Understanding the Disproportionate Burden of Rheumatic Diseases in Indigenous North American Populations

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KEYWORDS

• Indigenous • Rheumatic disease • Autoimmune disease • Epidemiology
• Health disparities

KEY POINTS

- There is an excess burden of many rheumatic diseases in Indigenous North American populations in the United States and Canada.
- Understanding the epidemiology of rheumatic diseases in indigenous populations is important for physicians, health care organizations, and the communities affected by the high burden of disease. This information can ensure the necessary allocation of health care resources as well as education of health care providers and community members.
- Risk factors associated with high rates of rheumatic disease in indigenous populations have not been fully elucidated, but likely include a combination of multiple genetic and environmental factors.

INTRODUCTION

Studies have found a high incidence and prevalence of several rheumatic diseases in indigenous North American (INA) populations in the United States and Canada (**Table 1**). In the 1980s and 1990s, studies focused on high rates of rheumatoid arthritis (RA) in INA populations and the associated HLA alleles,[1] as well as high rates of spondyloarthritis in association with HLA B27 positivity.[2] Recent studies have expanded on the increased risk of RA in relatives and those with preclinical autoantibodies.[3] In addition, the Centers for Disease Control and Prevention (CDC)-funded lupus registries recently evaluated the epidemiology of systemic lupus erythematosus (SLE) across all racial and ethnic categories in the United States and documented the highest prevalence of SLE in American Indian/Alaska Native (AI/AN) women.[4]

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Table 1
Summary of rheumatic disease epidemiology

Condition	Prevalence Summary	Prevalence Details	Incidence Summary	Incidence Details	Phenotype Summary
Rheumatoid arthritis	High	1.4%–7.1%[1,9,10]	High	2–10 times US white[1] Higher in relatives of people with RA[3]	High prevalence of seropositivity for RF, CCP, ANA[1,11,12] More nodules and erosions[1] Earlier age of onset[11] More large joint involvement[11]
Spondyloarthritis	High	2.5% overall[2] 1.5–2.7 times higher in First Nations vs non-First Nations in Alberta[10]	Unknown	—	High prevalence of HLA B27[14] Undifferentiated and reactive arthritis more common than AS[2] More severe disease in men[19]
Juvenile idiopathic arthritis	Probably high	79 per 100,000[23]	Unknown	—	Enthesitis-related arthritis overrepresented[23]
Systemic lupus erythematosus	High	270.6 per 100,000 women and 53.8 per 100,000 men[28]	High	7.4 per 100,000 person-years overall[28]	Early age of onset[25,33] Arthritis common[13,17,25,28] Renal disease may be more common[28]
Mixed connective tissue disease	Probably high	6.4 per 100,000[35]	Unknown	—	Synovitis and Raynaud most common manifestations[35]
Systemic sclerosis	Probably high	66 per 100,000 in 1 Oklahoma tribe[36] 47 per 100,000 in First Nations in Alberta[26]	Unknown	—	—
Sjogren syndrome	Maybe high	High proportion of cases in a cohort were AI but prevalence unknown[37]	Unknown	—	—
Inflammatory myopathy	Unknown	25 per 100,000 in First Nations in Alberta (low)[38] Concern of possible higher rates of statin-associated autoimmune myopathy in US AI/AN populations[39]	Unknown	—	—

Osteoarthritis	High	16.1 per 100 (2× as common as non-First Nations in Alberta)[43]	Unknown	—	Higher all-cause hospitalization rates, but lower rates of specialty care and joint replacement[43]
Crystal-associated arthritis	Low	0.8 per 100 First Nations (vs 1.2 per 100 non-First Nations) in Alberta[10]	Unknown	—	—
Self-reported arthritis	High	24.4% in AI/AN in NHIS in United States, vs 22.6% in non-Hispanic whites[44]	Unknown	—	—

This article provides an overview of the epidemiology of rheumatic diseases in INA populations. A systematic review was recently published on this topic,[5] and this article includes key studies available before that systematic review, as well as more recently published literature. When discussing future research directions, the importance of community engagement and a summary of past community engagement in rheumatic disease research are also highlighted. Systematic reviews have also been published recently describing rheumatic disease phenotype and outcomes,[6] health care utilization,[7] and mortality[8] in indigenous populations.

EPIDEMIOLOGY OF RHEUMATIC DISEASES

Rheumatoid Arthritis

A high prevalence of RA has been described in multiple INA populations, ranging from 1.4% to 7.1% in a 2005 review, compared with less than 1% in the general population.[1] The incidence of RA has not been studied as frequently, but ranged from more than 2 times expected to up to 10 times expected in 2 studies.[1] The prevalence of RA in different INA populations has varied, some of which can be attributed to differences in population prevalence and some to differences in study design. Since the review of this topic in 2005, two additional studies confirmed a high prevalence of RA. In Manitoba, Canada, RA was twice as common in First Nations compared with non-First Nations people based on claims data.[9] In Alberta, Canada, the prevalence of RA in First Nations people was 3.2%, three times higher than in non-First Nations people.[10] A recent study of a cohort of relatives of INA people with RA, who are at higher risk than the general population, found the incidence of inflammatory arthritis to be 9.2 per 1000 person-years.[3]

Several studies have described the phenotype of RA in INA populations. Older studies documented a high prevalence of seropositivity for rheumatoid factor (RF) (>90%) and antinuclear antibody (ANA) (>50%), with increased likelihood of rheumatoid nodules and erosions.[1] More recent studies have confirmed the high proportion of cases with positive RF and ANA[11] and described more than 80% seropositivity for anticyclic citrullinated peptide (CCP).[12] An exception was a study of Oklahoma tribal populations that found anti-CCP positivity in only 55% of patients with RA and RF positivity in only 58%, although ANA positivity was still common (62.5%).[13] An earlier age of onset and high frequency of large joint involvement have been described.[11]

Spondyloarthritis

Studies of spondyloarthropathy in the AN population in the 1980s found high rates of HLA B27 positivity in the population (25%–40%), but lower than expected prevalence of ankylosing spondylitis (AS).[14–17] Because a large proportion of cases was consistent with undifferentiated spondyloarthropathy rather than AS, studies were repeated in the 1990s with a broader set of criteria. In AN people in 2 regions of Northern and Western Alaska, the overall prevalence of spondyloarthropathy was 2.5%,[2] in comparison to approximately 0.9% to 1.4% in the US population,[18] including a high prevalence of reactive arthritis (1.0%) and undifferentiated spondyloarthropathy (1.3%), with AS being less common (0.4%).[2] Psoriatic arthritis was rare, with a prevalence of less than 0.1%.[2] A subsequent study identified more severe disease in AN men than women.[19] Older studies in Canadian Inuit and Indian populations also identified high prevalence of spondyloarthropathy.[20,21] A more recent study in Alberta, Canada using claims-based data found the prevalence of psoriatic disease (psoriasis and psoriatic arthritis) to be 0.3% in the First Nations population, with a standardized rate ratio (SRR) of 1.5 when compared with the non-First Nations population.[10] This same study

found AS prevalence to be 0.6%, with SRR of 2.7 in the First Nations compared with non-First Nations population.[10]

Juvenile Idiopathic Arthritis

Two studies using the older juvenile rheumatoid arthritis (JRA) classification criteria found a high prevalence of JRA in 2 Indian Health Service (IHS) regions[22] and in Southeast Alaska.[17] A recent study in Alaska using the International League Against Rheumatism classification criteria found the prevalence of JIA in AN children to be 79 per 100,000, higher than the reported prevalence of 50 per 100,000 in a recent study in Olmsted County, Minnesota.[23] In this study, although oligoarthritis was the most common form of JIA, enthesitis-related arthritis made up a higher proportion of cases (24%) than expected (1%–3%), and HLA B27 was positive in more than half of the children who were tested.[23]

Systemic Lupus Erythematosus

The incidence and prevalence of SLE were higher than expected in many studies of INA populations using regional or administrative data before 2013.[17,24–26] A national study published in 2013 using data from the US Medicaid population confirmed that incidence and prevalence of SLE were high in individuals identified as Native American, but not as high as in the US black population.[27] The CDC funded 5 population-based lupus registries, designed to address the limitations of epidemiologic data for SLE in multiple populations in the United States. The 5 registries used similar population-based surveillance methods, with medical record abstraction for verification of each case. The IHS registry catchment area included 3 administrative areas, Alaska, Phoenix, and Oklahoma City. Data from the 5 registries have been published, with the highest prevalence of SLE found in AI/AN populations in the IHS lupus registry.[28–32] Incidence of SLE was also high in AI/AN populations, but with wider confidence intervals. A metaanalysis has been conducted to estimate the prevalence of SLE in the United States and the number of people living with SLE in the United States, combining data from the 4 state-based registries and comparing it to the AI/AN prevalence determined by the IHS registry.[4] The highest prevalence of SLE was in AI/AN women (270.6 per 100,000) and men (53.8), compared with the next highest rates in black women (230.9) and black men (26.7).[4]

In INA populations, a few studies have described a younger mean age of onset of SLE.[25,33] Several studies have described arthritis as a more common manifestation of SLE than in other populations (>80%).[13,17,25,28] Renal disease, a predictor of higher mortality, has been reported in about 40% of INA people with SLE in several studies, a prevalence that is similar to that reported in blacks with SLE and higher than what has been reported in whites.[28]

Other Systemic Rheumatic Disease

A study in the 1980s suggested a high rate of overlap syndromes in INA populations in Canada.[34] A recent report using data collected in the IHS lupus registry found the age-adjusted prevalence of mixed connective tissue disease in AI/AN populations in the United States to be 6.4 per 100,000 by the primary definition, which was higher than the prevalence in a comparable study in Norway (3.8),[35] with no data available for comparison in North America. A study in the 1990s identified a very high prevalence of systemic sclerosis in 1 tribe in southeastern Oklahoma (66 per 100,000 overall).[36] Since then, 1 study found higher rates of systemic sclerosis in First Nations compared with non-First Nations people in Alberta, Canada, especially in women over the age of 45.[26] A recent study found an overrepresentation of AI patients in a

Sjogren syndrome cohort, leading the investigators to suspect a higher prevalence of Sjogren syndrome in this population.[37] Autoimmune inflammatory myopathy prevalence was studied in Alberta, Canada, with similar prevalence found in the First Nations compared with non-First Nations population.[38] Of note, the IHS issued a drug safety alert in January 2019 noting a high number of cases of statin-associated autoimmune myopathy, with plans for an epidemiologic investigation by the Food and Drug Administration.[39] Finally, a few studies of vasculitis are available. These studies have documented high rates of hepatitis B–associated polyarteritis nodosa in AN people in a region with high rates of hepatitis B infection,[40] low hospitalization rates for Kawasaki syndrome in children in IHS facilities,[41] and low incidence of biopsy-proven giant cell arteritis in AN people.[42]

Osteoarthritis and Self-Reported Arthritis

A recent study in Alberta, Canada found that osteoarthritis was twice as common in First Nations compared with non-First Nations people based on administrative claims data.[43] Self-reported arthritis is a common measure of the burden of arthritis in populations in national or state-based surveys. In the United States from 2013 to 2015, the age-adjusted prevalence of self-reported doctor-diagnosed arthritis in the National Health Interview Survey (NHIS) was 24.4% in AI/AN people, compared with 22.6% in non-Hispanic whites, with lower rates in other racial/ethnic groups.[44] A population-based cohort of AI/AN people in Alaska and the Southwestern United States found a higher age-adjusted prevalence of self-reported arthritis in AN people (26.1%) than in the general US population by NHIS at the time (21.5%) or in AI people in the Southwestern United States (16.5%).[45]

Crystal-Induced Arthritis

A few studies suggest a low prevalence of crystal-induced arthritis in INA populations, in contrast to indigenous populations of New Zealand, where a high prevalence of gout has been described.[46] A study in the 1980s found a low prevalence of gout (0.3%) in a Northwestern AN population.[15] A recent study using administrative claims data found lower prevalence of crystal-induced arthritis in First Nations compared with non-First Nations populations in Alberta, Canada, with an SRR of 0.7.[10]

RISK FACTORS FOR RHEUMATIC DISEASE

The risk of rheumatic disease is based on a combination of many genetic and environmental factors. Genetic factors have been studied more often and are summarized in later discussion. Environmental factors, such as tobacco use, stress and adverse childhood experiences, infections, the microbiome, socioeconomic status, and epigenetic factors, are all likely key risk factors, but few have been studied. In a study of the incidence of inflammatory arthritis in family members of INA people with RA, history of smoking was common (>75%) in both progressors and nonprogressors, with no statistically significant difference between groups.[3]

Genetic Risk Factors for Rheumatoid Arthritis and Spondyloarthritis

A unique shared epitope allele (HLA DRB1*1402) was identified with a high frequency in INA populations.[1] A metaanalysis of data from 3 INA populations in the United States confirmed an association of HLA DRB1*1402 and RA.[47] A recent study provided confirmation of the association of this allele with RA in INA populations and additional information on the mechanism of risk, related to the capacity to present citrullinated peptide antigens and T-cell expansion.[48]

As a possible explanation for high rates of spondyloarthritis, the prevalence of HLA B27 was found to be elevated in many INA populations, ranging from 25% to 40%,[14] in contrast to approximately 6% in the US population.[49]

FUTURE DIRECTIONS AND THE IMPORTANCE OF COMMUNITY ENGAGEMENT IN RHEUMATIC DISEASE RESEARCH WITH INDIGENOUS NORTH AMERICAN POPULATIONS

As described above, there are few studies of risk factors for rheumatic disease specifically in INA populations. Although more research is needed, it is important that researchers interested in studying rheumatic diseases in indigenous populations understand the community context and unique ethical considerations. Misconduct and misuse of research data and specimens have occurred too frequently, often in the context of secondary use without knowledge or consent of participants. The most recent widely known episode occurred when members of the Havasupai tribe were recruited for a study of diabetes, but with secondary use of specimens for genetic research on topics that were not acceptable to tribal members.[50] In order to avoid researcher misinterpretation of research findings or stigmatization of populations with high rates of disease, engagement of indigenous communities in research is critical. A systematic review was recently published evaluating the degree of community engagement in arthritis research.[51] Community engagement was most common during the data collection stage of arthritis research, with few studies engaging communities during the inception or interpretation and dissemination stage of research. Most community engagement was at the lower end of the spectrum, with few studies including meaningful community engagement. Processes that promote meaningful community engagement are recommended for arthritis studies in indigenous populations.[51]

SUMMARY

The prevalence of many rheumatic diseases is high in INA populations, especially RA, SLE, and spondyloarthritis, which have been studied most extensively. The risk factors underlying the high burden of rheumatic diseases in INA populations are not fully known. Understanding the epidemiology of rheumatic disease in INA populations is important for clinicians, health systems, and communities. Providing education to these stakeholders about the burden of disease and improving access to specialist care in these populations may help identify rheumatic diseases earlier and improve outcomes. Finally, community engagement in rheumatic disease research in INA populations is critical to ensure that research is culturally relevant and has the potential to benefit INA communities.

DISCLOSURE

The authors have nothing to disclose.

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