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Effect of age, menopause and cyclophosphamide use on damage accrual in systemic lupus erythematosus patients from LUMINA, a multiethnic US cohort (LUMINA LXIII)

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Sir – The prognosis and survival rates of patients with systemic lupus erythematosus (SLE) have improved over the years¹; thus, an increasing number of women with SLE are reaching the age of menopause. In addition, the use of cyclophosphamide therapy and the disease itself increase the risk of premature ovarian failure in these patients.² Therefore, as our LUMINA (Lupus in Minorities: Nature versus Nurture) cohort matures, we have been intrigued by the accrual of damage in our postmenopausal women. Previously, we have examined damage accrual in our cohort patients whose disease started before and after the menopause and concluded that it was age rather than the menopause that accounted for damage accrual in the postmenopausal women.³ With a larger number of LUMINA cohort patients, and more years of observation having occurred, we sought to re-examine this matter. We, therefore, examined the role of menopause versus age by regressing age on menopause so that the effect of menopause per se could be better determined.

The current analyses were limited to the women in the LUMINA cohort. Briefly, at entry into the cohort (T0), patients had disease duration ≤ 5 years, were ≥ 16 years of age and were of defined ethnicity (Hispanic from Texas and Puerto Rico, African American, or Caucasian). Damage at last visit (TL), the dependent variable, was ascertained with the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI). In those women who developed premature gonadal failure, this variable was excluded from the SDI so that damage could not be attributed to it. Disease activity was ascertained with the Systemic Lupus Activity Measure-Revised (SLAM-R) at diagnosis (TD), T0 and every subsequent visit.⁵ Menopause was defined as the presence of climacteric symptoms, amenorrhea lasting > 6 months, bilateral oophorectomy, increased follicle-stimulating hormone

values above the upper limit of normal for reproductive-age women and/or hormone replacement therapy. Premature gonadal failure was defined as per the SDI4 as either amenorrhea lasting >6 months (unrelated to hysterectomy) or menopause before age 40, regardless of its cause. For those patients whose menopause date had not been recorded in the database ($n = 12$, 11.5%), we used the age of 51 to define it, based on currently available literature data.⁶ No patient would have been classified as having premature gonadal failure based on this cut-off age.

Age, gender, ethnicity, menopause and variables previously found to be significant predictors of damage accrual^{7,8} were examined by univariable and multivariable linear regression analyses. Given the strong correlation between age and menopausal status, a simple linear regression was built with age as the dependent variable and menopausal status as the independent variable to obtain a residual, which is not correlated with menopausal status. Two different multivariable models were examined. In model 1 the variable was the residual; in model 2 the age at T0 was used instead. Variables with P values ≤ 0.05 were considered significant in these analyses.

Of the 567 women in the LUMINA cohort, 86 were excluded because SLE ensued after they became menopausal and 12 women were excluded because they were older than 51 at diagnosis. Of the remaining 469 women, 104 (22.2%) had become postmenopausal after SLE diagnosis, whereas 365 had not; all ethnic groups were represented in those who became postmenopausal and those who did not. Menopausal women were older than the others [T0 mean age were 37.4 (9.6) and 31.3 (8.0) years, $P < 0.0001$], had a longer total disease duration [95.3 (48.4) vs 60.5 (38.6) months, $P < 0.0001$], and had higher T0 and TL damage scores [1.0 (1.4) vs, 0.6 (1.0), $P = 0.004$ and 2.7 (2.6) vs 1.3 (1.8), <0.0001 , respectively]. No differences in the ethnic distribution or in the TD and T0 SLAM-R scores were found between women in both groups (data not shown). As shown in Table 1, menopause was independently associated with damage accrual at TL in these multivariable analyses [model 1 (t -test 2.19, $P = 0.0293$) and model 2 (t -test 2.02, $P = 0.0439$)]. However, given that about half of the women ($n = 48$) who had become menopausal had experienced premature gonadal failure, we decided to examine whether premature gonadal failure or cyclophosphamide, which is highly associated with its occurrence, could explain the apparent association of menopause with damage accrual. The results of these analyses are shown in Table 2; cyclophosphamide, but not premature gonadal failure, was associated with damage accrual after adjusting for the same variables noted in Table 1. Sensitivity analyses performed by assuming the age of menopause to be 50 or 52 for those patients in whom a precise age was not recorded did not alter these results (data not shown).

In addition to confirming the role of non-Caucasian ethnicity, disease duration and T0 damage in the accrual of damage in patients with lupus, we have evaluated the role of menopause and age in damage accrual^{7–9} and found age to be the decisive factor. We had hypothesized that menopause independent of age and disease duration will be predictive of damage accrual, given the increased risk for comorbidities such as cardiovascular disease, insulin resistance, osteoporosis and cognitive impairment in the postmenopausal years^{10–12}; however, the effect of menopause disappeared when cyclophosphamide was added. Of note, given the negligible number of patients who had received oral cyclophosphamide, our analyses were limited to those patients who received it by the intravenous route. Furthermore, lacking the precise dose of each intravenous cyclophosphamide administration we chose to use the number of pulses as a proxy, as previously reported (750–1000 mg/m² of body surface administered each time).¹³ Therefore, cyclophosphamide contributes to damage accrual over and above the damage caused on gonadal function. In fact, cyclophosphamide use has been reported to be an independent factor predictive of damage accrual.^{14–16} Of interest, this effect is not due to an increased number of malignancies, in our cohort (very few), so the effect of cyclophosphamide

is more deleterious than the published literature and our own clinical experience seem to suggest. These data clearly indicate that immunosuppressive therapy should be used cautiously and that less toxic medications are urgently needed for the management of patients afflicted with this disorder.

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Table 1Role of menopause in damage accrual in LUMINA patients by multivariable linear regression analyses^a

Model ^b	<i>t</i> -test	β standardized coefficient	<i>P</i> value
1	2.19	0.40	0.0293
2	2.02	0.39	0.0439

Abbreviation: LUMINA, Lupus in Minorities: Nature versus Nurture.

^a Adjusted for ethnicity, poverty, American College of Rheumatology criteria number at baseline (T0), disease duration, disease activity at diagnosis and/or T0, damage at T0 and the weighted average dose of glucocorticoids (as prednisone).

^b Model 1 includes the residual and model 2 age at baseline.

Table 2

Role of premature menopause in damage accrual in LUMINA patients by multivariable linear regression analyses^a

Variable	<i>t</i> -test	β standardized coefficient	<i>P</i> value
Age	3.84	0.03	<0.0001
Ethnicity			
Texan-Hispanic	4.24	0.98	<0.0001
Puerto Rican-Hispanic		Reference group	
African American	4.03	0.82	<0.0001
Caucasian	1.10	0.21	0.3121
Disease duration	6.46	0.12	<0.0001
Poverty	2.34	0.34	0.0196
ACR ^a criteria number at T0 ^b	2.50	0.10	0.0072
SLAM-R	0.35	0.00	0.7287
SDI at T0	15.16	0.96	<0.0001
Premature gonadal failure	0.60	0.13	0.5460
Glucocorticoid (weighted average dose)	1.30	0.01	0.1932
Cyclophosphamide (number of pulses)			
0		Reference group	
1–6	1.90	0.48	0.0577
>6	3.32	0.77	0.0010

Abbreviation: Lupus in Minorities: Nature versus Nurture; SLAM-R, Systemic Lupus Activity Measure-Revised; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; ACR, American College of Rheumatology; TO, baseline visit.