:2192–8)

Key Indexing Terms:
MENOPAUSE SYSTEMIC LUPUS ERYTHEMATOSUS DISEASE ACTIVITY

Systemic lupus erythematosus (SLE) is a multisystem disease that primarily affects women in their reproductive years. The female to male ratio is 9:1 in the reproductive years, much lower in the younger and older age groups[1]. Estrogen is believed to play a role in the development of SLE and in exacerbations of the disease[2]. The use of estrogen has been associated with an increased risk for developing SLE[3]. Animal models also support the notion that estrogen perpetuates the disease whereas ovariectomy ameliorates it[4].

Women who develop SLE in their postmenopausal years have been reported to have less active disease[5,6]. In particular, the frequency of renal disease is reduced compared to premenopausal women. Mok, *et al*[7] further observed that women who sustained premature ovarian failure during cyclophosphamide therapy had a lower frequency of flares overall, as

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well as a lower frequency of severe flares. In another retrospective study from the same group, the frequency of flares and severity of SLE were reduced after menopause[8]. However, the number of patients included in the study was small. Sánchez-Guerrero, *et al*[9] also studied the effect of menopause on a small group of 30 women. While disease activity was somewhat higher in the premenopausal period, they did not identify an increased frequency of flares. Thus, the influence of the hormonal changes at the time of menopause in women with established SLE remains unclear.

The overall objective of our study was to determine the effect of menopause on disease activity and course of SLE. To address this objective a 3 part study was carried out. The specific objective for part 1 was to examine the role of menopausal status on disease activity at presentation and through the course of SLE in the first 3 years. In part 2 we aimed to examine the role of the menopause on SLE activity and course in an individual woman as she crossed into the menopause. Part 3 was designed to discern the relative contribution of age and disease duration versus the menopausal effect. Therefore, we compared disease activity in women with SLE followed for a similar length of time (6 years) entirely within a premenopausal or postmenopausal era.

MATERIALS AND METHODS

Setting. The University of Toronto Lupus Clinic is a primary, secondary, and tertiary referral center for patients with SLE. The clinic was established in 1970 and since then has been following patients with SLE longitudinally according to a standard protocol. Patients are followed at regular intervals, 2-6 months apart. At each visit a complete history, physical examination, and laboratory evaluations are carried out. All the information is collected in a computer database. Variables necessary to calculate disease activity and damage scores are included in the prospective analysis.

Definition of menopause. Since hormone levels were not available in our prospective cohort, we defined menopause on the basis of 12 months of amenorrhea. This included women with natural, surgical, and medication-induced menopause. The date of menopause was identified from review of the database. When no data regarding the date of menopause were available, the mean age of menopause of our lupus cohort was used. This was established to be 47 years of age based on the median age of menopause in those postmenopausal women in our cohort for whom the data of the date of menopause were known.

Patient selection. Patients were identified from the University of Toronto lupus clinic database. The study design is outlined in Figure 1.

Part 1 of the study investigated the effect of menopause on disease activity and course in the first 3 years of disease. Two groups of women were compared: (A) an inception cohort of women with SLE diagnosed in the premenopausal years and followed for a minimum of 3 years in the premenopausal stage; and (B) an inception cohort of women with SLE diagnosed in the postmenopausal years and followed for a minimum of 3 years.

Part 2 evaluated the effect of menopause on disease activity and course of SLE on patients as they crossed into menopause. We recognize that some of that interval time is the perimenopausal period. A single group of women were included and identified as Group C. Patients followed in the clinic for at least 3 years before and 3 years after their menopause, and who had at least 3 clinic visits in each 3 year time interval, were included.

Part 3 investigated whether duration of followup rather than menopausal status affects disease activity and course of SLE. Two groups of patients were included: (D) patients followed for 6 years entirely in the premenopausal period; and (E) patients who had followup for 6 years entirely in the postmenopausal period.

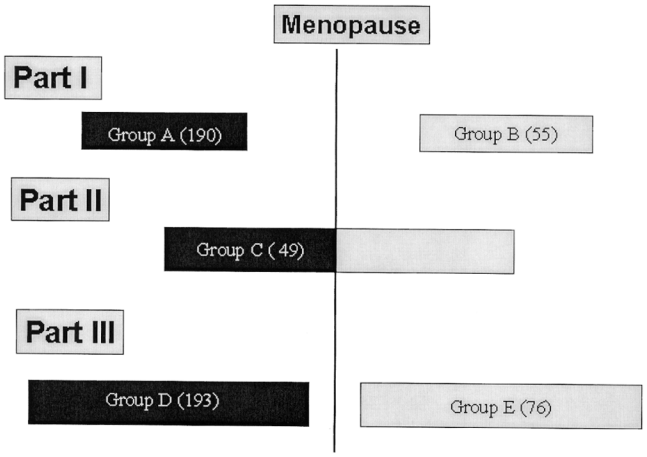

Figure 1. Study design.

While patients from Groups A and B have been included in Groups C, D, or E, the last 3 groups were mutually exclusive.

Assessment of disease activity. Disease activity was measured by the SLE Disease Activity Index 2000 (SLEDAI-2K)[10]. Information necessary to calculate the SLEDAI-2K score was collected at each visit. Disease activity was expressed as SLEDAI-2K measured at presentation to the clinic, as well as the adjusted mean SLEDAI-2K (AMS), which reflects disease activity over time[11]. In addition, we assessed the components of SLEDAI-2K contributing to disease activity. The number of flares, measured by the increase of SLEDAI-2K $\geq$ 4, was recorded for each cohort[12].

Assessment of damage. Damage accrued in the course of SLE was measured by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index[13], a validated measure to assess damage accrued in the course of SLE.

Statistical analysis. Descriptive statistics were used to present the mean and standard deviation or proportion of risk factors between patients in each part of the study. Comparisons were made using t-tests and chi-square tests for part 1 and part 3 while paired t-test and McNemar test were used for part 2. Multivariate linear regression model was used to establish the influence of menopausal status on change in AMS, number of flares, and SLICC damage while adjusting for other potentially important risk factors such as age at SLE diagnosis, disease duration at start of study, and SLEDAI-2K at presentation. Regressions were done using Groups C, D and E, which were mutually exclusive.

RESULTS

An inception cohort of 245 women with SLE was included in part 1 of the study. Of these, 190 were diagnosed and followed in their premenopausal years (Group A), and 55 patients were diagnosed and followed during their postmenopausal years (Group B). The mean age at diagnosis was 28.1 and 55.5 years, respectively. The mean age at menopause for Group B was 45.9 years. The number of visits during the 3 year period was 11.5 and 10.4, respectively. Among the postmenopausal women, 4 of the 55 were using hormone replacement therapy (HRT) at some point in the study interval. Evaluating disease activity and course in the first 3 years of disease revealed that SLEDAI-2K at presentation was similar in both groups (11.5 $\pm$ 8.3 and 11.6 $\pm$ 9.8, respectively), but that AMS for the 3 year

period was higher in the premenopausal group and this difference was statistically significant (6.6 ± 3.8 vs 5.0 ± 3.3, p = 0.003). While the flares in the first 3 years were higher in the premenopausal group, the difference did not reach statistical significance (Table 1). Of the SLEDAI-2K components, vasculitis, proteinuria, rash, pericarditis, and the presence of anti-DNA antibodies were significantly greater in the premenopausal group (Table 1). None of the other components of SLEDAI-2K was different.

Damage accrual was higher in the postmenopausal than in the premenopausal group both in the first year and at 3 years of disease. This reached significance at the 3 year point (Table 1). These results remained the same even when the 4 women taking HRT were removed from the analysis.

To further delineate the role of menopausal status in disease activity and damage, we then performed parts 2 and 3 of the study.

In part 2, 49 women (Group C) followed in the clinic for at least 3 years before and 3 years after their menopause with at least 3 clinic visits in each 3 year time interval were included. Their mean disease duration at entry to this study was 12.6 years and the mean age at menopause was 45.5 years. SLEDAI-2K at the start of each 3 year period was similar. The AMS during the 3 year interval, and the number of flares per 3 year interval, were lower in the postmenopausal 3 year period. Only AMS was significantly lower (Table 2), and this was not related to disease duration at the start of this study. SLICC/ACR damage index was greater during the 3 years in the postmenopausal period then in the premenopausal interval (p = 0.006). Of the 49 women, 14 took HRT at some point in the postmenopausal portion of the study period. The results remained unchanged even when the analysis was limited to the 35 women who never used HRT.

In part 3 of the study, 193 women with lupus (Group D) with a mean age of 27 and a mean disease duration of 5.1 years, who were followed in the lupus clinic for a minimum of 6 years entirely within the premenopausal period, were compared to 76 patients with lupus (Group E) with a mean age of 52 and a mean disease duration of 9.2 years who were followed in the lupus clinic for a minimum of 6 years entirely within the postmenopausal period (Table 3). The mean number of visits for Group D was 21.4 ± 6.3 and for Group E 19.0 ± 5.9. Of the 76 women in Group E, 11 took HRT at some point in the course of the study. SLEDAI-2K at first presentation to the lupus clinic was not different for women in the premenopausal period compared to women in the postmenopausal period (9.96 vs 11.45), but was higher among the premenopausal women at the start of the study (6.71 vs 4.86, p = 0.04). The number of flares was higher in the premenopausal women for the first 3 years but not the second 3 years. The change in number of flares is not different between the pre- and postmenopausal cohorts. AMS for the 6 years was higher in the premenopausal period (5.14 vs 3.54, p < 0.0001). This is seen in the first 3 years as well as in the second 3 years. Looking at the change in AMS between the first and second 3 years, the magnitude of the change is not different between the pre- and postmenopausal cohorts (–0.46 vs –0.61, p = 0.66).

To further examine the role of menopausal status on AMS, we plotted each 3-year AMS of patients in Groups C, D, and E (2 per patient) by age and menopausal status (Figure 2). The slopes of AMS in the pre- and postmenopausal periods are identical, indicating that it is time and not menopausal status

Table 1. Characteristics of an inception cohort of women with SLE beginning in the pre- or postmenopausal period.

	Premenopausal (Group A)	Postmenopausal (Group B)	p
No. of patients	190	55	
Caucasian/Black/Chinese/Other	151/17/11/11	50/3/1/1	
Age at diagnosis, yrs	28.1 ± 8.0	55.5 ± 9.0	< 0.0001
Age at menopause, yrs	NA	45.9 + 4.0	
No. of visits in 3 yr period	11.5 + 4.9	10.4 ± 4.9	0.12
SLEDAI-2K at presentation	11.5 ± 8.3	11.6 ± 9.8	0.94
AMS	6.6 ± 3.8	5.0 ± 3.3	0.003
No. flares in 3 yrs	2.1 ± 1.6	1.7 ± 1.6	0.13
Vasculitis	0.51 ± 1.07*	0.25 ± 0.56*	0.02
Proteinuria	0.58 + 0.99	0.28 ± 0.62	0.007
Rash	0.58 ± 0.59	0.36 ± 0.52	0.01
Pericarditis	0.012 ± 0.049	0.001 ± 0.009	0.005
DNA	0.49 ± 0.55	0.26 ± 0.33	0.0002
SLICC/ACR DI			
At 1 year	0.30 ± 0.74	0.52 ± 0.84	0.07
At 3 years	0.55 ± 1.14	0.95 ± 1.24	0.03

* Mean ± SD. Numbers reflect contribution of item to SLEDAI-2K scores. SLICC/ACR DI: Systemic Lupus Erythematosus International Collaborating Clinics/American College of Rheumatology damage index; SLEDAI-2K: SLE Disease Activity Index 2000.

Table 2. Characteristics of women with SLE followed for 3 years pre and 3 years post-menopause.

	Premenopausal (Group C)	Postmenopausal	p
n	49		
Caucasian/Black/Chinese/other	44/1/1/3		
Age at diagnosis, yrs	29.8 ± 9.5*		
Disease duration, yrs	12.6 ± 8.0		
Decade			
70	8 (16.3%)		
80	20 (40.8%)		
90	21 (42.9%)		
Age at menopause, yrs	45.5 ± 5.5		
No. of visits in 3 yr period	10.0 ± 4.5	9.6 ± 3.9	0.51
SLEDAI-2K			
At presentation	11.1 ± 8.8		
At start of interval	5.0 ± 5.5	5.1 + 4.1	0.98
Flares in 3 yrs	1.8 ± 1.6	1.4 ± 1.3	0.12
AMS	5.4 + 2.9	4.6 ± 2.5	0.05
SLICC/ACR DI			
At start of study	0.85 ± 1.18		
At 3 yrss	1.31 ± 1.47	1.76 ± 1.79	0.006

* Mean ± SD. Numbers reflect contribution of item to SLEDAI-2K scores. AMS: adjusted mean SLEDAI-2K.

that is associated with the decrease in disease activity.

SLICC damage index showed a greater damage in postmenopausal women at any of the time points of the study—at start ($p = 0.02$), at the 3 year point ($p = 0.0009$), and at the 6 year point ($p < 0.0001$). The increase in SLICC damage score is also more pronounced in the postmenopausal period with change from study start to 3 years ($p = 0.003$), from 3 years to 6 years ($p = 0.006$), and from study start to 6 years ($p = 0.0002$). However, the percentage increase from baseline was similar in both groups. The results remained the same even when the analysis was confined to the 65 women in Group E who did not take HRT.

To further delineate the effect of menopausal status on changes in disease activity and damage, multiple linear regressions were performed including age at diagnosis, disease duration, and SLEDAI-2K at presentation as independent variables. We included all the patients from Part 2 and from Part 3 in this analysis—that is, patients from Groups C, D, and E. Change in AMS was defined as the AMS in the second 3 years minus AMS in the first 3 years. As can be seen in Table 4, menopausal status represented in the study groups did not affect the magnitude of change in AMS. The magnitude of the change in AMS was not related to age at presentation, disease duration, or SLEDAI-2K at presentation. Change in number of flares is defined as the number of flares in the second 3 years minus number of flares in the first 3 years. In this regression, longer disease duration is associated with greater change in number of flares ($p = 0.002$). Change in SLICC/ACR damage index score used in the regression is determined by the damage score at the end of the 6 year period minus the damage score at the start of the study. Higher age at SLE diagnosis and increasing disease duration are both predictors of increased damage over the 6 year period ($p = 0.005$ and $p = 0.008$, respectively). None of the changes in AMS, number of flares, or SLICC/ACR damage index score was associated with menopausal status.

DISCUSSION

The prevailing concept is that patients with lupus in their premenopausal era have more active disease than women in their postmenopausal era. We confirmed this observation through part 1 of our study, comparing 190 patients who were premenopausal at diagnosis to 55 patients who were diagnosed and followed in their postmenopausal years. We showed that the disease activity over the first 3 years, measured by the AMS, was higher among premenopausal patients. They exhibited more vasculitis, proteinuria, rash, and pericarditis than the postmenopausal patients, and more frequently had anti-DNA antibodies. While flare rates were higher in the premenopausal women, this difference did not reach statistical significance, perhaps because flare is defined as an increase in SLEDAI-2K of 4 or more.

The implication of this part of the study was that the menopausal state may have contributed to disease amelioration. To test whether it was the menopause that influenced disease expression we performed part 2 of our study. We studied women who were diagnosed and followed for 3 years in their premenopausal era and followed for another consecutive 3 year period as they crossed into their postmenopausal era. The comparison between the first and second 3 year periods revealed that the AMS was reduced during the postmenopausal period compared to the premenopausal period. Thus the concept that postmenopausal status ameliorated disease activity could be supported by this part of the study.

Table 3. Characteristics of women with SLE followed for 6 years either entirely in the premenopausal or postmenopausal period.

	6 yrs Pre (Group D)	6 yrs Post (Group E)	p
N	193	76	
Caucasian/Black/Chinese/Other	147/23/17/6	67/6/1/2	
Age at diagnosis, yrs	24.6 ± 7.8	47.3 ± 11.8	< 0.0001
Age at menopause, yrs	NA	46.3 ± 3.7	
Disease duration at study start, yrs	5.1 ± 4.8	9.2 ± 9.5	0.0006
Decade			
1970s	27 (14.0%)	9 (11.8%)	
1980s	106 (54.9%)	35 (46.1%)	0.23
1990s	60 (31.1%)	32 (42.1%)	
SLEDAI-2K			
At presentation to clinic	9.96 ± 7.88	11.45 ± 9.22	0.19
At start of study	6.71 ± 6.66	4.86 ± 6.46	0.04
Flares			
In first 3 yrs	2.1 ± 1.7	1.5 ± 1.4	0.005
In second 3 yrs	1.7 ± 1.4	1.3 + 1.3	0.06
Change in flares	–0.41 ± 1.77	–0.18 + 1.26	0.23
AMS (6 yrs)	5.14 ± 2.91	3.54 ± 2.52	< 0.0001
AMS			
first 3 yrs	5.37 ± 3.33	3.84 ± 2.98	0.0006
second 3 yrs	4.90 ± 3.30	3.23 ± 2.50	< 0.0001
Change in AMS	–0.46 ± 3.12	–0.61 ± 2.20	0.66
Headache	0.53 ± 1.19*	0.28 ± 0.58*	0.02
Vasculitis	0.35 ± 0.72	0.16 ± 0.36	0.005
Proteinuria	0.50 ± 0.91	0.15 ± 0.47	< 0.0001
Pyuria	0.22 ± 0.41	0.10 ± 0.21	0.002
New rash	0.38 ± 0.47	0.26 ± 0.39	0.05
Low complement	0.76 ± 0.62	0.54 ± 0.61	0.009
DNA	0.65 ± 0.56	0.30 ± 0.41	< 0.0001
SLICC/ACR DI			
At start of study	0.48 ± 0.94	0.88 ± 1.31	0.02
At 3 yrs	0.85 ± 1.25	1.61 + 1.79	0.0009
Change in first 3 yrs	0.34 ± 0.75	0.74 ± 1.06	0.003
At 6 yrs	1.24 ± 1.59	2.38 ± 2.19	< 0.0001
Change in second 3 yrs	0.39 ± 0.74	0.78 + 1.10	0.006
Change in 6 yrs	0.72 + 1.11	1.50 + 1.64	0.0002

* Mean ± SD. Numbers reflect contribution of item to SLEDAI-2K scores.

However, the outstanding question was whether it was the menopause or duration of followup that affected disease activity state. To test that question we performed part 3 of our study. We compared 190 patients followed for 6 years entirely in their premenopausal era to 76 patients followed for 6 years entirely in their postmenopausal era. This study indicated that duration of followup and not menopause per se contributed to amelioration of disease activity over the period. The amelioration over time was not related to disease activity at onset or age at diagnosis. Further, the magnitude of change (slope) was constant over time, regardless of age and menopausal status, indicating that over a 6 year interval all patients improved to the same degree.

While both groups accrued damage over the 3 year followup, postmenopausal patients with lupus accrued significantly more damage than the premenopausal group, possibly related to the presence of comorbid conditions in the elderly population.

The linear regressions demonstrated that menopausal status was not associated with changes in AMS. Flare rate was associated with disease duration at the time of the study, indicating that like the AMS, flare rates decrease over time. Damage was associated with age and disease duration, as previously shown[14].

There are 2 possible limitations to our study. The first is that definite age at menopause was not known in 50% of our patients. We therefore used the age 47 based on the median age of menopause in those postmenopausal women in our cohort for whom the data of the date of menopause was known. This number is similar to that reported by Mok, *et al*[15] for Chinese patients with SLE (mean age at menopause 47.8), and by Lakshminarayanan, *et al*[16] for patients from the United

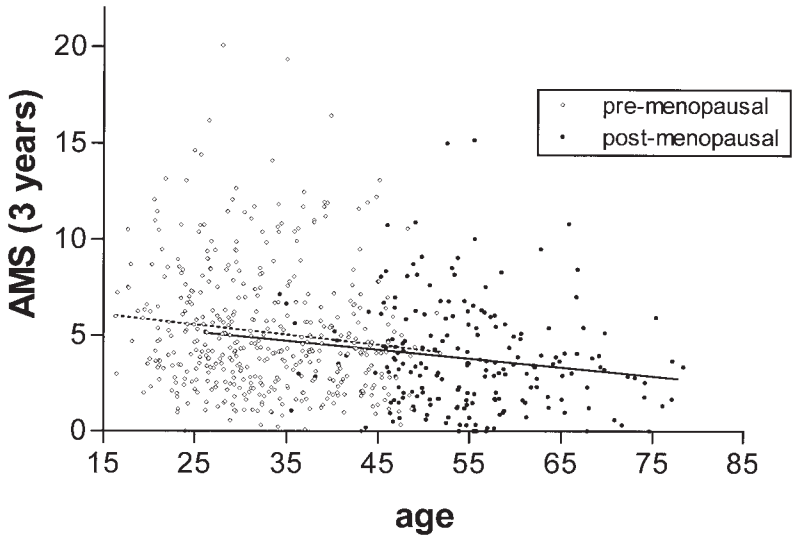

Figure 2. Groups C, D, and E. There are 2 points per patient: AMS in first 3 yrs and AMS in second 3 yrs. Age is age at beginning of 3 yrs intervals.

Table 4. Multivariate linear regressions.

	Change* in AMS Regression Coefficient ± SE	p	Change** in No. of Flares Regression Coefficient ± SE	p	Change *** in SLICC Regression Coefficient SE	p
Study Group†						
Group D vs (C + E)	0.69 ± 0.57	0.47	0.46 + 0.32	0.31	0.27 ± 0.25	0.49
Group E vs (C + D)	0.21 ± 0.63		–0.03 ± 0.35		0.21 ± 0.28	
Age at diagnosis of SLE	0.008 ± 0.023	0.73	0.022 ± 0.013	0.10	0.029 ± 0.010	0.005
Disease duration at start of study	0.046 ± 0.032	0.16	0.055 ± 0.018	0.002	0.038 + 0.014	0.008
SLEDAI-2K at clinic presentation	–0.022 ± 0.019	0.26	0.002 ± 0.011	0.84	0.016 ± 0.009	0.08

* Change in AMS = AMS in second 3 yrs minus AMS in first 3 yrs. ** Change in number of flare = number of flares in second 3 yrs – number of flares in first 3 yrs. *** Change in SLICC = SLICC score at 6 yrs minus SLICC score at start of study. † Study Group C: 3 yrs in premenopause and 3 yrs in postmenopause; Group D: 6 yrs entirely within the premenopausal era; Group E: 6 yrs entirely within the postmenopausal era.

States (median age at menopause 46). In our own cohort there was no significant difference in the age at menopause among the 3 major ethnic groups. Thus we believe that age 47 is an appropriate age to assign to patients for whom the date of menopause was unavailable. Moreover, among our patients in group B, all but 2 entered the cohort after age 50 in a postmenopausal status. Among the 49 patients in Group C, 9 women were assigned an age of menopause at 47. Even if we remove those women from the analysis the results remain the same. In Group E, among the 76 postmenopausal women of the 39 assigned to menopause age of 47, 34 were over the age of 50 when the study began and only 5 were included in the study between the ages of 47 and 50. Excluding these patients did not alter the results.

A second possible limitation involves including patients taking HRT in a menopausal grouping. In this respect we[17], and others[18], have shown that there is no significant effect on SLE disease activity with hormone replacement therapy in postmenopausal women. Further, as noted in the Results section, when we removed the patients taking HRT from the analyses the results remained the same.

In conclusion, we showed that disease activity is greater in premenopausal women. However, the apparent decrease in disease activity in the postmenopause is likely related to passage of time (older age and/or disease duration) and not to change in hormonal status. We showed that there is a constant rate of improvement over time, be it in the premenopause, across the menopause, or postmenopause. Our study thus demonstrates that clinicians should not be anticipating entry into the postmenopausal era in a patient's course as a period of disease improvement.

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