ABOUT THE AUTHOR

Rachel Asiniwasis, MD, MS(HS), FRCPC

Dr. Rachel Asiniwasis is a dermatologist and early-career clinician-researcher with a special interest in inflammatory dermatoses, remote outreach, virtual care, skin of color, Indigenous health, dermatologic health disparities, and translational research. She has been practicing in her hometown of Regina since 2014, after graduating residency at the University of Toronto. Recently, she graduated with a Master's of Science in Health Sciences in clinical and translational research. She is Plains Cree and Saulteaux on her father's side, and provides outreach dermatology clinics in the form of virtual care, teledermatology and in-person to various remote and northern Indigenous communities around Saskatchewan.

Affiliations: Founder, Origins Dermatology Centre
Associate Professor, University of Saskatchewan Division of Dermatology

AUTOIMMUNE RHEUMATIC DISEASE WITH CUTANEOUS MANIFESTATIONS IN NORTH AMERICAN INDIGENOUS POPULATIONS: A REVIEW OF REGIONAL PREVALENCE DATA AND DISEASE CHARACTERISTICS

Abbreviations: SLE: Systemic Lupus Erythematosus, **SSc**: Systemic Sclerosis, **NAI**: North American Indigenous, **MCTD**: Mixed Connective Tissue Disease, **ACR**: American College of Rheumatology, **IHS**: Indian Health Services (US).

Introduction

Patients with cutaneous findings of systemic autoimmune rheumatological disease often require a multidisciplinary approach to diagnosis and management. In general, the first signs of systemic rheumatological diseases may be skin manifestations, which prompt those affected to visit the dermatology clinic. The basis and presentations of conditions such as systemic lupus erythematosus (SLE) and systemic sclerosis (SSc) are complex, and involve genetic and environmental influences that are embedded in broad and overlapping factors of the socioecological model. This review recognizes that North American Indigenous (NAI) peoples are diverse, by region, language, culture, home environment, and more; therefore, generalizations are not intended. Furthermore, interpretations of the literature are limited by factors such as region and location (e.g., remote-rural vs. urban), sample size, study design, and statistical interpretations. Additionally, knowledge of biological and genetic predispositions of autoimmune diseases in the NAI population is lacking and beyond the scope of this article. The use of racial and ethnic terminologies can vary greatly and is often based in social concepts. These terms are also used in the context of current categorizations employed by the US Census or as categories that

are often used in clinical trials. Thus, further use of the term "North American Indigenous" (NAI) in this article takes this into account. It is worth noting that commonalities surrounding historical contexts and barriers to care are found for many NAI individuals and communities, for example for those living rurally and remotely. The purpose of this review is to provide a broad overview of what is known about mostly regional prevalence data and disease characteristics of autoimmune diseases such as SLE and SSc in the NAI population. Unique considerations surrounding barriers to care reported to be faced by some NAI populations will also be explored.

Discussion

Many observational regional studies across Canada and the United States (US) have demonstrated generally higher prevalence rates of SLE[1-8] and SSc[4,9] in NAI population samples. These studies are summarized in **Table 1**. Higher risks of other autoimmune diseases in NAI populations have been reported. For instance, a cross-sectional study from multiple regions of the US has demonstrated that Native Americans have a higher risk of Sjogren's syndrome and may present with less typical features, higher levels of disease activities, and extraglandular findings (**Table 1**).[10] In the US southwest, Behçet's disease may be more prevalent in the NAI population who may commonly present with a variety of skin manifestations (**Table 1**).[11] Mixed-connective tissue disease may also have a higher prevalence in NAI than in other populations.[12]

A considerable amount of data was found on the clinical manifestations of SLE in the NAI population. Notably, clinical manifestations of SLE may vary among individuals. Common clinical manifestations for example can include positive antinuclear antibody (ANA) positivity, arthritis, malar rash, and photosensitivity.[1,6,13]

Disease activity, manifestations, or outcomes of SLE or SSc may be worse or may not present in the typical manner, such as those described in the box below:

- A population-based study from southern Manitoba has demonstrated an association of NAI with higher severity index scores and younger age at diagnosis, more frequent vasculitis and renal complications, along with being more likely to receive immunosuppressive drugs or prednisone, and having increased mortality.[1]
- A Canadian cross-sectional study has found that NAI ethnicity is an independent risk factor for Raynaud's severity and gastrointestinal symptoms in those with SSc.[14]
- A population-based Indian Health Services (IHS) registry study that included the Oklahoma, Phoenix, and Alaska areas has shown that the three most common American College of Rheumatology (ACR) criteria met by Native Americans with SLE includes ANA positivity, hematologic disorder, and arthritis, with discoid rashes and neurologic disorders being the least common criteria met.[6]

With regards to potential genetic or hereditary predispositions, little is known. However, a genetic or family history risk for SLE may be present in some Indigenous populations.[3,6] For example, one of the highest prevalence rates of SLE worldwide has been identified in the Nuu-Chah-Nulth, an Indigenous group located in the Canadian Pacific Northwest.[2] SLE incidence rates may be higher in those of Crow, Arapahoe, and Sioux background, all of whom share regional commonalities and reside in the northern half of the US.[15] The highest worldwide prevalence rate of SSc has been identified in the Choctaw, and those with SSc who received care at the Oklahoma IHS had a higher prevalence of SSc compared with other Native American or white populations in the region. Among those with SSc, the disease phenotype was homogenous, and included diffuse scleroderma, pulmonary fibrosis, autoantibodies to topoisomerase-I, and associations with certain human leukocyte antigen (HLA) haplotypes.[9] Antifibrillin antibodies,[16] fibrillin-1,[17] and fibroblast gene[18] expression polymorphisms have been identified in those with native North American ancestry and have been associated with SSc in the Choctaw. These disease expressions may influence the disease course or be associated with increased susceptibility for

SSc,[18] or poorer survival.[16] In the context of Behçet's disease, mutations in the HLA-B51 gene family may be common in some regional Indigenous groups such as the Navajo and Pueblo.[11] Such studies raise questions as to whether there are genetic linkages unique to certain Indigenous groups with regards to prevalence findings and disease phenotypes.

Access to care remains a challenge for many individuals who reside rurally and remotely. Many studies include a rural population. Notably, rural populations, including some IHS catchment areas, face an uneven distribution of, and limited access to, specialists such as rheumatologists.[19] Barriers to care found in these studies include availability of healthcare (e.g., services provided at an urban-based tertiary care hospital such as direct-access to a rheumatologist, nephrologist, or in-house dialysis), and transportation barriers in which long-distance travel is required from remote communities.[3,6,18] Findings from these studies indicate that disparities reflected in disease outcomes are likely related to similarly identified barriers. For example, a review of 320 patients with SLE who received care within three IHS regions demonstrated that almost one-quarter of these patients were diagnosed by a primary care provider compared to urban-based specialists. However, specialist diagnosis of SLE was associated with better outcomes including a higher probability of an earlier diagnosis, receiving appropriate laboratory tests, having their SLE criteria classification documented, being tested for biomarkers of disease, and ever being treated with hydroxychloroquine.[19]

Most US data included in this review is gathered from IHS databases. It is important to keep in mind that the IHS represents a federally-operated rural healthcare delivery system that operates under the Department of Health and Human Services for status American Indian and Alaska Natives.[20] Therefore, many IHS-based studies likely represent more ruralized populations. However, recent US Census Bureau data indicates increasing representation of Native Americans, which shows that a majority of Native Americans now reside in urban areas and thus may be better represented in federal and state programs (e.g., Medicaid and Child Health Insurance Program) in which they may seek healthcare.[21] However, in Canada, a relatively higher proportion of Indigenous peoples live rurally.[22] Therefore, a limited diversity of the NAI population may have been captured in this data. Additional information is required to clarify characteristics of those seeking care outside of these registries, or those who have not participated in the studies included in this review. However, regardless of this issue, this review uncovered important themes. In particular, for rural-based NAI individuals who face barriers to care that are often based on the geographical location of their residence and the proximity and access to care.

Conclusions

This review has some limitations. First, this review provides a non-systematic summarization of heterogenous findings on the prevalence and disease outcomes of autoimmune diseases such as SLE and SSc in the NAI population. Analyzing and comparing differences in factors including regional location, study design, sample size, and statistical interpretation, among others is beyond the scope of this article. It remains unclear whether differences in these factors in the NAI population are related to a fundamental predisposition to these conditions, or to external factors such as systemic differences in health care access.

Knowledge of prevalence rates of SLE and SSc indicates the need for an increased awareness among clinicians of these diseases in the NAI population, and encourages further research initiatives to assess disease severity and outcomes, and to address gaps in treatment access.[6] This knowledge can potentially aid in screening of high-risk populations, which may facilitate early diagnosis and treatment, ultimately resulting in decreased morbidity.[3] In addition, better specialist access and primary care education for those who provide care to individuals with SLE are indicated.

Increased representation of the NAI population in clinical trials such as those for SLE may help clarify disease characteristics and therapeutic response. Despite the documented high population-based estimates of SLE, Indigenous peoples remain under-represented in randomized controlled trials of SLE, although their representation is increasing over time.[23] Any future Indigenous community-based studies should engage community input and approval using culturally competent research methodology frameworks.[19] Ultimately, gathering such knowledge and acknowledgement of population-specific differences in autoimmune and rheumatologic diseases in NAI peoples may help guide further studies on potentially diverse pathophysiology, and address barriers to care. On a practical level, it may assist clinicians in making more accurate diagnoses, thereby improving patient care.

Study/Country /Region	Study Design	Case Definition	Sample Size	Estimated Prevalence/Incidence**	Notes
(Peschken & Esdaile, 2000)[1] CAN Southern Manitoba	Regional arthritis center database search, medical record review (prevalence, disease course, survival)	SLE diagnosis (ACR criteria; diagnosed by rheumatology, hematology, nephrology, and general internal medicine)	n=49/257 Indigenous (19%) with SLE	Prevalence 42.3/100,000 Indigenous (twice-fold higher than general population at 20.6/100,000)	Indigenous ethnicity associated with: • Higher SLE disease severity index scores at diagnosis • Younger age • More frequent vasculitis and renal involvement • More likely to receive immunosuppressives or prednisone at most recent clinic visit • Four-fold increased likelihood of death
(Atkins et al., 1988)[2] CAN Pacific Northwest (Vancouver Island)	Retrospective, medical records	SLE	n=157 total requiring rheumatologist referral	Prevalence 348/100,000	Highest worldwide rates of SLE identified in the Nuu-Chah-Nulth Original article (abstract only*): Details extracted from Systematic review of rheumatic disease epidemiology in the Indigenous populations of Canada, the United States, Australia, and New Zealand (McDougall et al., 2017)[19]
(Houghton et al., 2006)[3] CAN British Columbia	Retrospective chart review	Pediatric (< 18) patients with SLE (ACR criteria) seen at the province's only tertiary care pediatric rheumatology clinic	n=6/40 Indigenous with SLE	Prevalence 8.8/100,000 (~2.5 fold higher compared to the pediatric general population at 3.3/100,000)	Family history of rheumatic disease more common in the Indigenous compared to non-Indigenous. Arthritis, myositis, and gastroenteritis common in the Indigenous. Limited by small sample size, and potential under-estimation of Indigenous case definitions.
(Barnabe et al., 2012)[4] CAN Alberta	Population-based registry stratified by FN status	SLE and SSc (ICD-9 codes)	Not specified	SLE prevalence (FN) 32.2/10,000 females, 3.2/10,000 males SSc prevalence (FN) 7.9/10,000 females, 1.3/10,000 males	Overall, prevalence of SLE and SSc comparable to FN and non-FN populations. On age stratification, FN females >age 45 had a two-fold higher prevalence of either SLE or SSc vs. non-FN females. Trend toward higher SLE prevalence in urban, and higher SSc prevalence in rural areas.
(Izmirly et al., 2021)[5] US National (CDC National Lupus Registry) and one Indian Health Services registry	Population-based registry	SLE (ACR criteria)	n=5,417 SLE cases (total)	Prevalence American Indigenous/ Alaska Native population: females 270.6/100,000, and males 53.8/100,000	American Indigenous/Alaska Native population "had the highest race-specific SLE estimates, both among females and males". [5] Multi-racial data included. Overall pooled prevalence from state registries was 72.8/100,000 py.
(Ferucci et al., 2014)[6] US Alaska, Phoenix area and Oklahoma regions	Population-based registry from IHS	SLE (ACR criteria)	n=285 cases	Prevalence 178/100,000 py (for females alone 271/100,000) Incidence 7.4/100,00 py (for Indigenous; females alone 10.4/100,000)	Estimates exceed most general population estimates. Female Indigenous adults found to have highest prevalence, most prominent in Phoenix area.

Study/Country /Region	Study Design	Case Definition	Sample Size	Estimated Prevalence/Incidence**	Notes
(Feldman et al., 2013)[8] US National (Medicaid database from 47 states)	Medicaid database (administrative billing claims/ICD-9 codes for SLE and demographics including self-reported race/ethnicity)	SLE (ICD-9 codes)	n=515/310,736 with SLE (Native American)	Prevalence 165.7/100,000 SLE, lupus nephritis 36.4/100,000 Incidence highest among African American females (38.6/100,000 py and Native American females (37.3/100,000 py)	Multi-racial data included. High SLE prevalence in Native American females (213.3/100,000) vs. males (48.9/100,000).
(Boyer et al., 1991)[7] US Alaska Native (Southeast coast; Tlingt, Haida, Tsimshian)	Patient care database	SLE	Not specified	Prevalence 112/100,000	High frequencies of both SLE and rheumatoid arthritis observed. Prevalence of SLE in Alaskan Natives approximately double vs. most white populations.
(Arnett et al., 1996)[9] US Oklahoma	Population estimates from an Oklahoma IHS database	SSc (ACR criteria)	n=28 Oklahoma Choctow cases	Prevalence 469/100,000 (full Choctaw), overall prevalence 66/100,000	Significantly higher prevalence in full blood quantum Choctaws (documentation of ancestry) – the highest prevalence documented. Homogeneity of phenotype: diffuse scleroderma, pulmonary fibrosis, autoantibodies to Topoisomerase-I, association with HLA haplotypes Other Native Americans in Oklahoma showed similar prevalence to white populations.
(Ferucci et al., 2017)[12] US IHS, Three regions of the US	Population-based registry from IHS	MCTD – (three case definitions encompassing rheumatologist diagnosis/ Alarcon-Segovia criteria)	n=61 Native American cases (all case definitions)	Prevalence 6.4 to 26.3 per 100,000 depending on definition used	MCTD prevalence higher in females. Authors concluded prevalence 'appears higher' than that in other populations.

Table 1. *Summary of SLE, SSc Disease Prevalence and Characteristics in North American Indigenous Peoples; courtesy of Rachel Asiniwasis, MD.*

*****Abstract only, Unable to locate or retrieve full text; therefore, information is based on the abstract.*
*******Confidence intervals, p-values and other statistical measures are not included in this table; details can be found in the primary source.*

Abbreviations: ***ACR:*** *American College of Rheumatology;* ***CAN:*** *Canada;* ***CDC:*** *Centers for Disease Control and Prevention;* ***FN:*** *First Nations;* ***HLA:*** *human leukocyte antigen;* ***IHS****: Indian Health Services;* ***MCTD:*** *mixed connective tissue disease;* ***SLE:*** *Systemic lupus erythematosus;* ***SSc:*** *Systemic sclerosis;* ***py:*** *person-years;* ***US:*** *United States*

Notes: *In the US, IHS represents a federally run health service within the Department of Human and Health Services for American Indigenous peoples and Alaska Natives, in recognition of the relationships between the federal government and tribes based on Article I, Section 8 of the 1787 Constitution, and being reflected in numerous treaties, laws, supreme court decisions and executive orders. It consists of 12 physical areas in the US, each having a base office located in Alaska, Albuquerque, Bemidji, Billings, California, Great Plains, Nashville, Navajo, Oklahoma, Phoenix, Portland, and Tucson. There are currently 170 IHS and tribally managed health centres based both in urban areas in urban areas and on-reserve, servicing approximately 2.6 million Native Americans belonging to 574 federally recognized tribes in 37 states. It largely represents a rural healthcare delivery system (IHS, 2021; KFF).*

Correspondence

Dr. Rachel Asiniwasis
Email: rasiniwasis@gmail.com

Financial Disclosures

Grants/Research Support: Leo, Pfizer, SHRF
Speakers Bureau and/or Honoraria: Abbvie, Pfizer, Lilly, Galderma, L'Oréal, Janssen, UCB, Bausch Health, Sanofi, Chronicle Companies, Arcutis, Novartis, Boehringer-Ingelheim, WoundPedia

References

1. Peschken CA, Esdaile JM. Systemic lupus erythematosus in North American Indians: a population based study. J Rheumatol. 2000;27(8):1884-891.
2. Atkins C, Reuffel L, Roddy J, Platts M, Robinson H, Ward R. Rheumatic disease in the Nuu-Chah-Nulth native Indians of the Pacific Northwest. J Rheumatol.1988;15(4):684-690.
3. Houghton KM, Page J, Cabral DA, Petty RE, Tucker LB. Systemic lupus erythematosus in the pediatric North American Native population of British Columbia. J Rheumatol. 2006;33(1):161-163.
4. Barnabe C, Joseph., Belisle P, Labrecque J, Edworthy S, Barr SG, et al. Prevalence of systemic lupus erythematosus and systemic sclerosis in the First Nations population of Alberta, Canada. Arthritis Care Res (Hoboken). 2012:64(1):138-143. https://doi.org/10.1002/acr.20656
5. Izmirly PM, Parton H, Wang L, McCune WJ, Lim SS, Drenkard C, et al. Prevalence of systemic lupus erythematosus in the United States: estimates from a meta-analysis of the Centers for Disease Control and Prevention National Lupus Registries. Arthritis Rheumatol. 2021:73(6):991-996. https://doi.org/10.1002/art.41632
6. Ferucci ED, Johnston JM, Gaddy JR, Sumner L, Posever JO, Choromanski TL, et al. Prevalence and incidence of systemic lupus erythematosus in a population-based registry of American Indian and Alaska Native people, 2007-2009. Arthritis Rheumatol. 2014;66(9):2494-2502. https://doi.org/10.1002/art.38720
7. Boyer GS, Templin DW, Lanier AP. Rheumatic diseases in Alaskan Indians of the southeast coast: high prevalence of rheumatoid arthritis and systemic lupus erythematosus. J Rheumatol. 1991;18(10):1477-1484.
8. Feldman CH, Hiraki LT, Liu J, Fischer MA, Solomon DH, Alarcón GS, et al. Epidemiology and sociodemographics of systemic lupus erythematosus and lupus nephritis among US adults with Medicaid coverage, 2000-2004. Arthritis Rheum. 2013;65(3):753-763. https://doi.org/10.1002/art.37795
9. Arnett FC, Howard RF, Tan F, Moulds JM, Bias WB, Durban E, et al. Increased prevalence of systemic sclerosis in a Native American tribe in Oklahoma. Association with an Amerindian HLA haplotype. Arthritis Rheum. 1996;39(8):1362-1370. https://doi.org/10.1002/art.1780390814
10. Scofield RH. Sharma R, Pezant N, Kelly JA, Radfar L, Lewis DM, et al. American Indians have a higher risk of Sjögren's Syndrome and more disease activity than European Americans and African Americans. Arthritis Care Res. (Hoboken). 2020;72(8):1049-056. https://doi.org/10.1002/acr.24003
11. Muruganandam M, Rolle NA, Sibbitt WL, Jr, Cook GB, Emil NS, Fangtham M, et al. Characteristics of Behcet's disease in the American Southwest. Semin Arthritis Rheum. 2019;49(2):296-302. https://doi.org/10.1016/j.semarthrit.2019.03.003
12. Ferucci ED, Johnston JM, Gordon C, Helmick CG, Lim SS. Prevalence of mixed connective tissue disease in a population-based registry of American Indian/Alaska Native People in 2007. Arthritis Care Res, 2017;69(8):1271-1275. https://doi.org/10.1002/acr.23135
13. Gaddy JR, Vista ES, Robertson JM, Dedeke AB, Roberts VC, Klein WS, et al. Rheumatic disease among Oklahoma tribal populations: a cross-sectional study. J Rheumatol. 2012;39(10):1934-1941. https://doi.org/10.3899/jrheum.110984
14. Bacher A, Mittoo S, Hudson M, Tatibouet S; Canadian Scleroderma Research Group, Baron M. Systemic sclerosis in Canada's North American Native population: assessment of clinical and serological manifestations. J Rheumatol. 2013;40(7):1121-1126. https://doi.org/10.3899/jrheum.121212
15. Morton RO, Gershwin ME, Brady C, Steinberg AD. The incidence of systemic lupus erythematosus in North American Indians. J Rheumatol. 1976;3(2):186-190.
16. Mejia Otero C, Assassi S, Hudson M, Mayes MD, Estrada-Y-Martin R, Pedroza C, Mills TW, et al. Antifibrillarin antibodies are associated with Native North American Ethnicity and poorer survival in systemic sclerosis. J Rheumatol. 2017;44(6):799-805. https://doi.org/10.3899/jrheum.160574
17. Tan FK, Wang N, Kuwana M, Chakraborty R, Bona CA, Milewicz DM, et al. Association of fibrillin 1 single-nucleotide polymorphism haplotypes with systemic sclerosis in Choctaw and Japanese populations. Arthritis Rheum. 2001;44(4):893-901. https://doi.org/10.1002/1529-0131(200104)44:4<893::AID-ANR146>3.0.CO;2-3
18. Zhou X, Tan FK, Reveille JD, Wallis D, Milewicz DM, Ahn C, et al. Association of novel polymorphisms with the expression of SPARC in normal fibroblasts and with susceptibility to scleroderma. Arthritis Rheum. 2002;46(11):2990-2999. https://doi.org/10.1002/art.10601
19. McDougall JA, Helmick CG, Lim SS, Johnston JM, Gaddy JR, Gordon C, et al. Differences in the diagnosis and management of systemic lupus erythematosus by primary care and specialist providers in the American Indian/Alaska Native population. Lupus. 2018;27(7):1169–1176. https://doi.org/10.1177/0961203318763529
20. Forquera R. The Seattle Indian Health Board. Urban Indian Health: Issue Brief [Internet]. Menlo Park, CA: Kaiser Family Foundation; November 2001. Available from https://www.kff.org/wp-content/uploads/2001/10/6326urbanindianhealth.pdf
21. Urban Indian Health [Internet]. Seattle, WA: Urban Indian Health Institute. 2023. [Date of Access: November 1, 2023] Available from: https://www.uihi.org/urban-indian-health/
22. Profile of Indigenous Canada: Trends and Data Needs [Internet]. Organisation for Economic Cooperation and Development (OECD). 2022. [Date of Access: November 1, 2023] Available from: https://www.oecd-ilibrary.org/sites/e6cc8722-en/index.html?itemId=/content/component/e6cc8722-en
23. Falasinnu T, Chaichian Y, Bass MB, Simard JF. The representation of gender and race/ethnic groups in randomized clinical trials of individuals with systemic lupus erythematosus. Curr Rheumatol Rep.2018;20(4):20. https://doi.org/10.1007/s11926-018-0728-2