Health Disparities in Systemic Lupus Erythematosus

Christine A. Peschken, MD, MSc, FRCPC

KEYWORDS

• Systemic lupus erythematosus • Health disparities • Social determinants of health

KEY POINTS

- In systemic lupus erythematosus (SLE), increased incidence and prevalence, more severe disease, and worse outcomes are well described in nonwhite ethnicities.
- Low adherence to lupus medications is common and relates to mistrust, cultural attitudes to health and disease, and poor patient-provider communication.
- Poverty significantly affects damage accrual and mortality for patients with SLE; recent evidence suggests the mechanism may be though chronic socioeconomic stressors.
- Health care access is adversely influenced by racism and geography, and contributes to poor adherence and increased damage and mortality. Ethnic minorities and the poor may be at higher risk for hazardous environmental exposures contributing to the burden of SLE in these populations.
- Epigenetic changes may provide the link between social adversity and poor lupus outcomes, and may provide a pathway to a better understanding of SLE pathogenesis and personalized treatment approaches.

INTRODUCTION

Health disparities have been defined as differences in the incidence, prevalence, outcomes, and burden of diseases and other adverse health conditions that exist among different population groups, and, most importantly, these differences are considered unnecessary and avoidable.[1] The study of health disparities has been recognized as a priority by multiple countries, groups, and government bodies.[2,3] Systemic lupus erythematosus (SLE) in many ways can be seen to epitomize health disparities. SLE is more prevalent among women and in ethnic minority and Indigenous populations. Outcomes are also worse in these groups, as well as in people of lower socioeconomic status. The many factors that influence outcomes in SLE are complex, overlapping, and closely associated with each other. Ethnic differences in incidence, prevalence,

Rady Faculty of Health Sciences, University of Manitoba, RR149 Arthritis Centre, 800 Sherbrook Street, Winnipeg, Manitoba R3A1M4, Canada
E-mail address: christine.peschken@umanitoba.ca

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and outcomes are the most prominent and best-described disparity in SLE; herein is a brief review of disparities closely associated with ethnicity. Particular emphasis is placed on Indigenous North Americans with SLE because there is a paucity of data for this group.

INCIDENCE, PREVALENCE, AND MORTALITY

Differences in incidence and prevalence rates between ethnic groups have been clearly documented over many years.[4] The US Centers for Disease Control and Prevention (CDC) has funded surveillance programs as part of a national public health agenda for lupus to prioritize a coordinated and multifaceted public health approach to lupus[5] and have recently shown that the prevalence of SLE in the United States was highest among American Indian/Alaskan native (Indigenous North American) women (271; 95% confidence interval [CI], 238, 307) and black women (230.9; 95% CI, 178.2, 299.2), followed by Hispanic women (120.7; 95% CI, 84.0, 173.4) compared with white women and Asian Pacific Islander women, both of whom had a prevalence about 84 per 100,000.[6] This work echoes multiple previous publications documenting the higher incidence and prevalence rates in essentially all nonwhite ethnic/racial groups.[7]

Patients with SLE have long been known to have excess mortality, with rates of 2 to 5 times that of the general population, confirmed in a recent meta-analysis including more than 26,000 patients with SLE.[8] Jorge and colleagues[9] showed that this mortality gap has not improved in recent decades. Ethnic disparities in mortality from lupus are stark. Yen and colleagues,[10] using the CDC's national vital statistics system mortality database, showed that SLE was among the leading causes of death in young women. Overall, SLE was in the top 20 leading causes of death for all women and ranked 10th in women aged 15 to 24 years. However, SLE was the fifth leading cause among black and Hispanic women aged 15 to 24 years after excluding injury as a cause of death from the analysis. In another study of more than 40,000 patients with prevalent SLE, Indigenous North American and black patients had the highest mortalities, with lower risks among Hispanic and Asian patients with SLE, after accounting for demographic and clinical factors.[11] Similarly, in a Canadian study, Indigenous North Americans had a 2-fold hazard ratio for mortality compared with white SLE patients, after adjustment for income, education, and rural residence.[12] Also striking in this study was the young age at death of Indigenous patients compared with white patients from the same center. Mean age at death was 50 years in Indigenous patients, compared with 64 years for white patients, translating into potential years of life lost for Indigenous patients of 6.5 per 1000 compared with 2.6 per 1000 in white patients.

RENAL OUTCOMES

Lupus nephritis remains one of the most serious complications of SLE; disparities in renal outcomes mirror disparities in incidence, prevalence, and mortality. The LUMINA (Lupus in Minorities, Nature vs Nurture) study showed higher frequency of lupus nephritis in US African American and Hispanic patients[13] compared with white patients. In a larger Medicaid study of more than 34,000 patients with SLE, all nonwhite patients, including African American, Asian, Hispanic, and Indigenous North American, had a higher prevalence of lupus nephritis.[14] Similarly, in the United Kingdom, Chinese, Afro-Caribbean and Indo-Asian patients with SLE had more frequent nephritis,[15] and, in Canadian cohorts, Asian, black, and Indigenous Canadian patients with SLE had more frequent nephritis.[12,16,17] In addition to more frequent development of nephritis, nonwhite patients develop nephritis earlier in their disease course

compared with white patients.[13,18] Progression to end-stage renal disease (ESRD) also differs between ethnicities: higher rates of progression to ESRD caused by SLE were described in African American, Asian, and Indigenous North American patients, with no changes in outcomes over the last decade.[19] Higher rates of renal damage/ESRD in nonwhite patients were also reported in Canadian and European cohorts.[17,20,21] In our single-center cohort, both Asian and Indigenous North American patients with SLE had a higher likelihood of developing nephritis, and a 5-fold risk of ESRD compared with white patients (**Fig. 1**). After adjustment for income, education, age, damage, and additional disease manifestations, the hazard ratio for ESRD was more than 6-fold for Asian and Indigenous patients with lupus nephritis compared with white patients with lupus nephritis.

Ward[22] showed that ESRD caused by lupus nephritis was increased in areas with higher rates of hospitalizations for ambulatory care–sensitive conditions, and also in areas with Medicaid insurance for a higher proportion of hospitalizations, suggesting insufficient coverage to access appropriate and/or quality care. Nonwhite ethnicity and lack of private insurance were associated with suboptimal quality of care for ESRD care in another large US study.[23]

Mortality in patients with lupus nephritis is more complex. Among more than 8000 Medicaid patients with lupus nephritis, Indigenous North American and black patients had higher mortality compared with white patients, whereas Asian and Hispanic patients with lupus nephritis had a lower mortality after adjustment for comorbidities and sociodemographic factors.[11] Although lupus nephritis as well as progression to ESRD was more frequent in Asian compared with Indigenous and white patients (see **Fig. 1**), preliminary Canadian data showed higher mortality in Indigenous North American patients with lupus nephritis and ESRD compared with Asian and white patients.[21] US Asian and Hispanic patients with ESRD caused by lupus nephritis also had lower mortality compared with white and African American patients.[24] Higher mortality in African Americans with ESRD caused by lupus has been found in several studies.[25,26] Overall improvement in mortality for patients with SLE with ESRD was recently shown, but the gap between white people and African Americans remained.[27]

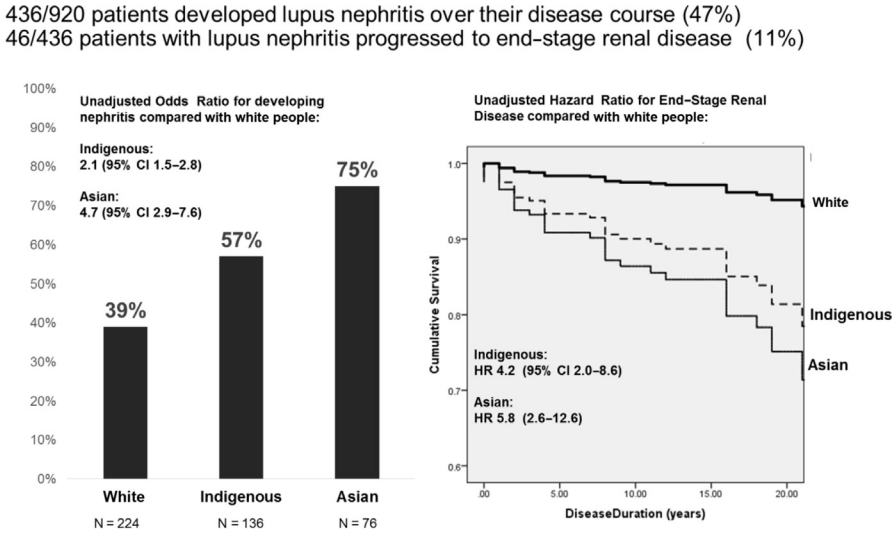

Fig. 1. Lupus nephritis in a single-center cohort. HR, hazard ratio.

ADHERENCE

Medication adherence is recognized as an important issue worldwide in the management of chronic disease,[28] including lupus.[29] Poor adherence to prescribed medications is associated with poor overall outcomes, disease progression, and an estimated burden of billions of dollars per year in avoidable direct health care costs.[28,30] Although low adherence is widespread, the frequently asymptomatic nature of lupus flares may contribute to low adherence,[31] particularly in lupus nephritis.[32,33] Almost 30 years ago, Petri and colleagues[34] reported that poor outcomes in black patients with SLE were related to low adherence rather than race or socioeconomic status. Since then, multiple studies have documented lower adherence in nonwhite patients.[11,31,35–39] This lower adherence includes adherence to hydroxychloroquine, recognized as important background therapy in SLE, which is reportedly lower in ethnic minorities,[40] and adherence to common immunosuppressive medications for SLE.[41]

Note that adherence to treatment implies that agreement to a care plan has initially been established between the patient and the health care provider. There is ample evidence that this initial agreement is often lacking, particularly in ethnic minorities, thus it perhaps should not be surprising that these groups have low overall rates of adherence. Adherence depends heavily on trust in the provider and the health care system, and on the patient-physician relationship and communication.[28,31] There is often a high degree of mistrust among ethnic minorities toward health care providers, based on a combination of past history of mistreatment and current perceived discrimination.[31,42] Experiences of discrimination in health care are pervasive among ethnic minorities and are associated with poor health care behaviors, including low adherence.[43] Cultural differences may also affect adherence; ethnic minorities may view health, illness, and medication through a different cultural lens.[28,31,44–46] These differences must be acknowledged and incorporated into health education and doctor-patient communication to improve adherence.

POVERTY

The association between poverty and poor disease outcomes has been well established in lupus[47–49]; income levels and ethnicity frequently cluster together. In the LUMINA cohort, investigators showed that poverty, not ethnicity, predicted increased mortality in SLE, with the effect of ethnicity only becoming evident in multivariate models with poverty removed.[50] Cooper and colleagues[51] found ethnicity and low income to be independently associated with poor outcomes in terms of increased damage. More recently, several studies have shown that neighborhood poverty (residing in an area with high poverty rates) contributes to damage and mortality independently of individual income level, although living in an area with a high proportion of people living in poverty accentuated the effect of individual low income on damage accrual.[52] Yelin and colleagues,[47] in the Lupus Outcomes Study, showed that the impact of poverty on mortality was through increased damage accrual. Importantly, there was a rapid normalization of damage accrual among patients with SLE who exited poverty.[52] Higher levels of perceived stress have been shown to be a likely mechanism for the effect of poverty on damage accrual. In a qualitative analysis, chronic socioeconomic stressors such as food insecurity, housing inability, and medical care insecurity, combined with exposure to crime, significantly affected patients with SLE. These stressors were described as requiring all of the patients' focus and attention, leaving SLE symptoms neglected until unavoidable.[53] There is increasing evidence of the impact of poverty on such decision making. Some researchers refer to bandwidth: the brain's

ability to perform basic functions required for decision making. When taxed by such stressors as those discussed earlier, less bandwidth is available, leading to potentially undesirable health-related choices and behaviors.[54]

HEALTH CARE ACCESS

Access to health care is strongly linked to outcome of SLE, with clear demonstrations of increased damage accrual and increased mortality in low-income patients with lupus with less access. However, access to care goes beyond the merely financial and includes disparities in patient-physician communication[55] and concerns about racism and cultural safety within health care.[56–58]Experiences of racism and poor communication are deterrents to seeking health care, even when available. This tendency has been clearly shown for both Canadian and American Indigenous patients, who frequently characterize health care interactions as negative, with associated reluctance to seek care.[58–60]

Access to health care is also influenced by geography. In a nationwide US survey, rural residents and African Americans had a greater travel burden when seeking medical care.[61] In a South Carolina study, increased travel burden translated into more missed appointments and missed medications.[62] Mean travel time to lupus-associated medical care was approximately 57 minutes (ranging from 4 to 150 minutes), and the average distance to rheumatologists was approximately 85 km (53 miles). In Canada, Indigenous patients frequently live in remote communities. Indigenous people experience specific challenges accessing health care across all geographic regions, but challenges are greatest in rural and remote communities.[63] In our region, more than half of Indigenous patients lived greater than 160 km (100 miles) away, with 30% living more than 500 km (300 miles) from rheumatology care, frequently without road access. We showed that distance from rheumatology care had a significant impact on mortality (**Fig. 2**). Low income and educational attainment both increased mortality, independently of ethnicity (see **Fig. 2**). Indigenous patients were overrepresented in the low-income, low-education, and remote-from-care groups, showing the overlapping nature of these factors. In a Cox proportional hazards model, after adjusting for gender, onset age, disease duration and severity, and damage, as well as income and education, Indigenous ethnicity remained an independent risk for mortality (hazard ratio, 1.8; 95% CI, 1.1–3.0).[12]

ENVIRONMENTAL EXPOSURES

Environmental exposures are increasingly recognized as contributing to both the onset and subsequent disease course of SLE. There is robust evidence that cigarette smoking is associated with both the onset of SLE and a more severe disease course.[64] Here too, disparities may play a role: tobacco use, although reduced overall, has shifted from a mainstream behavior to a behavior that is mainly is concentrated among marginalized populations.[65] Maynard and colleagues[66] found that, in both white people and African Americans with SLE, individuals in the lowest income category had the highest frequency of current or past smoking; similarly, the lowest education category was also associated with the highest frequency of smoking. Secondhand smoke exposure in nonsmokers has also been shown to be higher in nonwhite people and in the poor.[67] Silica exposure has also been clearly shown to contribute to the development of SLE, and there is emerging evidence that exposure to air pollution, solvents, heavy metals, and pesticides may contribute to lupus development and disease activity.[68–71] These exposures vary by occupation and neighborhood residence. Thus, ethnic minorities and the poor are more likely to be exposed to

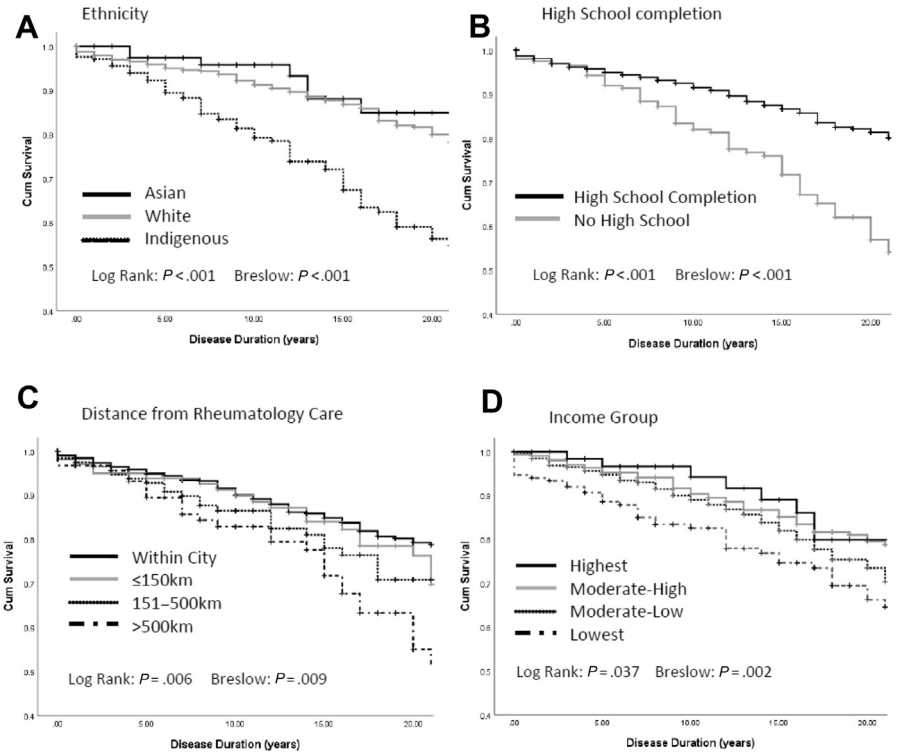

Fig. 2. Kaplan-Meier survival curves factors influencing mortality in Systemic lupus erythematosus patients from a single-center cohort. (*A*) Ethnicity. (*B*) High School Completion. (*C*) Distance from rheumatology care. (*D*) Household income.

hazardous substances in their neighborhoods and harmful working environments through low-wage jobs, further contributing to poor health outcomes.[72]

EPIGENETIC CHANGES

SLE is known to be caused by interactions between susceptibility genes and environmental factors. Distinct differences in disease-susceptibility genetic variants between ethnic groups have been described,[73,74] but, overall, genetic studies have failed to adequately explain the variable susceptibility, disease course, and outcomes of SLE across diverse populations.[75,76] Epigenetic mechanisms may provide that link.[77] In a study to address the clinical heterogeneity of SLE, Lanata and colleagues[78] identified clustering of severe disease phenotypes with nonwhite ethnicity, and also methylation differences between the clinical clusters, possibly reflecting environmental exposures that affect races differentially. Although studies linking specific adverse experiences or behaviors to epigenetic changes in SLE are lacking, mounting evidence across many diseases suggests that epigenetic mechanisms may provide a causal link between social adversity and health disparity.[79] Further epigenetic research promises to shed light on the molecular pathways through which such exposures are translated into quantifiable increased risk of SLE and poor SLE outcomes.[80]

SUMMARY

As clinicians look with optimism and hope toward recently approved and “pipeline” drugs, they should keep in mind the ample evidence showing that improving the

environments in which patients live, work, and receive care, from health care systems and neighborhoods, to environmental exposures, to experiences of discrimination, would have a far greater impact on SLE outcomes than new medications. Without attention to these modifiable disparities, outcomes for vulnerable patients with SLE will continue to lag.

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