Early discoid lupus erythematosus protects against renal disease in patients with systemic lupus erythematosus: longitudinal data from a large Latin American cohort

GJ Pons-Estel1, LD Aspey2, G Bao3, BA Pons-Estel4, D Wojdyla5, V Saurit6, A Alvarellos6, F Caeiro6, MJ Haye Salinas6, El Sato7, ER Soriano6,8,9, LTL Costallat10, O Neira11, A Iglesias-Gamarr12, G Reyes-Llerena13, MH Cardiel14, EM Acevedo-Vásquez15, R Chacón-Díaz16 and C Drenkard13

1Department of Autoimmune Diseases, Institut Clínic de Medicina i Dermatologia, Barcelona, Spain; 2Department of Dermatology, Emory School of Medicine, Atlanta, USA; 3Division of Rheumatology, Emory School of Medicine, Atlanta, USA; 4Servicio de Reumatología, Hospital Provincial de Rosario, Rosario, Argentina; 5GLADEL Consultant, Universidad Nacional de Rosario, Rosario, Argentina; 6Servicio de Reumatología, Hospital Privado, Córdoba, Argentina; 7Departamento de Medicina, Universidade Federal da Sãopaulo (UNIFESP), Sãopaulo, Brazil; 8Sección de Reumatología, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina; 9Fundación Dr Pedro M Catoggio para el Progreso de la Reumatología, Buenos Aires, Argentina; 10División de Reumatología, Universidad Estadual de Campinas, Campinas, Brazil; 11Sección de Reumatología, Hospital del Salvador, Facultad de Medicina, Universidad de Chile, Santiago, Chile; 12Facultad de Medicina, Universidad Nacional de Colombia, Bogota, Colombia; 13Servicio Nacional de Reumatología, Centro de Investigaciones Médico Quirúrgicas (CIMEQ), La Habana, Cuba; 14Centro de Investigación Clínica de Morelia, Morelia, México; 15Servicio de Reumatología, Hospital Nacional ‘Guillermo Almenara Irigoyen’, School of Medicine, Universidad Nacional Mayor de San Marcos, Lima, Perú; and 16Servicio de Reumatología, Hospital Universitario, Caracas, Venezuela

Objectives: The objective of this study was to examine whether early discoid lupus erythematosus (DLE) would be a protective factor for further lupus nephritis in patients with systemic lupus erythematosus (SLE).

Methods: We studied SLE patients from GLADEL, an inception longitudinal cohort from nine Latin American countries. The main predictor was DLE onset, which was defined as physician-documented DLE at SLE diagnosis. The outcome was time from the diagnosis of SLE to new lupus nephritis. Univariate and multivariate survival analyses were conducted to examine the association of DLE onset with time to lupus nephritis.

Results: Among 845 GLADEL patients, 204 (24.1%) developed lupus nephritis after SLE diagnosis. Of them, 10 (4.9%) had DLE onset, compared to 83 (12.9%) in the group of 641 patients that remained free of lupus nephritis (hazard ratio 0.39; \( P = 0.0033 \)). The cumulative proportion of lupus nephritis at 1 and 5 years since SLE diagnosis was 6% and 14%, respectively, in the DLE onset group, compared to 14% and 29% in those without DLE (\( P = 0.0023 \)). DLE onset was independently associated with a lower risk of lupus nephritis, after controlling for sociodemographic factors and disease severity at diagnosis (hazard ratio 0.38; 95% confidence interval 0.20–0.71). Conclusions: Our data indicate that DLE onset reduces the risk of further lupus nephritis in patients with SLE, independently of other factors such as age, ethnicity, disease activity, and organ damage. These findings have relevant prognostic implications for SLE patients and their clinicians. Further studies are warranted to unravel the biological and environmental pathways associated with the protective role of DLE against renal disease in patients with SLE.

Key words: Systemic lupus erythematosus; lupus nephritis; discoid lupus erythematosus; survival analysis; GLADEL cohort

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune multisystem condition characterized by a broad spectrum of clinical manifestations and disease severity that ranges from mild to life threatening. Onset manifestations are cutaneous in approximately 50% of SLE patients, while between 55% and 90% present with skin
lesions sometime during the course of the disease.\textsuperscript{1} It has been suggested that the prognosis of SLE differs according to the initial clinical presentation, and that certain lupus-specific cutaneous manifestations, such as discoid lupus erythematous (DLE), may be associated with mild disease in SLE.\textsuperscript{2–6}

DLE, the most common form of chronic cutaneous lupus, is characterized by scarring inflammatory plaques that heal leaving central scars, atrophy and dyspigmentation.\textsuperscript{1} DLE is commonly observed as a single entity without significant systemic involvement.\textsuperscript{7} However, between 5\% and 11\% of SLE patients present with DLE as the onset manifestation, and a smaller proportion develop DLE within 3–5 years of diagnosis.\textsuperscript{8–10}

Former reports suggest that there is a negative association between DLE and lupus nephritis (LN) in patients with established SLE.\textsuperscript{11} However, until recently, the evidence supporting such an association was mostly derived from retrospective studies conducted with small samples from the dermatology setting.\textsuperscript{11} Moreover, prior studies tended to have low representation of patients from ethnic minorities, who are at higher risk of LN compared to white populations. Two large multiethnic cohorts of SLE patients were recently examined to determine the association of DLE with systemic manifestations, including renal disease.\textsuperscript{12,13} While DLE was found to reduce the risk of end-stage renal disease in a transversal study conducted by Santiago-Casas et al.,\textsuperscript{12} an association between DLE and LN could not be confirmed. Similarly, Merola et al.\textsuperscript{13} did not find a relationship between DLE and renal disease in a nested case control study among patients with SLE. A more recent study from a predominantly Caucasian cohort in Canada reported that SLE patients with DLE at inception were less likely to have active renal disease compared to those who never had cutaneous lupus erythematosus (CLE).\textsuperscript{14}

Given the poor outcomes associated with renal disease in SLE, the potential protective risk of DLE against LN may impact the clinical screening of SLE patients, particularly among those without DLE at onset. The study presented here takes advantage of longitudinal data collected from a large multiethnic Latin American cohort for a period of nearly 5 years. We sought to examine whether the occurrence of DLE preceding the diagnosis of SLE was associated with a lower risk of LN.

Patients and methods

Patients

The Latin American group for lupus study (GLADEL or Grupo Latino Americano De Estudio del Lupus) has established a longitudinal multiethnic inception cohort of Latin American patients with SLE. Participants’ enrolment and data collection started in 1997 by establishing a common protocol, consensus definitions, and outcome measures in 34 centers distributed among nine Latin American countries.\textsuperscript{15} GLADEL investigators (board certified rheumatologist or internist with experience in SLE management) were trained in data collection and data entry prior to study initiation. The study was conducted according to the Declaration of Helsinki for research in humans, and following local institutional review board regulations.

GLADEL has enrolled 1480 patients with a recent diagnosis (\leq 2 years) of SLE. The diagnosis was made based on clinical and laboratory features, and according to the expertise of the investigators (rheumatologist or qualified internist with experience in SLE).\textsuperscript{15} Fulfilment of four American College of Rheumatology (ACR) SLE classification criteria\textsuperscript{16,17} at the time of diagnosis was not necessary. Also, disease diagnosis could occur subsequent to a patient accruing at least four ACR criteria. Data collected longitudinally included socioeconomic, demographic and clinical characteristics, treatment features, and laboratory tests. The overall characteristics of the GLADEL cohort have been described in detail elsewhere.\textsuperscript{15}

Hypothesis and study design

We hypothesized that early occurrence of DLE (DLE onset) would reduce the risk of further LN in patients with a diagnosis of SLE. To test our hypothesis, we used a longitudinal design to compare the time from SLE diagnosis to the occurrence of LN between SLE patients with and without DLE onset.

DLE onset was defined as either a clinical or clinical-pathological diagnosis of DLE by a board certified dermatologist, or a discoid rash documented according to the ACR criteria for the classification of SLE (erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions)\textsuperscript{15,16} by a GLADEL investigator during physical examination, at or before the diagnosis of SLE.
The outcome for this study was the occurrence of LN after SLE diagnosis, which was defined using clinical and/or histological criteria documented by a GLADEL investigator and attributed to lupus glomerulonephritis. The clinical criteria included proteinuria greater than 0.5 g per day on two or more occasions and the presence of cellular casts in the urinalysis; the histological criterion was a renal biopsy compatible with LN histopathology class II–V, according to the World Health Organization. In order to ensure a causal relationship between the predictor and the outcome, SLE patients with prevalent LN were excluded. Prevalent LN was defined as the documentation of LN before or within 60 days of the date of SLE diagnosis. The 60-day period was considered appropriate for performing the initial laboratory workup necessary to assess LN in the clinical setting.

Variables previously found to be associated with LN were examined as potential confounders. Among sociodemographic factors, we included gender, age at diagnosis, age at first ACR criteria, ethnicity (Mestizo, African–Latin American and white), delay to diagnosis, place of residency, socioeconomic status, education, and medical insurance. Disease severity at diagnosis was assessed using the SLE activity index (Systemic Lupus Erythematosus Disease Activity Index; SLEDAI) and the SLE damage index (Systemic Lupus International Collaborating Clinics/ACR Damage Index; SDI). Because patients with prevalent LN at diagnosis were excluded, the renal domain of the SLEDAI or SDI measures would not contribute to the overall scores of those instruments. Prior exposure to antimalarial, immunosuppressant (azathioprine; cyclophosphamide), or a high dose of glucocorticoid (≥60 mg of prednisone or equivalent glucocorticoid dose) drugs was dichotomized according to their use/non-use prior to SLE diagnosis.

Statistical analyses

In descriptive analyses, patient characteristics were summarized using frequency and percentage for categorical variables, and mean and standard deviation (SD) for continuous variables. For each patient, we determined the time (in years) from the date of SLE diagnosis to the earliest date of LN that was documented after the diagnosis. In those cases without LN during follow-up, observation was censored at the time of the last visit. Kaplan–Meier curves and log-rank tests were used to compare time to LN event between patients with and without DLE onset, overall and by race (white vs. non-white). Then, univariate and multivariate Cox proportional hazard regression analyses were conducted to examine the association between DLE onset and LN. Potential confounders were grouped in three categories: (a) sociodemographics; (b) treatment before diagnosis; and (c) disease severity at diagnosis (disease activity; organ damage). Bootstrap bagging was used to select predictors of LN in the final multivariate model. In brief, 1000 datasets were obtained by random sampling with replacement (bootstrap sampling). The bootstrap sample was analyzed using forward stepwise Cox regression with an entry criterion of \( P < 0.20 \) and a retention criterion of \( P < 0.05 \). Covariates were retained in the final model if they appeared in at least 50% of the models. The fit of the final multivariate model was examined with the Hosmer–Lemeshow-type goodness of fit test. Predictors were examined for the proportional hazards assumption with Schoenfeld residuals versus time plots or with log-log transformation of the Kaplan–Meier survival curves for continuous or categorical variables, respectively. The assumption was further confirmed using the time-varying covariate approach. A ratio of at least 20 events per degree of freedom of the model was maintained. Results were summarized using hazard ratio (HR) and 95% confidence interval (CI).

For SLEDAI at diagnosis (21.7% of the patients with missing data), multiple imputation was used to generate 25 imputed datasets, which were used to assess whether the effect of DLE onset on LN would be modified by adding SLEDAI at diagnosis to the model. To determine the robustness of our results, we performed complete case sensitivity analysis. Multivariate models were created using the same approach as described above.

All statistical analyses were performed with SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

Results

Description of the study population

Among 1480 SLE patients from the GLADEL cohort, 615 with prevalent LN and 20 without follow-up after diagnosis were excluded (Figure 1). Thus, we examined a sample of 845 GLADEL participants, 93 (11.0%) of whom had DLE onset and 204 (24.1%) developed LN during the follow-up. The median disease duration from SLE diagnosis to LN was 0.9 years (interquartile range 0.4–2.5). Renal biopsy compatible with LN was documented in 61 (29.9%) patients. Among the
143 (70.1%) remaining patients who met the renal ACR criteria, 21 also had increased serum creatinine attributed to subjacent LN. There were 183 (21.7%) subjects with missing data on SLEDAI at diagnosis. No significant differences were found for sociodemographic and clinical characteristics between patients with and without SLEDAI data, with the exception of a higher proportion of antimalarial and high-dose steroids among those with missing SLEDAI data (data not shown).

Sociodemographic and clinical features at diagnosis are shown in Table 1. The sample was predominantly represented by women (91.8%), patients of non-white ethnicity (54.7% Mestizos or African–Latin Americans), and low socioeconomic status (57.8%). The mean age at SLE diagnosis was 30.9 years (SD 12.4). The mean activity and damage indexes at diagnosis were 9.6 (SD 5.5) and 0.6 (SD 0.9), respectively. Nearly 11% of patients were on antimalarial drugs at diagnosis and fewer than 2% were on immunosuppressive therapies.

Factors associated with time to LN

Univariate survival analysis

As shown in Table 2, the age at diagnosis of patients in the LN group was younger (mean age 28.4 (SD 11.7)) compared to those without LN (mean age 31.7 (SD 12.6)). Per 5-year increase of age at diagnosis, the HR of LN was 0.90 (95% CI 0.85–0.96; \( P = 0.0014 \)). Non-white ethnicity and low socioeconomic status (compared to medium or high) were associated with 1.53 and 1.35-fold increased risk of LN, respectively. Higher education was protective against LN (HR 0.90 per 3-year increase; 95% CI 0.82–1.00; \( P = 0.049 \)). DLE onset was present in 10 out of 204 (4.9%) patients who further developed LN, compared to 83 out of 641 (12.9%) who did not. DLE onset was significantly associated with a lower risk of further LN (HR 0.39; 95% CI 0.20–0.73; \( P = 0.0033 \)). The organ damage score (SDI) at diagnosis was significantly higher among SLE patients who further developed LN. Per each unit increase in SDI, there was a 1.24-fold increased risk of LN (\( P = 0.0007 \)). As for SLEDAI at diagnosis and treatment prior to SLE diagnosis, no association was found with further LN.

In Kaplan–Meier analysis, the estimated proportion of SLE patients who developed LN at 1 and 5 years was 6% and 14% for those with DLE onset compared to 14% and 29% for those without DLE onset (log-rank test, \( P = 0.0023 \)) (Figure 2). When patients were categorized by ethnicity, the proportion of non-white SLE patients who developed LN at 1 and 5 years was 4% and 9% for those with DLE onset, compared to 17% and 34% for those without DLE onset (log-rank test, \( P = 0.0007 \)). Within white
patients, LN at 1 and 5 years was observed in 8% and 20% of those with DLE onset, compared to 10% and 23% of those without DLE, respectively ($P = 0.53$) (Figure 2).

**Multivariate survival analyses**

Table 3 depicts multivariate models created to examine the effect of DLE onset on time to LN after controlling for potential confounders, which were grouped in categories. The first model shows that the HR of LN among patients with DLE onset was 0.38 (95% CI 0.20–0.71) after controlling for sociodemographic factors, of which only age at diagnosis and ethnicity were significantly associated with the outcome. DLE onset remained significantly associated with LN (HR 0.39; 95% CI 0.21–0.74) after controlling for drugs used prior to SLE diagnosis. Similarly, the protective effect of DLE onset remained constant (HR 0.38; 95% CI 0.20–0.73) when it was controlled for the effect of disease activity and organ damage. The final model showed a slightly lower HR of LN (HR 0.38; 95% CI 0.20–0.71) for DLE onset, which was independent of the effect of age at diagnosis, ethnicity, and organ damage. Table 3 also shows the reliability (proportion of times a covariate was selected by bootstrap bagging) of risk factors in the model. The highest reliability was for DLE (89.3%) and age at diagnosis (89.6%), followed by SDI at diagnosis (81.0%), and ethnicity (73.5%). Reliability was less than 30% for the other covariates examined in the model (data not shown). The multivariate model provided a good fit of the data (Hosmer–Lemeshow goodness-of-fit test, $P = 0.10$).

**Sensitivity analyses**

We examined 662 patients with complete data (Table 4). While DLE onset, age at diagnosis and SDI at diagnosis remained significantly associated with LN, non-white ethnicity was no longer selected in the final model. The overall direction of the associations and HRs were similar to those found in the multiple imputation model shown in Table 3; however, lower reliability percentages were found in the sensitivity analysis.

**Discussion**

In the largest Latin American cohort of SLE patients, the early occurrence of DLE was
Figure 2  Cumulative incidence of lupus nephritis in systemic lupus erythematosus patients by discoid lupus erythematosus at onset, overall and stratified by race (white, non-white).

Table 3  Predictors of lupus nephritis in patients with SLE by multivariate Cox proportional regression analysis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DLE+ demographics</th>
<th>DLE+ treatment</th>
<th>DLE+ SDI &amp; SLEDAI</th>
<th>Full model</th>
<th>Final model</th>
<th>Reliability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95%CI)</td>
<td>HR (95%CI)</td>
<td>HR (95%CI)</td>
<td>HR (95%CI)</td>
<td>HR (95%CI)</td>
<td></td>
</tr>
<tr>
<td>DLE onset</td>
<td>0.38 (0.20–0.71)**</td>
<td>0.39 (0.21–0.74)**</td>
<td>0.38 (0.20–0.73)**</td>
<td>0.39 (0.20–0.74)**</td>
<td>0.38 (0.20–0.71)**</td>
<td>89.3</td>
</tr>
<tr>
<td>Sociodemographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis (per 5-year †)</td>
<td>0.98 (0.97–0.99)**</td>
<td>0.90 (0.85–0.97)**</td>
<td>0.98 (0.97–0.99)**</td>
<td></td>
<td></td>
<td>89.6</td>
</tr>
<tr>
<td>Delay to diagnosis (per 6-month †)</td>
<td>1.00 (0.99–1.00)</td>
<td>0.99 (0.97–1.02)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education (per 3-year †)</td>
<td>0.98 (0.94–1.02)</td>
<td>0.94 (0.83–1.06)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender, female</td>
<td>0.78 (0.49–1.26)</td>
<td>0.84 (0.52–1.35)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity, non-white</td>
<td>1.48 (1.10–1.98)***</td>
<td>1.47 (1.09–1.97)</td>
<td>1.52 (1.14–2.02)***</td>
<td></td>
<td></td>
<td>73.5</td>
</tr>
<tr>
<td>Low socioeconomic status</td>
<td>1.24 (0.88–1.74)</td>
<td>1.19 (0.85–1.68)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uninsured or underinsured</td>
<td>0.93 (0.70–1.24)</td>
<td>0.94 (0.70–1.25)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical assessment at diagnosis</td>
<td></td>
<td>1.01 (0.98–1.03)</td>
<td>1.00 (0.98–1.03)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLEDAI (per 1-unit †)</td>
<td></td>
<td>1.23 (1.08–1.41)***</td>
<td>1.24 (1.07–1.44)****</td>
<td>1.27 (1.12–1.45)*</td>
<td></td>
<td>81.0</td>
</tr>
<tr>
<td>SDI (per 1-unit †)</td>
<td></td>
<td>1.13 (0.73–1.77)</td>
<td>1.10 (0.69–1.76)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment prior to diagnosis</td>
<td></td>
<td>0.51 (0.13–2.06)</td>
<td>0.52 (0.13–2.11)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antimalarial</td>
<td>1.53 (0.85–2.74)</td>
<td>1.28 (0.69–2.36)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SLE: systemic lupus erythematosus; DLE: discoid lupus erythematosus; SDI: Systemic Lupus Collaborating Clinics/American College of Rheumatology Damage Index; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; HR: hazard ratio; CI: confidence interval; antimalarial: chloroquine and/or hydroxychloroquine; immunosuppressant: azathioprine and/or cyclophosphamide.

*aPrednisone or equivalent glucocorticoid dose.

**P < 0.001; ***P < 0.005; ****P < 0.01; *****P < 0.05.
associated with a lower risk of further LN. We found that the accrued proportion of LN was at least double in patients without DLE onset compared to those with DLE onset. Our data also pinpoint that while among non-white patients the proportion of LN at both 1 and 5 years was approximately 4-fold lower in those with DLE onset compared to those without DLE, non-significant differences were present in the white group. However, the multivariate analysis supported the fact that SLE patients with DLE onset had a significantly lower risk (HR 0.38) of LN, independently of the effect of ethnicity and other well-recognized risk factors for renal disease in SLE, such as age, disease severity and socioeconomic status. 18,27–30

LN is one of the SLE manifestations most strongly associated with patient morbidity and mortality. 31,32 LN and its clinical complications also impose an enormous burden on the healthcare system and society. 33–35 Therefore, the identification of early clinical markers associated with a lower risk of renal disease in SLE has prominent prognostic significance to patients and the public health. Our findings can also be valuable to clinicians, who may consider closer screening of renal involvement in SLE patients without DLE.

Although reports derived from small selected samples suggested that DLE is negatively associated with severe systemic manifestations in general, and with LN in particular, 11,36 findings from three recent large studies showed contradictory results. 12–14 Santiago-Casas et al. 12 studied the relationships of DLE with a wide range of clinical manifestations and organ damage in the PROFILE multiethnic cohort. While a negative association between DLE and end-stage renal disease was uncovered in the study, the authors were unable to confirm the potential protective effect of DLE against LN. Merola et al. 13 did not find any relationships between renal disease and DLE when they compared ACR criteria between 117 SLE patients with DLE and 926 SLE patients without DLE. Drucker et al. 14 recently reported that the prevalence of active renal disease at 1 and 5 years was significantly lower in SLE patients with early onset DLE (29.2% and 39.0%, respectively) compared to those who did not have CLE over follow-up (44.4% and 58.2%, respectively). Although those studies have contributed to overcome former biases related to the low representativeness of ethnic minorities and small sample sizes, their results are conflicting and are predominantly derived from cross-sectional analyses. Therefore, the prognosis value of DLE on renal disease in patients with SLE has remained unclear.

Using a longitudinal design, our study underscored the significance of DLE occurring early in the disease course, as a prognostic marker for a lower incidence of LN. It was suggested that when DLE is associated with SLE, the discoid rash frequently precedes the occurrence of systemic manifestations. 37–39 Therefore, we thought that by examining DLE onset as the main predictor of LN, as opposed to DLE after SLE diagnosis, we would be able to provide more insightful information to clinicians and lupus patients. Moreover, the identification of DLE onset as a protective marker of renal disease in SLE points to potential differential immune mechanisms that might occur early in the disease course. 40 For instance, recent studies have identified candidate genes and genomic regions that may contribute to the pathogeneses of CLE and DLE via dysregulated antigen presentation (HLA-DQA1), apoptosis regulation, RNA processing, and interferon response (MICA, MICB, MSH5, TRIM39 and RPP21). 41 It has also been suggested that differential expression of genes associated with apoptosis and type 1 IFN signaling may explain underlying mechanisms of skin and systemic lupus. 42 Moreover, environmental factors such as sun exposure or smoking have been found to modify the transcription of genes associated with the production of autoantibodies implicated in the pathogenesis of DLE and renal disease in SLE, such as anti-Ro/La and anti-DNA. 43 Interestingly, although our study was not specifically designed to examine racial differences in the association between DLE onset and LN, our findings suggest that ethnicity may modify such an association. In particular, while among non-white subjects the proportion of LN was significantly lower in those with DLE onset compared to those without DLE, the negative association between DLE onset and LN was not significant in white subjects. Those findings point to potential ethnic disparities in immune pathways.

### Table 4  Sensitivity analysis of patients with complete data on SLEDAI

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HR (95% CI)</th>
<th>P value</th>
<th>Reliability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLE onset</td>
<td>0.45 (0.23–0.88)</td>
<td>0.020</td>
<td>65.1</td>
</tr>
<tr>
<td>Age at diagnosis (per 5-year †)</td>
<td>0.98 (0.96–0.99)</td>
<td>0.0040</td>
<td>81.7</td>
</tr>
<tr>
<td>SDI at diagnosis (per 1-unit †)</td>
<td>1.22 (1.05–1.42)</td>
<td>0.0082</td>
<td>50.9</td>
</tr>
</tbody>
</table>

SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; DLE: discoid lupus erythematosus; SDI: Systemic Lupus Collaborating Clinics/American College of Rheumatology Damage Index; HR: hazard ratio; CI: confidence interval.
that might be implicated in the progression to LN in people with SLE who have discoid rash as the onset manifestation. Whether DLE onset would prompt closer monitoring and management of LN in non-white patients with SLE also warrants further research. Thus, hypothesis-driven studies derived from our findings can potentially contribute to tease out gene–socio-environmental pathways that lead to the immune dysfunction implicated in the progression from DLE to SLE and LN.

Our study has some limitations. First, although the GLADEL protocol recommends obtaining expert opinion by a dermatologist for the diagnosis and management of SLE patients with cutaneous conditions, the referral to a dermatologist is on the judgment of the GLADEL investigator. Thus, our DLE definition included either a dermatologist-confirmed diagnosis, or a discoid rash documented by an experienced study physician during physical examination, according to the ACR classification criteria. Consequently, we cannot exclude underascertainment of SLE patients with non-classic DLE who may not have been referred to the dermatologist. Misclassification of patients with photosensitive lesions, particularly among individuals of color, cannot be excluded. However, because the study physician examined all GLADEL participants on at least two different occasions, patients with temporary photosensitive rashes are less likely to be misclassified. Moreover, the location and severity of discoid lesions were not documented; consequently the potential effect of skin activity and extension of dermatological lesions on the outcome could not be teased out. Second, histopathological examination of the LN class was not obtained in all SLE patients with clinical LN. Because renal biopsies are performed among GLADEL patients according to the treating physician’s decision, and the accessibility for the procedure, it is possible that SLE patients without renal biopsy may have had less severe renal involvement, or may have faced barriers to adequate healthcare access. Likewise, autoantibodies were not examined before the SLE diagnosis, which limited our ability to investigate potential biomarkers that would have been insightful to understand early pathogenic mechanisms associated with the progression of SLE to LN. Thus, we were unable to examine the prospective significance of autoantibodies, such as anti-Ro and anti-La, which have been reported to cluster with DLE and mild systemic manifestations in patients with SLE. Because the dates when therapeutic drugs were prescribed over the course of the disease were not collected, we could not examine the potential modifying effect of treatment after SLE diagnosis on the incidence of LN. However, we were able to examine the main SLE medications prescribed prior to a definite diagnosis of SLE, and none of the main drugs indicated for lupus were associated with LN in the multivariate models. Finally, nearly 20% of cases had missing data on SLEDAI at diagnosis. However, we performed multiple imputations to build the predictive model, which was consistent with findings from complete case analyses, reassuring us that disease activity did not have a significant effect on further LN.

This study has several strengths. First, we studied an inception cohort of patients with SLE, who have been longitudinally followed up regarding the occurrence of clinical manifestations. Since the early descriptions in the 1970s suggesting a negative association between DLE and LN, several investigators have attempted to determine the prognostic significance of DLE in patients with SLE. However, previous studies have several limitations, such as selected or small sample size and retrospective or cross-sectional design. To our knowledge, this is the first longitudinal study on this matter that has used survival analysis to establish the association between DLE onset and LN over time. Both the main predictor and outcome have been well documented by trained physician-investigators, and causality can be established more rigorously. Second, the large sample size and high proportion of Mestizos and African–Latin American patients with increased genetic susceptibility to renal disease makes the GLADEL cohort an ideal population to identify clinical prognosis markers for LN. To our knowledge, this is the first large-scale study on the prognostic significance of DLE among Latin American patients with SLE. Moreover, the representation of patients from the full socioeconomic spectrum along with data on treatment, disease activity and organ damage at SLE diagnosis allowed us to describe the independent effect of DLE onset on the outcome, after controlling for factors that have been consistently associated with renal disease. Thus, these findings can be potentially generalized to a broad spectrum of Latin American patients with SLE.

In summary, early DLE was found to be protective against further LN in a large and ethnically diverse Latin American population of individuals with SLE. Patients with DLE at onset were approximately 62% less likely to develop LN, compared to those without DLE onset.

LN is a severe manifestation associated with mortality and disability; consequently, our findings
have relevant prognostic implications for SLE patients in general, and those with DLE in particular. Our study also emphasizes the importance of early renal screening in high-risk SLE subpopulations, such as those patients without DLE. Moreover, our data point to the need for investigations to unravel genetic, immune and environmental factors implicated in the pathways associated with the protective role of onset DLE on LN in patients with SLE.

Acknowledgments

The authors are grateful to Daniel Villalba and Leonardo Grasso for providing expert assistance with the ARTHROS (version 6.0) software.

Author contributions

All authors were involved in drafting or revising this article critically for important intellectual content, and all authors approved the final version to be published. Drs Cristina Drenkard and Bernardo A Pons-Estel have full access to the data-set used for the study and take responsibility for data integrity and accuracy of the analyses performed.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by grants from the Federico Wilhelm Agirica Foundation Research (to BAPE); STELLAR (Supporting Training Efforts in Lupus for Latin-American Rheumatologists) Program funded by Rheuminations, Inc. and Institut d’Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS)–Beca de Formació i Contractació de Personal Investigador (to GJPE).

CD and GB are supported in part by the NIH (R01AR065493) and the CDC (U01-DP14-004).

References

Early DLE protects against renal disease in patients with SLE

GJ Pons-Estel et al.


Appendix 1

**Members of the GLADEL study group**

In addition to the authors, the following individuals are members of the GLADEL Study Group and have incorporated at least 20 patients into the database:

- From Argentina, Luis J Catoggio, María Flavia Ceballos Recalde and Edson Velozo (Sección de Reumatología, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina; Fundación Dr Pedro M Catoggio para el Progreso de la Reumatología, Buenos Aires); Jorge A Manni, Sebastián Gramaudo and Judith Sarano (Instituto de Investigaciones Médicas ‘Alfredo Lanari’, Buenos Aires); José A Maldonado-Cocco, Maria S Arriola and Graciela Gómez (Instituto de Rehabilitación Psicofísica, Buenos Aires); Mercedes A García, Ana Inés Marcos and Juan Carlos Marcos (Hospital Interzonal General de Agudos ‘General San Martín’, La Plata); Hugo R Scherbarth, Jorge A López and Estela L Motta (Hospital Interzonal General de Agudos ‘Dr Oscar Alend’, Mar del Plata); Susana Gamron, Laura Onetti and Sandra Bulubisich (Hospital Nacional de Clínicas, Córdoba); Silvana Gentiletti, Norberto Quagliatto, Alberto A Gentiletti and Daniel Machado (Hospital Provincial de Rosario, Rosario); Marcelo Abdala and Simón Palatnik (Universidad Nacional de Rosario, Hospital Provincial del Centenario, Rosario); Guillermo A Berbotto and Carlos A Battagliotti (Hospital Escuela ‘Eva Perón’, Granadero Baigorria).

- From Brazil, Eloisa Bonfa and Eduardo F Borba (Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo; Alexandre Wagner S Souza (Universidade Federal...
de São Paulo); Manoel Barros Bertolo and Ibsen Bellini Coimbra (Faculdade de Ciências Médicas, Universidade Estadual de Campinas); João C Tavares Brenol, Ricardo Xavier and Tamara Mucenic (Hospital das Clínicas do Porto Alegre, Universidade Federal do Rio Grande do Sul); Fernando de Souza Cavalcanti, Angela Luzia Branco Duarte and Claudia Diniz Lopes Marques (Centro de Ciências da Saúde, Universidade Federal de Pernambuco); Nilzio Antonio da Silva, Ana Carolina de O e Silva and Tatiana Ferracin Pacheco (Faculdade de Medicina, Universidade Federal de Goiás, Goiânia); from Colombia, Jose Fernando Molina-Restrepo (Hospital Pablo Tobon, Uribe), Javier Molina-López, Gloria Vásquez, Luis A Ramirez and Oscar Uribe (Universidad de Antioquia, Hospital Universitario ‘San Vicente de Paul’, Medellín); Antonio Iglesiass-Rodriguez (Universidad del Bosque, Bogotá), Eduardo Egea-Bermejo (Universidad del Norte, Barranquilla); Renato A Guzmán-Moreno and José F Restrepo-Suárez (Clínica Saludcoop 104 Jorge Piñeros Corpas and Hospital San Juan de Dios, Universidad Nacional de Colombia, Bogotá).

From Cuba, Marlene Guibert Toledano and Alfredo Hernández-Martínez (Centro de Investigaciones Médico Quirúrgicas, Havana).

From Chile, Loreto Massardo and Sergio Jacobelli (Escuela de Medicina, Pontificia Universidad Católica de Chile, Santiago); Leonardo R Guzmán (Hospital del Salvador, Facultad de Medicina, Universidad de Chile, Santiago).

From Guatemala, Abraham García-Kutzbach, Claudia Castellanos and Erwin Cajas (Hospital Universitario Esperanza, Ciudad de Guatemala).

From Mexico, Donato Alarcón-Segovia and Virginia Pascual-Ramos (Instituto Nacional de Ciencias Médicas y Nutrición ‘Salvador Zubirán’, Mexico Distrito Federal); Leonor A Barile-Fabris (Hospital de Especialidades Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social, Mexico Distrito Federal, Mexico); Mary-Carmen Amigo and Luis H Silveira (Instituto Nacional de Cardiología ‘Ignacio Chávez’, Mexico Distrito Federal); Ignacio García De La Torre, Gerardo Orozco-Barocio and Magali L Estrada-Contreras (Hospital General de Occidente de la Secretaría de Salud, Guadalajara, Jalisco); María Josefina Sauza del Pozo, Laura E Aranda Baca and Adelfia Urenda Quezada (Instituto Mexicano de Seguro Social, Hospital de Especialidades No. 25, Monterrey, Nuevo León); Guillermo F Huerta-Yáñez (Hospital de Especialidades Miguel Hidalgo, Aguascalientes).

From Peru, José Luis Alfaro-Lozano and Jorge M Cucho-Venegas (Hospital Nacional ‘Guillermo Almenara Irigoyen’, Essalud, Lima); María Inés Segami, Cecilia P Chung and Magaly Alvar Linares (Hospital Nacional ‘Edgardo Rebagliatti Martins’, Essalud, Lima).

From Venezuela, Isaac Abadi Neriza Rangel and Soham Al Snih Al Snih (Hospital Universitario de Caracas); Maria H Esteva-Spinetti and Jorge Vivas (Hospital Central de San Cristóbal).