

Current Opinion in Rheumatology

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Current Opinion in Rheumatology was launched in 1989. It is one of a successful series of review journals whose unique format is designed to provide a systematic and critical assessment of the literature as presented in the many primary journals. The field of Rheumatology is divided into 15 sections that are reviewed once a year. Each section is assigned a Section Editor, a leading authority in the area, who identifies the most important topics at that time. Here we are pleased to introduce the Journal's Section Editors for this issue.

SECTION EDITORS

Kenneth Saag

Kenneth Saag, MD, MSc, is *Jane Knight Lowe* Professor of Medicine, Division of Clinical Immunology and Rheumatology, at the University of Alabama at Birmingham (UAB) in Birmingham, Alabama, USA and Professor of Epidemiology, at the UAB School of Public Health.



Dr Saag is a native of Chicago, and following studies in engineering at the University of Michigan, USA, he returned to Chicago for medical school and Internal Medicine Residency at Northwestern University, USA. He then traveled to the University of Iowa, USA, for his rheumatology and epidemiology training and remained on the faculty there until moving to UAB in 1998.

Dr Saag is the founding Director of the Agency for Health Care Research and Quality Deep South Center for Education and Research on Therapeutics, the UAB Center of Research Translation in Gout and Hyperuricemia, and the UAB Outcomes Research Center. He also serves as a Vice Chair for the UAB Department of Medicine. He has published over 300 peer reviewed manuscripts; has also authored more than 100 reviews, editorials, and book chapters. Recently he published the first edition of the clinical handbook *Diagnosis and Management of Osteoporosis*.

Dr Saag is the Secretary of the American College of Rheumatology (ACR) and Past President of the Board of Trustees of the National Osteoporosis Foundation.

George C. Tsokos

George C. Tsokos is a Professor of Medicine at Harvard Medical School and chief of the Division of Rheumatology and Clinical Immunology at Beth Israel Deaconess Medical Center in Boston, MA. His laboratory has led the field of molecular abnormalities on immune cells in patients with systemic lupus erythematosus and has identified previously unknown pathways that have served as the basis for novel treatments currently in various phases of development. More recently, he has launched studies to decipher the interaction between immune and kidney resident cells and to identify local processes that enable renal injury.



Dr Tsokos has served in various leadership positions, including president of the Clinical Immunology Society, the member of the boards of directors for the American College of Rheumatology and the Lupus Foundation of America, member or chair of multiple federal study sections, and editor or member of the editorial boards for top scientific journals. He holds a MERIT Award from the National Institutes of Health and has received several prestigious awards, including the Kirkland, Lee C. Howley Sr. Prize, and Evelyn V. Hess awards; the Distinguished Basic Investigator Award from the American College of Rheumatology; the Lupus Insight Prize from the Lupus Research Alliance; the Carol Nachman Prize for Rheumatology; and the Dr. Marian Ropes Physician Achievement Award. He is a Master of the American College of Physicians and the American College of Rheumatology, a member of American Association of Physicians and Fellow of AAAS.

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Epidemiology and outcomes of rheumatoid arthritis

Lauren E. Klingemann^a, Ted R. Mikuls^{a,b} and Bryant R. England^{a,b}

Purpose of review

This review aims to summarize recent developments in the epidemiology of rheumatoid arthritis (RA) focusing on disease burden, risk factors, and disease outcomes.

Recent findings

Globally, the prevalence of RA is increasing, affecting an estimated 17.6 million people worldwide. Emerging data implicate other environmental and occupational inhaled exposures apart from cigarette smoking as RA risk factors. Risk models integrating clinical, serological, and imaging data are useful in predicting the pre-RA to RA transition. Extra-articular manifestations and multimorbidity are key complications of RA that drive excess mortality and avoidable hospitalizations, though overall mortality trends in RA are improving. RA-associated interstitial lung disease is recognized to affect the lungs of early RA patients, and risk models based on clinical and advanced biomarker phenotyping have shown potential for risk stratification. Large cohort studies have identified heart failure and valvular heart disease as cardiovascular complications in RA, in addition to atherosclerosis. Observational studies continue to evaluate the safety of TNF inhibitors in the setting of cancer.

Summary

RA prevalence is rising globally, while mortality rates are declining. Continued investigation aimed at elucidating RA risk factors, the transition from pre-RA to RA, extra-articular involvement, and multimorbidity remains critical to optimize patient outcomes.

Keywords

epidemiology, outcomes, rheumatoid arthritis

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease with a primary manifestation of inflammatory arthritis [1]. RA results from a complex interplay between genetic susceptibility, various environmental triggers, and autoantibody production which lead to systemic inflammation and immune-mediated joint destruction [2–4]. Untreated or undertreated RA can lead to irreversible joint damage and progressive disability. Beyond articular manifestations, RA is also characterized by systemic involvement [1], with interstitial lung disease (ILD) and cardiovascular disease (CVD) complications contributing substantially to the excess morbidity and premature mortality of RA [1–3,5]. This review aims to summarize the recent findings on the epidemiology and outcomes of RA, focusing on published studies over the last year (Tables 1 and 2).

BURDEN OF RHEUMATOID ARTHRITIS

According to the 2021 Global Burden of Disease Study, the prevalence of RA has increased worldwide and is estimated to affect 17.6 million individuals [6].

The global age-standardized prevalence rate increased by 14.1% over the last three decades, and projections from the Global Burden of Disease Study estimate a continued rise in the prevalence of RA to 31.7 million by 2050. These findings highlight the rising global burden of RA.

RHEUMATOID ARTHRITIS RISK FACTORS

Cigarette smoking has long been established as the strongest environmental risk factors for the development of RA [7]. The Global Burden of Disease 2021 found the age-standardized rates of smoking-attributable RA burden declined in many regions, with declining smoking rates likely contributing [8^{*}]. Despite this decline, the global number of deaths

^aDepartment of Internal Medicine, Division of Rheumatology, University of Nebraska Medical Center and ^bVeterans Affairs Nebraska-Western Iowa Healthcare System, Omaha, Nebraska, USA

Correspondence to Bryant R. England, MD, PhD, 986270 Nebraska Medicine, Omaha, NE 68198-6270, USA. Tel: +1 402 559 7288; e-mail: Bryant.England@unmc.edu

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KEY POINTS

- The prevalence of RA is currently estimated at 17.6 million people worldwide and is predicted to continue to increase over the coming years.
- Cigarette smoking remains a significant modifiable risk factor associated with RA risk and progression with recent data providing support for the lung-joint axis hypothesis; data on other inhaled exposures as risk factors for RA development continue to emerge.
- Models integrating clinical, serological, and imaging data show potential for accurately predicting which individuals with pre-RA will transition to clinically apparent RA and could be used to design future prevention trials.
- Multimorbidity and extra-articular complications of RA lead to avoidable hospitalizations and premature mortality; early identification, comprehensive management, and personalized treatment of patients with RA is essential.

and disability-adjusted life years due to smoking-attributable RA simultaneously increased with population growth and aging as contributing factors. Smoking is also associated with worse RA outcomes and decreased response to RA treatment [9]. Primary care providers may be less likely than rheumatologists to perceive smoking as having a significant impact on RA disease activity, though both specialties support the use of pharmacotherapy, quit-lines, peer-support groups, and education to assist patients in smoking cessation [10[■]]. While cigarette smoking rates are on the decline [11], ongoing provider and system-level interventions are needed to further mitigate the risk and complications of RA attributed to smoking.

Data on mechanisms linking cigarette smoking to RA continue to emerge. Bronchoalveolar lavage fluid, peripheral blood, and synovial tissue from anticitrullinated protein antibody (ACPA)-positive, treatment-naïve, new-onset RA patients who were smokers had increased clonal expansion of CD4⁺ and CD8⁺ T cells compared to nonsmokers, and this expansion was especially pronounced in smokers

Table 1. Recent findings on the at risk and pre-rheumatoid arthritis populations

Stage	Key findings
At-risk (genetically predisposed but without autoimmunity)	<ul style="list-style-type: none"> • Smoking <ul style="list-style-type: none"> ◦ Age-standardized rates of smoking-attributable RA declined in many regions, while deaths and disability-adjusted life years due to smoking-attributable RA increased [8[■]]. ◦ ACPA-positive, treatment-naïve, new-onset RA patients who were smokers had increased clonal expansion of CD4⁺ and CD8⁺ T cells vs. nonsmokers with identical T cell receptor clonotypes identified in lung, joint, and blood, supporting the lung-joint axis model hypothesis [12[■]]. ◦ Smoking is linked to elevated levels of IgA antimodified protein antibodies, suggesting inflammation originating at mucosal sites contributes to systemic autoimmunity [13[■]]. • Other inhaled exposures <ul style="list-style-type: none"> ◦ Higher levels of nitrogen oxides were associated with incident overall RA, while elevated levels of ozone, and PM₁₀ were associated with incident seronegative RA [14[■]]. ◦ PM_{2.5} was associated with RA-ILD risk, but not incident RA [14[■]]. However, a separate study demonstrated that exposure to PM_{2.5} components was moderately associated with RA risk, with ammonium being the strongest contributor [15[■]]. ◦ Exposure to any of thirty-two inhalable occupational agents was associated with increased risk of ACPA-positive RA. The risk increased with increased number of agents and duration of exposure [16]. • Diet <ul style="list-style-type: none"> ◦ Healthy diet patterns (e.g., anti-inflammatory diet, healthy eating index, Mediterranean diet) are associated with decreased RA risk [17[■]].
Pre-RA (autoimmunity present but no clinically apparent RA)	<ul style="list-style-type: none"> • Risk factors for transition to clinically apparent RA <ul style="list-style-type: none"> ◦ Factors associated with higher risk of progression to RA included having a first-degree relative with RA, intermittent symptoms (vs. continuous), >1 h of morning stiffness, reported joint swelling, symptom duration <12 months, ACPA concentrations >3-times the upper limit of normal, and positivity for both ACPA and RF [18[■]]. • Risk model development <ul style="list-style-type: none"> ◦ Optimal EULAR/ACR pre-RA to RA risk-stratification model performance occurred when imaging features were added to clinical (morning stiffness, patient-reported joint swelling, and difficulty making a fist) and serologic (elevated C-reactive protein, RF, and ACPA) markers [19].

ACPA, anticitrullinated protein antibodies; ACR, American College of Rheumatology; EULAR, European Alliance of Associations for Rheumatology; PM₁₀, particulate matter <10 μm; PM_{2.5}, fine particulate matter <2.5 μm; RA, rheumatoid arthritis; RA-ILD, rheumatoid arthritis-associated interstitial lung disease; RF, rheumatoid factor.

Table 2. Recent findings on outcomes in rheumatoid arthritis

Outcome	Findings
Multimorbidity	<ul style="list-style-type: none"> • Multimorbidity patterns of cardiovascular disease, chronic pain, and mental health and substance abuse were associated with higher RA disease activity and poorer functional status [21[■]]. • Multimorbidity was associated with higher risk of RA flares and lower likelihood of achieving remission [22[■]]. • Individuals with RA had higher rates of preventable hospitalizations compared to non-RA controls due to multimorbid conditions [23[■]].
RA-ILD	<ul style="list-style-type: none"> • Moderate/high RA disease activity and age ≥ 60 at diagnosis were associated with RA-ILD [25[■]]. • Biomarker themes of innate and allergic responses, autoantibodies, adipokines, alarmins, tissue remodeling, and neutrophil chemotaxis were associated with RA-ILD [26[■]]. • Genes involved in inflammation, fibrosis, epigenetic modification, and macrophage activation all had increased expression in peripheral monocytes of patients with RA-ILD [27[■]].
Cardiovascular disease	<ul style="list-style-type: none"> • Individuals with RA had increased risk of developing HFpEF, but not HFrEF compared to non-RA comparators [29[■]]. • RA was associated with increased risk of HFpEF, HFpEF-related death, HFrEF, and HFrEF-related death [30[■]]. • RA was associated with increased risk of aortic stenosis, aortic stenosis related death, aortic valve intervention [31[■]], aortic regurgitation, and mitral regurgitation [32].
Cancer	<ul style="list-style-type: none"> • RA was associated with decreased rates of cervical cancer screening, while breast, prostate, and colorectal screening rates were similar between RA and non-RA patients [35[■]]. • Using low dose chest CT, lung cancer detection rates were similar between RA and non-RA patients [36[■]]. • Increased rates of cancer recurrence and mortality were not seen in RA patients on TNF inhibitors [37,38[■],39[■]].
Mortality	<ul style="list-style-type: none"> • RA patients have a 23% higher all-cause mortality risk compared to non-RA controls with cardiovascular and pulmonary causes of death contributing to 70% of excess death [41]. • The estimated age-standardized death rate decreased by 23.8% between 1990 and 2020 [6].

CT, computed tomography; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; RA, rheumatoid arthritis; RA-ILD, rheumatoid arthritis-associated interstitial lung disease; TNF, tumor necrosis factor.

carrying *HLA-DRB1* shared epitope alleles [12[■]]. Additionally, many T cell receptor clonotypes were identical in lung, joint, and blood, suggesting that lung mucosal exposure to cigarette smoke may lead to expansion and circulation of autoreactive T cells which then seed the joints. This association is further supported by data demonstrating that smoking is predominantly linked to elevated levels of IgA (rather than IgG) antimodified protein antibodies, suggesting that inflammation originating at mucosal sites such as the lungs contribute to systemic autoimmunity seen in RA [13[■]]. These data further strengthen the lung-joint axis model as a plausible mechanism in RA development and substantiate cigarette smoking as a key modifiable risk factor for RA.

Given the body of evidence on cigarette smoking and RA risk, there is interest in whether other inhaled exposures may similarly act as risk factors for RA. A recent case-control study within the Veterans Affairs Healthcare System found that higher levels of nitrogen oxides were associated with incident overall RA while elevated levels of ozone, and particulate matter less than 10 μm (PM₁₀) were associated with incident seronegative RA. Fine particulate matter less than 2.5 μm (PM_{2.5}) was associated with RA-ILD risk, but not incident RA [14[■]]. In contrast, a cohort study from Canada found that exposure to PM_{2.5} components was moderately associated with RA risk, with ammonium being the strongest contributor [15[■]]. A

separate Swedish case-control study found that exposure to any of thirty-two inhalable occupational agents was associated with increased risk of ACPA-positive RA. The risk increased with increased number of agents and duration of exposure [16]. These findings provide support to the hypothesis that inhalational exposures besides cigarette smoke such as fossil fuel combustion, fire smoke, ozone, and occupational agents may also be environmental risk factors for RA.

Aside from inhalational risk factors, diet has been widely studied for its potential contribution to RA risk. A recent systematic review and meta-analysis of 12 observational studies found that healthy dietary patterns were associated with almost 50% lower odds of developing RA [17[■]]. The authors found the specific dietary patterns of the anti-inflammatory diet (odds ratio [OR] 0.56), healthy eating index diet (OR 0.60), and the Mediterranean diet (OR 0.88) to be associated with decreased risk of RA. While inherent limitations to these types of studies prevent drawing causal inferences, these findings provide support that diet may be a modifiable lifestyle factor that meaningfully influences RA risk.

PRE-RHEUMATOID ARTHRITIS RISK FACTORS AND RISK MODELS

The transition from at-risk to clinical RA has been termed the pre-RA period, with this period consisting

of heterogeneous trajectories. A large cohort study of 617 individuals positive for ACPA, rheumatoid factor, or both and arthralgia, but no clinical arthritis on examination were followed for up to 5 years with 33.7% developing RA [18[■]]. Factors independently associated with higher risk of progression to RA included having a first-degree relative with RA, intermittent symptoms (vs. continuous), more than 1 h of morning stiffness, reported joint swelling, and symptom duration less than 12 months. The strongest risk factors were ACPA concentrations more than three times the upper limit of normal (hazard ratio 4.65) and dual positivity for ACPA and rheumatoid factor (hazard ratio 6.83). In individuals with at least three of the aforementioned risk factors, the risk of developing clinically apparent RA increased to 58.2%.

A joint European Alliance of Associations for Rheumatology/American College of Rheumatology committee utilized data from 10 arthralgia-based cohorts ($n=2293$ at-risk patients) to derive a risk-stratification model to predict inflammatory arthritis onset within 1 year [19]. They found that a model consisting of morning stiffness, patient-reported joint swelling, difficulty making a fist, elevated C-reactive protein, rheumatoid factor, and ACPA had an area-under-the-curve (AUC) of 0.80 (95% confidence interval [95% CI] 0.77–0.83). Including MRI-detected subclinical inflammation as an additional variable, the AUC increased to 0.87 (0.82–0.90). This study highlights the ability of integrating clinical symptoms, serology, and imaging to identify individuals at high risk for progressing to RA, which is critical to informing the design and conduct of future prevention trials.

MULTIMORBIDITY

Once RA develops, it frequently leads to the development of other diseases and, consequently, multimorbidity defined by the presence of multiple chronic conditions [20]. The relationship between RA and multimorbidity appears to be bi-directional, with multimorbidity also complicating RA treatment. In a multicenter prospective RA cohort, multimorbidity patterns of CVD, chronic pain syndromes, and mental health and substance use disorders were strongly associated with higher RA disease activity by 28-joint Disease Activity Scores (DAS28) and worse functional status over the disease course [21[■]]. A separate cohort study of 659 patients with incident RA in Olmsted County also found that multimorbidity independently predicted a higher risk of RA flares (OR 1.29; 95% CI 1.03–1.53) and lower odds of achieving remission [22[■]]. These data illustrate the potential importance of identifying and managing multimorbidity to optimize RA outcomes.

Perhaps the most concerning feature of multimorbidity in RA is its potential to mediate or exacerbate adverse RA-related health outcomes [20]. A recent population-based study analyzing avoidable hospitalizations found that patients with RA had significantly higher rates of potentially preventable hospitalizations compared to matched non-RA controls [23[■]]. These hospitalizations were due to ambulatory care-sensitive conditions such as pneumonia, heart failure, and diabetes complications, which if properly managed in the ambulatory setting may have prevented or reduced the need for hospitalization. These findings suggest that patients with RA, particularly those who are multimorbid, may not be receiving adequate ambulatory care and may require alternative care delivery models to prevent avoidable hospitalizations.

RHEUMATOID ARTHRITIS ASSOCIATED INTERSTITIAL LUNG DISEASE

ILD is among the most significant extra-articular manifestations of RA due to its dramatic impact on morbidity and mortality [24]. While ACR/CHEST released the first formal guidance on screening for RA-ILD, accurate risk models for the development of ILD in RA are lacking. A multicenter prospective cohort study of early RA patients (<2 years RA duration) who all underwent high-resolution computed tomography (CT) found 11% had RA-ILD [25[■]]. Age at least 60 years at RA diagnosis and moderate/high disease activity were strongly associated with RA-ILD. However, risk models based on clinical variables performed inconsistently, suggesting the need for improved RA-ILD risk models. In a large cross-sectional study of 2001 U.S. veterans with RA, peripheral biomarker signatures were derived using unsupervised machine learning to risk stratify RA-ILD, which outperformed models utilizing clinical risk factors alone [26[■]]. Biomarker themes of innate and allergic responses, autoantibodies, adipokines, alarmins, tissue remodeling, and neutrophil chemotaxis were significantly associated with RA-ILD. Utilizing a transcriptomic-approach to analyze gene expression of monocytes in RA-ILD, a separate study found that peripheral monocytes in patients with RA-ILD had increased expression of genes involved in inflammation, fibrosis, epigenetic modification, and macrophage activation [27[■]]. Together, these reports suggest that multiple pathways are involved in RA-ILD development, and utilizing biomarkers from these pathways may improve RA-ILD risk stratification. With effective risk models we will be better equipped to systemically identify RA-ILD and prevent delays in diagnostic tests and specialty care identified in a large claims-based analysis [28[■]].

CARDIOVASCULAR DISEASE IN RHEUMATOID ARTHRITIS

CVD represents another well established extra-articular manifestation of RA, which contributes to overall morbidity of RA. While atherosclerosis has been most widely studied in RA, recent studies have identified other CVD complications. A matched cohort study with robust adjustment for traditional CVD risk factors found that individuals with RA had a near two-fold increased risk of developing incident heart failure with preserved ejection fraction (HFpEF) compared to those without RA [29]. In contrast, the risk of heart failure with reduced ejection fraction (HFrEF) was not significantly increased in RA. Complementing these findings, a separate matched cohort study with 67850 patients with RA and 570933 controls investigated the risk and temporal trends of heart failure [30]. Between 2000 and 2019, RA was associated with increased risk of HFpEF (adjusted hazard ratio [aHR] 1.51, 95% CI 1.46–1.57), HFpEF-related deaths (2.05, 1.76–2.39), HFrEF (1.34, 1.30–1.38), and HFrEF-related death (1.45, 1.29–1.63). Over this period, there was no improvement observed in heart failure risk in patients with RA.

Valvular heart disease is a cardiac manifestation that may be underrecognized in RA. A cohort study of 73070 patients with RA matched to 639268 patients without RA found that RA was associated with an approximate 50% increased risk of aortic stenosis as well as an increased risk of aortic valve intervention (surgical or transthoracic aortic valve replacement) and aortic stenosis-related death [31]. These findings were confirmed in a separate cohort study of 6673 patients with RA matched with 486072 patients without RA [32]. In this study, RA was also found to be significantly associated with other valvular heart disease, aortic regurgitation and mitral regurgitation. Understanding the mechanisms linking RA with heart failure and valvular disease will be essential for developing strategies to reduce the frequency of these complications in RA.

CANCER

Patients with RA are at a higher risk of select cancers, most notably lymphoma and lung cancer, while concurrently at reduced risk of other cancer types such as colorectal and breast cancer with inconsistent patterns of risk reported for cervical and prostate cancer [33,34]. Whether differences in cancer screenings in RA underly some of these findings is not well understood. A recent retrospective, matched population-based cohort study of 1614 patients with RA and 1597 patients without RA evaluated cancer screening in patients with RA compared to the non-RA comparators [35]. RA was associated with

a decreased cervical cancer screening rate (aHR 0.83; 95% CI 0.72–0.96) while breast, prostate, and colorectal cancer screening rates were similar between RA and non-RA comparators. Use of low dose chest CT for lung cancer screening was not evaluated in this study. A separate study investigating low dose chest CT found that patients with RA were more likely to have a positive screen and incidentally detected parenchymal lung disease, though similar cancer rates, compared to matched non-RA patients [36].

Since the initial availability of biologics for RA, cancer risk related to their use has been, and continues to remain, a concern. Recent studies have suggested that initiation of biologic disease-modifying antirheumatic drugs (DMARDs), specifically tumor necrosis factor (TNF) inhibitors, after cancer treatment may not result in higher relapse rates [37]. Supporting this, a retrospective Danish cohort study with 720 patients with a history of RA and solid cancer in remission found that there was no increased risk of recurrence accompanying initiation of any biologic DMARD (hazard ratio 0.92, 95% CI 0.38–1.73), TNF inhibitors (1.10; 0.21–3.16), or rituximab (0.94, 0.32–2.11) when compared to conventional synthetic DMARDs [38]. Additionally, a study of the Surveillance, Epidemiology, and End Results Medicare-linked dataset found no significant increase in all cause or cancer-specific mortality among patients with early stage colorectal, lung or prostate cancer and RA who received TNF inhibitors within three years after their cancer diagnosis compared to those who received conventional DMARDs [39]. While these retrospective studies are prone to selection and confounding bias and do not prove safety, they do provide reassurance when biologics are clinically indicated and help support shared-decision making.

RHEUMATOID ARTHRITIS RELATED MORTALITY

It has long been recognized that patients with RA have excess mortality risk [40]. Recent evidence from a large cohort study of U.S. veterans with incident RA suggests that this excess mortality is still present; however, the mortality gap is narrowing [41]. Over the 17-year period that this study examined, patients with RA were found to have a 23% higher all-cause mortality risk compared to matched non-RA controls. Notably, patients diagnosed with RA between 2012 and 2017 had lower relative mortality risks than those diagnosed from 2000 to 2005, which may reflect improvements in RA management. Cardiovascular and pulmonary causes of death were the leading contributors, accounting for 70% of excess deaths. The improvement in RA-related mortality reported in this study has also been observed in other

studies, including the 2021 Global Burden of Disease Study [6]. The estimated age-standardized death rate was 0.47 (0.41–0.54) per 100 000 population, which represented a 23.8% decrease from 1990. These reassuring findings suggest that modern disease management strategies are improving survival, but to fully mitigate excess RA-related mortality, additional efforts are necessary.

CONCLUSION

Globally, the prevalence of RA appears to be rising; however, excess mortality risk related to RA appears to be improving [6,42^{*}]. It is encouraging that current treatment approaches seem to be improving long-term outcomes, though opportunities for further improvements clearly remain. With a goal of reducing RA burden, efforts will be needed to improve the management of extra-articular manifestations and multimorbidity in addition to refining models developed for pre-RA risk stratification and disease prevention.

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Conflicts of interest

B.R.E. research support and consulting from Boehringer-Ingelheim. T.R.M. has received prior research support from Horizon Therapeutics (Amgen) and has consulted for Horizon, Merck, UCB, and Olatec Therapeutics.

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- of special interest
- ■ of outstanding interest

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Comorbidities in idiopathic inflammatory myopathies: population-based evidence on risk subgroups and implications for delivery of care

Maria Emilia Romero Noboa, Irakli Tskhakaia and James S. Andrews

Purpose of review

Idiopathic inflammatory myopathies (IIMs) carry substantial extra-muscular comorbidities. The purpose of this review is to provide a focused synthesis of recent population-based data on the epidemiology of key comorbidities in IIMs: atherosclerotic cardiovascular disease (ASCVD), venous thromboembolism (VTE), psychiatric and neurocognitive disorders, and bone health.

Recent findings

IIM patients have approximately two-fold increased risk of ASCVD and of other cardiovascular events, like VTE. These risks likely result from several factors, including chronic systemic inflammation, physical inactivity, treatment side effects. Anti-HMGCR immune necrotizing inflammatory myopathy (IMNM), is a subtype of IIM that requires special consideration regarding dyslipidemia management, where statin alternatives are necessary. Furthermore, psychiatric and neurocognitive comorbidities are common, and likely under-recognized among IIM patients, and perhaps especially so in inclusion body myositis (IBM) patients. Finally, IIM patients have an increased risk of accelerated bone loss likely due to systemic inflammation, muscle damage and physical inactivity, and glucocorticoid exposure.

Summary

Cardiovascular care, psychiatric/neurocognitive disorders, and osteopenia/osteoporosis are highly prevalent and often underrecognized in IIMs. Effective management of these IIM-associated comorbidities requires a multidisciplinary, comprehensive care approach, and further work is needed to adapt existing risk-stratification and screening tools for the unique needs of IIMs patients.

Keywords

bone health, cardiovascular disease, idiopathic inflammatory myopathies, psychiatric conditions, venous thromboembolism

INTRODUCTION

Idiopathic inflammatory myopathies (IIMs) are a rare, with incidence estimates ranging from 0.2 to 2 per 100 000 person years and prevalence from 2 to 25 per 100 000 people [1]. IIMs are a heterogeneous group of diseases with varying clinical presentation, pathology, and response to treatment. IIM usually presents with symmetric proximal weakness, but other features can include arthritis, Raynaud's phenomenon, interstitial lung disease, and skin rashes (e.g. heliotrope rash, Gottron's sign). Classification of IIMs now includes several main subtypes: dermatomyositis, polymyositis, immune-mediated necrotizing myopathy (IMNM), antisynthetase syndrome (ASyS), sporadic inclusion body myositis (IBM), and overlap myositis. Each IIM subtype can be further characterized by auto-antibody profiles, organ involvement, and histopathology [2].

IIMs are associated with substantial risk of extra-muscular comorbidities, and this risk varies by IIM subtype. This review aims to provide a focused synthesis of population-based data on the epidemiology of specific, key comorbidities in IIMs: atherosclerotic cardiovascular disease (ASCVD), venous thromboembolism (VTE), psychiatric and neurocognitive disorders, and bone health.

Division of Clinical Immunology and Rheumatology, Department of Medicine, University of Alabama at Birmingham, Birmingham, Alabama, USA

Correspondence to James S. Andrews, MD, Division of Clinical Immunology and Rheumatology, Department of Medicine, University of Alabama at Birmingham, 1825 University Boulevard, Room 178F, Birmingham, AL 35233, USA. Tel: +1 205 934 9031; e-mail: jaandrews@uabmc.edu

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KEY POINTS

- IIM has an almost two-fold increased ASCVD risk compared to the general population. Risk may be greatest during the first year after diagnosis and among those receiving oral glucocorticoids.
- Anti-HMGCR-IMNM patients are likely at uniquely increased risk of sub-optimal dyslipidemia management, and should be considered for nonstatin lipid-lowering agents.
- IIM patients experience up to four times the risk of VTE compared to the general population, and the risk may be greatest during the first year after diagnosis and among APLA positive patients.
- Psychiatric and neurocognitive disorders, including depression, anxiety, and cognitive impairment, are highly prevalent yet underrecognized in IIM, and IBM patients may be particularly vulnerable.
- Osteopenia and osteoporosis occur in up to one-third of IIM patients, with fracture rates several-fold higher than in controls and frequent asymptomatic vertebral fractures.
- Systemic inflammation, glucocorticoid exposure, and immobility are major contributors to accelerated bone loss and fracture susceptibility in IIM.

CARDIOVASCULAR DISEASE IN IDIOPATHIC INFLAMMATORY MYOPATHY

Population-based risk

IIM patients have an almost two-fold increased ASCVD risk compared to the general population. ASCVD event (e.g. myocardial infarction) risk is likely greatest during the first year after IIM diagnosis [3,4]. In a retrospective cohort study using a national administrative electronic database of Israeli patients with dermatomyositis and polymyositis diagnosed between 2000 and 2016, incidence rates per 10000 person-years of ischemic heart disease (35.77 vs. 21.62), cerebrovascular accident (28.78 vs. 10.43), peripheral vascular disease (7.50 vs. 4.90), and overall ASCVD (66.11 vs. 33.29) were higher in dermatomyositis/polymyositis compared to the general population. Notably, having an overlap with another rheumatic condition [odds ratio (OR) 2.93], elevated C-reactive protein (CRP) (OR 1.03), antiphospholipid antibodies (APLA) (OR 2.33), and chronic oral glucocorticoids use (OR 1.06) were related to increased odds ratio of having an ASCVD event [4]. In a French retrospective observational cohort study, ASCVD risk is further increased by cardiac involvement at the time of IIM diagnosis [5]. A

retrospective cohort study of 35553 IIM patients in the TriNetx registry demonstrated that the overall median time to develop an ASCVD event was 12.5 years, and was 9.7 years in polymyositis compared to 14.3 years in dermatomyositis [6[■]]. Lastly, in a Swedish population-based study using data from 2002 to 2011, IIM patients had over three-fold increased mortality risk compared to that of the general population. Among 224 IIM patients who died from any cause, 28% of deaths were due to diseases of the circulatory system. The most common ASCVD causes of death were ischemic heart disease (39%), other forms of heart disease (28.6%), and cerebrovascular disease (13%) [7]. Thus, similar to patients with other systemic rheumatologic diseases, IIM patients experience increased risk of ASCVD compared to that of the general population, and this increased risk likely contributes to mortality risk for IIM patients.

Pathogenesis, contributors

Cardiovascular risk among IIM patients is likely multifactorial, resulting from various factors including chronic systemic inflammation and myocardial inflammation, accelerated coronary atherosclerosis, IIM disease-specific treatments (e.g. corticosteroid use), decreased physical activity and associated its comorbidities (e.g. hypertension and dyslipidemia) [8]. A systemic review of studies of dermatomyositis, polymyositis, and ASyS conducted from 1956 to 2022 identified hypertension, diabetes mellitus, smoking, and alcoholism as important risk factors for ASCVD events; despite the fact that diabetes mellitus, smoking, and alcoholism were less prevalent among IIM patients than the general population [9]. In a Swedish cross-sectional single-center study of 109 IIM patients and 20 age and sex-matched controls, the prevalence of traditional cardiovascular risk factors like high BMI, diabetes mellitus, and dyslipidemia, was greater among IIM patients than healthy controls. Further, ECG abnormalities and elevated NT-proBNP and cardiac troponin were also more prevalent in IIM patients than controls. Cardiac enzyme abnormalities were especially prevalent among IIM patients with previous cardiac involvement [10[■]]. Cardiac MRI (CMRI), too, demonstrates subclinical cardiac involvement in IIM patients. In a cross-sectional study of 55 IIM patients, 9% had T1 CMRI suggestive of abnormal inflammation and fibrosis. In addition, abnormal T2 CMRI findings were more common among non-IBM IIM than IBM patients and healthy controls, suggesting that myocardial edema and subclinical cardiac inflammation may vary by IIM subtype [11[■]].

Special considerations on dyslipidemia management in Idiopathic inflammatory myopathy and anti-HMGCR immune-mediated necrotizing myopathy

Despite their increased ASCVD risk, IIM patients face unique clinical challenges in dyslipidemia management compared to other rheumatologic diseases, and these challenges likely contribute to suboptimal secondary ASCVD prevention. In the above retrospective cohort analysis of over 35 000 IIM patients in the TriNetx registry, 40% had a diagnosis of hyperlipidemia. However, only 25% of those with hyperlipidemia were prescribed a lipid-lowering medication [6[¶]]. Concerns about muscle toxicity side effects of lipid-lowering medications likely contribute to the undertreatment of dyslipidemia in IIM patients. Anti-HMGCR-IMNM patients are likely at uniquely increased risk of sub-optimal dyslipidemia management given their IIM-subtype-specific contraindication to statin medications. This contraindication makes ASCVD risk management especially challenging in anti-HMGCR IMNM, and evaluation of statin alternatives is needed. The American College of Cardiology and American Heart Association suggest ezetimibe, PCSK9 inhibitors, and bempedoic acid as alternative lipid-lowering agents for patients with statin intolerance [12]. In a 2025 case series and literature review, PCSK9 inhibitors were associated with clinically significant LDL reductions without disease relapse or worsening IMNM over a mean follow-up of 18 months [13]. Similarly, an observational cohort of 11 patients with neuromuscular disorders (four with IMNM) found that both PCSK9 inhibitors were well tolerated without myopathy exacerbation in a median follow-up time of 14 months [14].

Delivery of care

ASCVD risk reduction in IIM is often suboptimal. For example, in a retrospective quality assessment study of 1321 IIM patients who were eligible for lipid-lowering therapy, only 53% of patients were on therapy. Also, only 10% of patients underwent coronary artery calcium scoring and/or measurement of carotid intima-media thickness to guide ASCVD risk management [15]. We argue that cardiovascular care in IIM requires a multidisciplinary approach with regular cardiovascular risk assessment.

VENOUS THROMBOEMBOLISM

Population-based risk

IIM carry an increased risk of VTE. In a review of dermatomyositis and polymyositis patients, the cumulative incidence of VTE was 4%, or 16.2 VTE per 1000

IIM patient-years [16]. In a 2018 meta-analysis that included six studies with 9045 patients with polymyositis/dermatomyositis, IIM was associated with an approximately four-fold increased risk of VTE compared to healthy controls [OR 4.31; 95% CI (2.55–7.29)]. VTE risk may be greater in dermatomyositis [OR 11.6; 95% CI (6.5–20.6)] compared to polymyositis [OR 6.9; 95% CI (4.1–11.5)]. Both DVT (OR 4.9; 95% CI: 1.4–17.1) and pulmonary embolism (OR 4.7; 95% CI: 2.2–10.3) were more likely in IIM patients than healthy controls [17]. More recently, a 2024 nationwide population-based study in Israel of 1557 dermatomyositis and polymyositis patients observed that the incidence rate of pulmonary embolism was significantly higher in dermatomyositis (OR 3.4) and polymyositis (OR 5.7) compared to matched controls [18]. Finally, a retrospective analysis of 1144 IIM patients in China observed that VTE occurred in 54% of patients from 6 months before IIM diagnosis onwards [19].

Pathogenesis, contributors

The pathogenesis of increased VTE risk in IIM is unknown. One hypothesized mechanism is that pathologic systemic inflammation leads to procoagulant mismatch. Under this hypothesis, procoagulant factor activity is increased and fibrinolysis activity is decreased. Further mechanistic studies are needed to help elucidate the increased VTE risk in IIM [16].

A retrospective longitudinal IIM cohort identified several VTE risk factors. Among 312 IIM patients, 12% developed an arterial or venous thrombotic event, of which 65% were a VTE. Disease duration less than 1 year was the strongest VTE risk factor, with an estimated incidence-rate ratio of 6.5 (95% CI 1.9–22.4). Other identified VTE risk factors were older age, previous thrombotic event, hypertension, and family history of premature myocardial infarction. Elevated erythrocyte sedimentation rate, but not CRP, was associated with VTE risk [20^{¶¶}].

In addition, the role of SSA/SSB, Ro52, and APLA in VTE risk in IIM has been studied. In a retrospective analysis of 94 patients with IIM, 35% were anti-SSA/SSB positive and 58% were anti-Ro52 positive. There was no difference in VTE risk between anti-SSA/SSB, anti-Ro52, and seronegative groups [21]. However, in the nationwide population-based study in Israel, a subgroup analysis observed that dermatomyositis/polymyositis APLA-positive, compared to APLA-negative, patients had significantly higher rates of pulmonary embolism (OR 19.7) [18].

Intravenous immunoglobulin and risk of venous thromboembolism

The ProDERM trial was a phase 3 placebo-controlled randomized controlled trial ($n=95$) that

demonstrated the efficacy of IVIg in dermatomyositis. Among safety outcomes assessed, the incidence of thromboembolic events was 1.54 per 100 patient-months when the trial protocol permitted a maximum infusion rate of 0.12 ml/kg/min. After a protocol amendment reducing the maximum permitted infusion rate to 0.04 ml/kg/min, the incidence decreased to 0.54 per 100 patient-months [22].

Interestingly, in a cohort study of 458 DM patients of whom 39 received IVIg (mean treatment duration = 33 months), there was no statistically significant difference in DM-associated VTE risk between of IVIg-exposed and -unexposed patients (3 vs. 6%, respectively). Notably, patients that experienced VTE typically had at least 1 additional underlying VTE risk factor, including malignant neoplasm [23]. Lastly, a retrospective observational cohort study of 312 IIM patients (including dermatomyositis, ASyS, IMNM, and IBM) found that VTE risk did not differ between IVIg-exposed (OR 1.2; 95% CI 0.5–2.7) and -unexposed patients (OR 0.6; 95% CI 0.2–1.3) [20^{***}].

Delivery of care

VTE prevention in IIM patients currently relies on traditional risk assessment tools and anticoagulation strategies from the general population. These approaches mirror clinical recommendations in other systemic autoimmune rheumatic diseases [24]. Special consideration in IIM should be given to the increased prevalence of malignancy and the association with VTE risk.

PSYCHIATRIC AND NEUROCOGNITIVE DISEASE

Population-based risks

Psychiatric and neurocognitive comorbidities are increasingly recognized as important determinants of adverse clinical outcomes in idiopathic inflammatory IIM. Depression, anxiety, fatigue, sleep disturbance, and cognitive dysfunction not only reduce quality of life; but they may also impair adherence to immunosuppressive therapy, increase healthcare utilization, and contribute to excess mortality. In a single-center retrospective cohort spanning 52 years and including 149 IIM patients, in whom over 90% developed irreversible damage or comorbidities, more than half experienced depression, though the true prevalence may be higher. Patients' median HAQ-DI score was 2.09, which indicates severe disability. These findings emphasize the likely need to incorporate mental-healthcare into comprehensive IIM management [25].

Survey data further highlight the psychosocial burden of myositis. In a web-based survey of 195 adults with dermatomyositis, 83% reported disease-related mental stress and 87% expressed dissatisfaction with available support. Patients reported fatigue and muscle weakness as the most distressing symptoms, underscoring the interaction between physical and psychological wellbeing [26^{*}]. A nationwide Taiwanese cohort of 3477 polymyositis/dermatomyositis patients and 13908 controls demonstrated a 62% higher incidence of psychiatric disorders (IRR 1.62) in IIM, with depression as the most common disorder (IRR 2.25). Notably, patients exhibited nearly double the suicide risk (IRR 1.99), paralleling patterns reported in other systemic rheumatic diseases [27^{***}]. Further, IIM patients have increased risk of fibromyalgia, and the presence of fibromyalgia is increasingly recognized as a risk factor for self-harm [27^{***},28,29]. High-dose corticosteroid exposure amplified the risk of psychiatric diagnosis, suggesting that IIM treatment may also contribute to psychiatric comorbidities in IIM patients [27^{***}].

IBM patients may be especially susceptible to psychiatric comorbidities. In an Australian cross-sectional survey of 101 IBM patients, 78% of participants scored in the moderate-to-severe depression range on the Patient Health Questionnaire-9 (PHQ-9), which represents a significantly greater burden than what is often reported in systemic lupus erythematosus and rheumatoid arthritis [30^{**},31,32]. Multivariable models demonstrated that each one-point increase in PHQ-9 score was associated with a 2.75-point decline in Personal Wellbeing Index scores (PWI), which assesses satisfaction across various life domains. In contrast, self-reported physical disability scores were not associated with wellbeing scores [30^{**}]. These findings suggest that psychiatric symptoms may have an equal, if not greater, impact on overall wellbeing than physical disability in IBM.

Pathogenesis, contributors

The mechanisms underlying these psychiatric comorbidities are multifactorial. Interferon (IFN) signaling – with type I IFN predominating in dermatomyositis and type II IFN in ASyS and IBM – is a hallmark of IIM biology and has been linked to depression and fatigue in other autoimmune conditions [33,34]. Mitochondrial dysfunction, oxidative and endoplasmic reticulum (ER) stress, and dysregulated cell-death pathways such as pyroptosis and necroptosis further contribute to low energy states, “brain fog,” and fatigue [35]. Behavioral and iatrogenic drivers also likely play a role. For example, corticosteroid-induced mood changes, chronic pain, sleep disruption, and inactivity often contribute to

psychiatric morbidity [27[■]]. Qualitative studies highlight how reduced exercise, fear of exacerbations, and logistical barriers fuel anxiety and depression. Conversely, facilitators such as education, individualized exercise programs, and positive social support improve participation and mental health [36[■]].

Delivery of care; mental health integration

Given the prevalence and impact of psychiatric and neurocognitive symptoms in IIM, we support incorporation of structured screening for adverse mental health symptoms into clinical care. Although, to our knowledge, few IIM-specific tools exist, clinicians could consider using the PHQ-9 for depression, GAD-7 for anxiety, and PROMIS measures for additional psychosocial domains. The PWI may provide added insight into wellbeing, particularly in IBM. Additional instruments such as sleep questionnaires, Montreal Cognitive Assessment (MoCA), and IBM-Functional Rating Scale (FRS) could help contextualize psychiatric symptoms. Future studies should evaluate whether integrating these assessments into routine care improves mental health and quality of life outcomes.

BONE HEALTH

Population-based risks

IIM patients may be a particular increased risk of bone health comorbidities compared to other rheumatic diseases. Muscle damage and atrophy, physical inactivity, and falls all likely contribute to accelerated bone loss and fracture risk. In a Hong Kong single-center, retrospective case-control study of 230 participants (IIM=65; nonrheumatological controls = 65; RA = 50; SLE = 50), reduced lumbar spine and femoral neck BMD on DXA was significantly more frequent in IIM than nonrheumatological controls (73.8 vs. 43.1%); and osteoporosis was nearly doubled (29.2 vs. 13.8%). In the same cohort, systemic inflammation, immobility, and glucocorticoid use were also identified as contributors to accelerated bone loss in IIM [36[■]]. Multicenter observational data suggest that gaps in bone health screening may contribute to adverse bone health outcomes in IIM. In a two-center UK/Hong Kong cohort study ($n=51$; UK = 20, HK = 31), most patients had a history of current or prior glucocorticoid use, yet only 50% (UK) and 35% (HK) had recently undergone a DXA to assess BMD. Among those who had undergone a DXA (UK = 20; HK = 11), 35% had osteopenia, 36% osteoporosis, and 25% (UK) and 64% (HK) met osteoporosis treatment thresholds

based on FRAX and BMD measures [37[■]]. Lastly, a 2024 review of 11 studies of osteoporosis and fracture risk in IIM noted an overall 13–33% prevalence of osteoporosis in IIM, a higher fracture rate in IIM compared to healthy controls (18 vs. 5%), a vertebral-fracture accrual rate of 26.2 per 100 patient-years when prior vertebral fracture is present in IIM, and that roughly half of IIM patients have asymptomatic vertebral fractures [38].

Pathogenesis, contributors

Elevated systemic inflammation, metabolic dysregulation, reduced mobility, and falls likely contribute to adverse bone health outcomes in IIM. A 2024 scoping review suggested that pro-inflammatory cytokine-driven inflammation may be mitigated by a Mediterranean diet rich in omega-3 fatty acids, vitamin D, and antioxidants, supporting further investigation of dietary interventions [39].

Delivery of care

A multifaceted approach is likely necessary to optimize bone health in IIM. Periodic fracture-risk assessments (FRAX ± BMD) may help identify at-risk patients, and clinicians also could consider evaluation for asymptomatic vertebral fractures. Calcium and vitamin D supplementation, antiosteoporotic therapy, minimization of glucocorticoid exposure, addressing fall risk through rehabilitation, and nutritional support could each help improve outcomes [37[■],38]. Bone health should be regarded as a core comorbidity domain in IIM, and future studies should evaluate benefits of integrating screening and prevention into routine myositis care [36[■]].

CONCLUSION

IIM is a diverse group of rare autoimmune conditions that lead to significant adverse health conditions including increased risk of cardiovascular conditions, VTE, psychiatric and neurocognitive disease, and osteoporosis and osteopenia. Specific risks vary by IIM subtype. Dyslipidemia undertreatment, in particular, contributes to increased ASCVD risk in IIM. IBM patients may be especially at risk for adverse psychiatric comorbidities. Finally, IIM patients experience accelerated bone loss and increased fracture risk. Future work should seek to establish care models that integrate screening and other preventive measures into routine clinical IIM care.

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Conflicts of interest

There are no conflicts of interest.

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In this case-control study of 65 IIM patients and age and sex-matched nonrheumatological controls, reduced bone mineral density and osteoporosis were more common in IIM than controls (74 vs. 43%, and 29 vs. 14%, respectively). Hip BMD was lowest in the IIM cohort (0.641 g/cm²) compared with RA (0.663 g/cm²) and SLE (0.708 g/cm²).

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Are lupus outcomes improving?

Sumatha Channapatna Suresh and Richard Furie

Purpose of review

Significant progress has been made in improving the outcomes of patients with systemic lupus erythematosus (SLE) largely through advances in drug discovery as well as enhancements in overall clinical management. This review provides insights into the basis for observed improvements in long-term outcomes through analyses of organ damage, mortality, healthcare utilization, and quality of life.

Recent findings

Patients with SLE in the first half of the twentieth century faced a 50% chance of surviving beyond 7 years. However, in modern times, age standardized mortality has greatly improved, and comorbidities that adversely affect outcomes are receiving far more attention than in prior eras.

Summary

It is a remarkable era for patients with SLE, with multiple targeted therapies transforming management. Yet, damage prevention still begins with early diagnosis and rapid attainment of remission. Treat to target strategies should be coupled with adjunctive measures, such as strict blood pressure control as well as cardiovascular and metabolic risk management.

Keywords

lupus nephritis, lupus outcomes, mortality trends, remission in systemic lupus erythematosus, systemic lupus erythematosus, systemic lupus erythematosus damage

INTRODUCTION

Systemic lupus erythematosus (SLE) is a complex autoimmune disease with heterogeneous presentations and outcomes that are influenced by race, sex, age at onset, organ involvement, and socioeconomic status. The global incidence is estimated to be approximately 5.14 per 100 000 person-years with a higher incidence noted in women (8.82 per 100 000 person years) [1]. Approximately 25–50% of patients develop lupus nephritis within 5 years of diagnosis, and 5–30% progress to end-stage kidney disease (ESKD) within 10 years of diagnosis [1,2].

The outlook for patients with SLE in the 1940s was quite poor. In fact, the 7-year survival was approximately 50% [3,4]. With the discovery of compound E (cortisone), and its administration to patients with rheumatic diseases, outcomes in SLE improved [5,6]. However, for those with lupus nephritis, the introductions of hemodialysis and ultimately kidney transplantation were major milestones, favorably impacting survival [7,8]. The second half of the 20th century and particularly the first quarter of the 21st century witnessed major advances in SLE treatment. Azathioprine, cyclophosphamide, mycophenolate, and methotrexate provided needed medications to subdue immune system hyperactivity so characteristic of SLE [9–16]. In 2011, a historic event occurred with the Food

and Drug Administration (FDA) approval of belimumab for patients with SLE, the first drug approved for SLE via the traditional route of two phase 3 trials [17,18]. Subsequently, belimumab was approved for lupus nephritis [19], voclosporin for lupus nephritis [20], and obinutuzumab for lupus nephritis [21[■]], whereas anifrolumab was approved for SLE [22,23].

Have these new therapeutic interventions as well as the greater awareness of the toxicities of glucocorticoids and other background therapies, the role of treating comorbid conditions, such as hypertension, hyperlipidemia, and osteoporosis, or earlier recognition and intervention affected outcomes? Intuition would definitively say yes. But how does one assess whether patients with SLE are doing better? Are they living longer? Has the rate of damage accrual been reduced? Is there less morbidity, healthcare utilization, or hospitalization? The answers to these questions are difficult to ascertain given the enormous heterogeneity of the patient population, as outcomes

Division of Rheumatology, Northwell, Great Neck, New York, USA

Correspondence to Richard Furie, MD, 865 Northern Boulevard Suite 302 Great Neck, NY 11021, USA. Tel: +1 516 708 2551; e-mail: rfurie@northwell.edu

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KEY POINTS

- Mortality in SLE has improved over the past two decades, but kidney disease, heart failure, and infection-related mortality continue to rise, particularly among women and racial minorities.
- LLDAS and DORIS remission are validated predictors of reduced damage, better quality of life and lower mortality.
- New therapeutics such as Belimumab, Voclosporin, Anifrolumab, and obinutuzumab have improved remission rates and slowed eGFR progression.
- Further improvement in lupus mortality and outcome will require early treat-to-target approach with aggressive cardiometabolic risk reduction.

are influenced by many elements, including race, sex, age of disease onset, organ involvement, socioeconomic status, and timely access to healthcare.

METHODS, CHALLENGES, AND PITFALLS OF MEASURING SYSTEMIC LUPUS ERYTHEMATOSUS OUTCOMES

Determining whether outcomes have improved over time is a rather challenging task, the analysis of which can be approached through the interrogation of several different metrics, including disease activity indices [e.g. Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), British Isles Lupus Assessment Group (BILAG)], SLE responder indices [e.g. Systemic Lupus Erythematosus Responder Index (SRI), BILAG-Based Composite Lupus Assessment (BICLA)], LN responder indices [Complete Renal Response (CRR), Partial Renal Response (PRR), Primary Efficacy Renal Response (PERR)], SLE disease activity states [Lupus Low Disease Activity State (LLDAS), Definition of Remission in SLE (DORIS)], patient-reported health-related quality of life (PROs) (e.g. SF-36), damage accrual [SLICC/ACR damage index (SDI)], or mortality.

Standardized responder indices, such as SRI or BICLA, first used in the belimumab and epratuzumab programs, respectively, remain in use in modern times [17,18,24,25]. Their counterparts in lupus nephritis clinical trials are CRR and PERR [19]. Thus, these responder indices potentially provide a mechanism with which to compare trial outcomes from different eras. However, as these measures are relatively new and just recently incorporated into SLE and lupus nephritis clinical trials, more time will be necessary to identify favorable trends in outcomes.

Furthermore, comparing trial results is fraught with major hurdles due to differences in designs, such as entry criteria, the composition of the cohort under study, and/or background medication rules.

With the recent introduction of DORIS (Definition of Remission in SLE) remission and Lupus Low Disease Activity State (LLDAS), the SLE community has yet additional outcome measures [26,27]. Whereas SRI and BICLA are grounded on relative changes in disease activity, LLDAS and DORIS are based on the attainment of an absolute level of disease activity. Furie *et al.* [28–30] have correlated SRI and BICLA achievement to metrics used in everyday practice, and similarly investigators have shown the numerous health benefits to LLDAS and DORIS attainment for LLDAS and DORIS. Longer times in LLDAS or remission correlated with less damage accrual and improved QOL to name just a few of the benefits [31,32,33*] (see Table 1).

Patient-reported health-related quality-of-life instruments, such as the SF-36, have been incorporated into most SLE clinical trials as secondary endpoints. Unfortunately, statistical significance has rarely been attained in clinical trials with PROs. Damage accrual utilizing the SLICC/ACR Damage Index is yet another strategy for assessing whether contemporary interventions have impacted outcomes in a favorable way. Lastly, absolute changes in mortality rates over time as well as age standardized mortality ratios afford the SLE community a method to examine trends in outcomes.

ARE OUTCOMES IN SYSTEMIC LUPUS ERYTHEMATOSUS IMPROVING?

Systemic lupus erythematosus responder indices

SRI responses in those patients administered belimumab 10 mg/kg in BLISS-52 and BLISS-76 were 58 and 43.2% with effect sizes of 14 and 9.7, respectively [17,18]. A decade later, the SRI response rate in those patients in TULIP-2 who were administered anifrolumab 300 mg was 55.5% with an effect size of 18.2 [23]. With this limited example, one easily sees the problem of using existing responder indices and clinical trial data to evaluate trends in outcomes.

Similar difficulties arise in attempting to compare outcomes in lupus nephritis trials – different designs, endpoints, and timing of endpoints. For example, the belimumab LN study, BLISS-LN, enrolled patients with pure class V on entry biopsy as well as background cyclophosphamide [19]. In a post hoc analysis of BLISS-LN where patients with pure class V or those on background cyclophosphamide were removed from analysis, improvement in

Table 1. Treat-to-target approach in real world registries

Study	Design	Follow-up (mean)	Key findings
LUMINA Cohort Ugarte-Gil <i>et al.</i> , 2019 [31]	Multiethnic cohort. 1993–2009 N: 483	6 years	Time in LLDAS correlated with better QoL on SF-36 and lower damage
SLICC Inception Cohort (2022) Ugarte-Gil <i>et al.</i> [41]	Observational study N: 1652	7.7 years	mLLDAS achieved in 5.6% of visits. Time spent in mLLDAS was associated with a 25–35% reduction in damage compared to those not in mLLDAS.
SLICC, Golder <i>et al.</i> , 2022 [32]	Prospective, APLC cohort observational study N: 1707	2.2 years	47.9% of visits met LLDAS; 78% patients met LLDAS at least once. LLDAS attainment protected against flare and damage accrual.
Greek cohort Pitsigavdaki <i>et al.</i> , 2024 [36 [¶]]	Retrospective observational N: 348	5 years	Sustained LLDAS for >6 months in 80%; DORIS remission in 41% resulted in reduced damage accrual (hazard ratio: 0.58) and severe flares (0.14). LLDAS without DORIS was also protective.
Kandane-Rathnayake <i>et al.</i> (APLC-HDAS study 2025) [33 [¶]]	Multinational prospective Cohort with SLE with high disease activity (SLEDAI >10) N: 1029	2.7 years	LLDAS achieved 71%; DORIS in 41%; flare reduction by 28% (hazard ratio: 0.72) and damage by 54% (hazard ratio: 0.22). Sustained LLDAS >12 months further reduced damage by 78%.
Kandane-Rathnayake <i>et al.</i> (APLC-mortality-2022) [34]	Multinational prospective longitudinal N: 4106	2.8 years	LLDAS attained at least once in 81% of survivors vs. 54% of decedents; 50% of time in LLDAS associated with 49% lower mortality (hazard ratio: 0.51). Steroid-free remission was protective (0.51)

LLDAS, Lupus Low Disease Activity State; QoL, quality of life.

CRR was observed compared to the native cohort [35[¶]]. Despite an attempt to standardize the study population and have it resembled other studies, sufficient differences remained. Thus, for the near future, using traditional lupus nephritis clinical trial outcomes driven by reductions in proteinuria will be unlikely measures to assess long-term changes in efficacy. Rather, in the future, histologic remission or urinary biomarkers correlated to long-term clinical outcomes will mitigate some of the existing challenges of determining whether response rates are increasing.

Definition of Remission in SLE and Lupus Low Disease Activity State remission

Recent therapeutic strategies and guidelines emphasize a treat-to-target approach, in order to decrease damage accrual and to ultimately reduce mortality [36[¶],37^{¶¶},38,39^{¶¶},40^{¶¶}]. Evidence from large observational cohorts, such as SLICC and LUMINA, shows that maintenance of LLDAS is strongly associated with lower SDI accrual and better QoL, with a clear dose–response relationship between time in LLDAS and reduced SDI accrual [31,33[¶],36[¶],41,42[¶]] (Table 1). While SLE trials have not included target metrics as primary end points, a growing number of post hoc analyses have been performed. Studies of the belimumab BLISS and anifrolumab TULIP trials suggest these targets are achievable and meaningful (Table 2).

Reflecting the clinical impacts of attainment of DORIS or LLDAS, the 2023 EULAR recommendations for the management of SLE as well as the 2025 American College of Rheumatology SLE treatment guidelines emphasize the treat-to-target approach using LLDAS or DORIS remission criteria [38,39^{¶¶},40^{¶¶}].

Although DORIS and LLDAS are less complex than SRI or BICLA, they remain dependent on SLEDAI and its inherent idiosyncrasies. Furthermore, comparing outcomes of DORIS or LLDAS from various studies is accompanied by some of the same obstacles as comparing outcomes using responder indices.

Outcomes in lupus nephritis

Complete renal remission (CRR) is generally defined as a reduction in proteinuria to less than 0.5 g/day and no significant worsening of kidney function (10–15%) from baseline within 6–12 months of initiation or escalation of therapy [47]. Proteinuria reduction 1 year into treatment is the most reliable noninvasive predictor of long-term kidney survival with a positive-predictive value of 94% when urinary protein creatinine ratio (UPCR) decreases to less than 0.7 g/day [48–51].

For decades, cyclophosphamide formed the cornerstone of induction therapy for proliferative lupus nephritis, with landmark studies in the 1980s–1990s

Table 2. Post hoc analyses of clinical trials evaluating Lupus Low Disease Activity State or Definition of Remission in SLE attainment

Study/year	Drug/duration	Design/intervention	Key findings
Morand <i>et al.</i> , 2023 [43]	Anifrolumab N: 819; 52 weeks	Early pooled post hoc analysis of TULIP-1 and TULIP-2	30% achieved LLDAS in anifrolumab group by week 52. OR: 1.8
Morand <i>et al.</i> , 2025 [44]	Anifrolumab-TULIP LTE N: 369; 4 years	Post hoc analysis of TULIP-LTE	LLDAS in anifrolumab group was 37 vs. 17% in placebo. DORIS remission achieved in 30% in anifrolumab group compared to 18% in the placebo group
Parodis <i>et al.</i> , 2024 [45]	Belimumab N: 3086; 52 weeks	Pooled post hoc analysis of five phase III trials (BLISS-52, BLISS-76, BLISS-NEA, BLISS-SC, EMBRACE)	LLDAS (17 vs. 10%) and DORIS (8 vs. 6%). Belimumab significantly attained remission targets and improved QoL.
Oon <i>et al.</i> [46]	Belimumab N: 167052 weeks	BLISS-52 and BLISS-76	LLDAS achieved in 12.5% (belimumab) vs. 5.8% (placebo) in BLISS-52 and 14.4% (belimumab) vs. 7.8% (placebo) in BLISS-76.

DORIS, Definition of Remission in SLE; LLDAS, Lupus Low Disease Activity State; QoL, quality of life.

demonstrating improvement in proteinuria and kidney function well before modern CRR definitions evolved [9]. In 1996, Gourley *et al.* [52] reported an 85% renal remission rate with the combination of cyclophosphamide and methylprednisolone in a small trial. In the early 2000s, mycophenolate mofetil (MMF) was shown to provide comparable efficacy to cyclophosphamide [14,15,11]. In the current era, combining mycophenolate and voclosporin increased the CRR rate to over 40% while maintaining favorable safety [20,53²²].

In the largest lupus nephritis study to date, BLISS-LN, belimumab added to standard of care outperformed standard of care alone [19]. A total of 224 patients with proliferative and/or membranous lupus nephritis received belimumab and standard of care, whereas 224 received placebo and standard of care. At week 104, significantly more patients (43%) in the belimumab group than in the placebo group (32%) achieved the primary endpoint, PERR. Attainment of CRR was also more frequent in the belimumab group (30 vs. 20%) (Table 3). Renal-related event or death, a key secondary endpoint that reflected adverse outcomes, was significantly less frequent among patients who received belimumab compared to those who received placebo. Belimumab reduced the risk of a sustained 30 or 40% decline in estimated glomerular filtration (eGFR) and was also shown to attenuate the annual rate of eGFR decline [54].

Following on the success of the NOBILITY LN clinical trial, obinutuzumab, a potent anti-CD20 monoclonal antibody, was put to the test in phase 3 REGENCY trial [21²²,55]. CRR at week 76 was attained in 46.4% of the study participants who received obinutuzumab and mycophenolate compared

to a rate of 33.1% among those who received placebo and mycophenolate. The ultimate in depletion of cells of B-cell lineage has been achieved with cell therapy with some small studies observing CRR rates over 90% [56²²,57²²].

Table 3 summarizes the results of key lupus nephritis trials. It must be emphasized that clinical trial results may not replicate real world kidney responses (Table 4). Lupus nephritis trial endpoints have been defined by reductions in proteinuria; histologic outcomes have largely been omitted. A major limitation of CRR is that it may not correlate with histological response. Repeat biopsy studies have shown 50% of patients meeting CRR still harbor active inflammation on kidney biopsy, while some in histologic remission still have proteinuria above the CRR threshold owing to chronic scarring [58]. A recent systematic review-based proposal favored biopsy-based definition of histologic remission for guiding treatment, as it correlated more strongly with long-term survival [59²²].

Damage accrual

Contributions to damage come from activity of the disease itself as well as medications, especially steroids, used to control disease activity. Damage accrual is associated with increased mortality in SLE [65]. Thus, evaluating rates of damage accrual through the decades is an opportunity to assess whether outcomes are improving. In a Spanish cohort (RELESSER registry), 20% of patients developed new damage within a year, mainly cerebrovascular or cardiovascular events, which continued beyond 5 years [66²²]. A meta-analysis demonstrated a 34% increased risk of death for each 1-point

Table 3. Response rates in lupus nephritis trials

Trial	Year	Design	CRR definition	CRR rate	References
Cyclophosphamide	1996	RCT – 5-year follow-up Cyc+ IV MP N: 81	<1 g proteinuria No doubling in creatinine <10 dysmorphic RBCs Prevention of dialysis	85%	Gourley <i>et al.</i> [52]
EURO LUPUS	2002	RCT High vs. Low dose Cyc N: 90	<1 g proteinuria No doubling in creatinine <10 dysmorphic RBCs prevention of dialysis	HR: 1.26 low vs. high dose	Houssiau <i>et al.</i> [12]
Mycophenolate mofetil (MMF)	2005	RCT – 24 weeks MMF vs. IV Cyc N: 370	Return to within 10% of normal baseline creatinine proteinuria and urine sediment	22% (MMF) vs. 5.8% (CYC)	Ginzler <i>et al.</i> [11]
AURORA-1	2021	Placebo-controlled RCT 1:1 - 52 weeks Voclosporin + MMF N: 357	UPCR <500 mg/day Stable renal function (eGFR >60 ml/min/1.73 m ²) No confirmed decrease in eGFR of >20% No administration of rescue medications	41% (voclosporin) vs. 23% (placebo)	Rovin <i>et al.</i> [20]
AURORA-2	2023	Longterm safety Voclosporin+MMF (N: 216)	UPCR <500 mg/day Stable renal function (eGFR >60 ml/min/1.73 m ²) No confirmed decrease in eGFR of >20% No administration of rescue medications	50% at 36 months; Confirmed sustained CRR and stable renal function over 3 years	Saxena <i>et al.</i> [53 ^{***}]
BLISS-LN	2020	RCT 104 weeks Belimumab + standard therapy N: 448	UPCR: <0.7 Without 20% worsening and eGFR > 60 ml/min/1.73 m ² No use of rescue therapy	30% (belimumab) vs. 20% (placebo)	Furie <i>et al.</i> [19]
REGENCY	2024	Placebo-controlled 52 weeks Obinutuzumab + standard therapy N: 271	UPCR <0.5 g/day eGFR at least 85% of baseline value No intercurrent events	46% (obinutuzumab) vs. 33% (placebo)	Furie <i>et al.</i> [21 ^{***}]

CRR, complete response rate; GFR, estimated glomerular filtration rate.

increase in SLICC Damage Index (SDI) [67]. Hydroxychloroquine use has been associated with lower rates of damage accrual, longer remission, and reduced cardiovascular risk in SLE [68[•],69].

In the biologic era, the development of organ damage appears to be somewhat modifiable. Damage accrual rates are not sufficiently high enough to evaluate differences in SDI during a 1-year study. However, long-term extension studies of biologics have provided adequate numbers of patient-years to evaluate SDI changes over time. In the belimumab long-term extensions of the BLISS-52 and BLISS-76 studies, all participants were able to receive belimumab; hence, there was no placebo group. Organ damage was evaluated every 48 weeks using the

SDI. At year 8, of patients in BLISS-52 and BLISS-76, respectively, there were mean changes of 0.2 and 0.4 from baseline SDI scores of 0.6 and 1.2. Without a comparator, the impact of these changes cannot be fully appreciated. Therefore, to compare rates of damage accrual between belimumab and standard of care, propensity score matched biologic naive patients enrolled in the University of Toronto longitudinal cohort served as the comparator group. Over 5 years, the mean SDI treatment difference was 0.453 in favor of those on belimumab compared to those on standard therapy. Patients treated with belimumab were 60% less likely to progress to higher SDI scores over any given year of follow-up, compared with standard therapy [70,71].

Table 4. Responses rates in lupus nephritis real world experience

Study/year	Design	Follow-up/ sample size	CRR definition	CRR rates
Zhang <i>et al.</i> , 2023, China [60]	Real-world retrospective and prospective cohorts comparing MMF vs. CYC induction in LN	12 months Class III–V LN N: 195	24 h urine protein <0.5 <10% change in baseline serum creatinine	72.8% (MMF) vs. 57.6% (Cyc) at 12 months
Izcovich <i>et al.</i> , 2025 [61]	Systematic review and network meta-analysis	12 months 37 RCTs N: 5450	UPCR <0.5–0.7 Stable eGFR RR: ratio of CRR probability vs. control	VCS+MMF RR: 1.9 BEL+MMF RR: 1.47 Obi+MMF RR: 1.43 CYC RR: 0.90 MMF+tacrolimus RR: 1.5 CRR plateau 45–60% with combination vs. 31% in MMF
O'Neill <i>et al.</i> , 2024 Enlight-LN registry from UK	Retrospective	6 months class III–V LN refractory or relapsing N: 12	No formal CRR defined PRR: >50% reduction in proteinuria and eGFR stability	40% achieved partial renal remission
Lin <i>et al.</i> , 2025 [62]	Retrospective	14 months N: 224	UPCR <0.5 eGFR >90 ml/min OR <10% decline	Earlier CRR in belimumab group
Gatto <i>et al.</i> , 2021 [63] BeRLiSS-LN study	Multicenter Italian cohort	22–36 months N: 91	UPCR ≤0.7 eGFR ≥60 ml/min/1.73 m ² without rescue therapy	38.4% achieved CRR 70% achieved PRR
Abdelkarim Aloub <i>et al.</i> , 2022 [64]	Retrospective single center on rituximab use in LN	6 months N: 40	CRR not explicitly defined Improvement via decrease in SLEDAI-2K, decrease in proteinuria and creatinine	90% had complete or partial response 5% were nonresponders

CRR, complete renal response; eGFR, estimated glomerular filtration rate; LN, lupus nephritis; MMF, mycophenolate mofetil; PRR, partial renal response; RR, relative risk; SLE, systemic lupus erythematosus.

Although the anifrolumab 3-year long term extension was placebo-controlled, attrition resulted in inadequate numbers of placebo-treated patients to perform an analysis of SDI accrual rates between anifrolumab-treated and placebo-treated patients. Therefore, a similar methodology as in the aforementioned study was utilized to compare SDI accrual rates in anifrolumab-treated patients in the long-term extension to the University of Toronto cohort [72]. Over a 4-year period, the mean change in SDI was 0.425 points lower in the anifrolumab-treated patients than in the Toronto cohort. Patients in the anifrolumab arm were 72% less likely to experience an increase in SDI over the 4 years.

SLE patients are at four times higher risk of developing irreversible kidney damage, and early

high-dose corticosteroid exposure increases damage accrual risk by 1.2 times [73,74]. Preservation of kidney function is the goal of therapy and is not only achieved through reductions in inflammatory activity in the kidney but by also controlling blood pressure, sodium intake, and proteinuria. The long duration of the double-blind period in the three pivotal trials that led to the approvals of belimumab, voclosporin, and obinutuzumab for lupus nephritis afforded an analysis of drug effects on eGFR. The slope of eGFR, assessed between weeks 24 and 104, demonstrated an annual rate of decline in eGFR to be less in the belimumab-treated group than in the placebo group (−2.12 vs. −5.72 ml/min/1.73 m²/year; $P=0.04$) [54]). The voclosporin 2-year extension study (AURORA 2) demonstrated an eGFR slope

of $-0.2\text{ml/min}/1.73\text{m}^2$ in the voclosporin group and $-5.4\text{ml/min}/1.73\text{m}^2$ in the control group [53[■]]. In phase II obinutuzumab LN trial (NOBILITY), obinutuzumab reduced the first eGFR decline of 30 or 40% by 80 and 91%, respectively. Patients receiving obinutuzumab had a significantly slower decline in eGFR from week 12 through week 104 than patients receiving placebo, with an annualized eGFR slope advantage of $4.1\text{ml/min}/1.73\text{m}^2/\text{year}$ [75[■]]. In the phase III LN trial, REGENCY, the change in eGFR between baseline and week 76 favored obinutuzumab but did not reach statistical significance (2.31 vs. $-1.54\text{ml/min}/1.73\text{m}^2$) [21[■]]. eGFR data at week 104 is eagerly awaited.

Two real-world studies and an emulated clinical trial found that SGLT2 inhibitors improved kidney outcomes and significantly lowered the risk of lupus nephritis, dialysis, kidney transplant, heart failure, and all-cause mortality compared to SGLT2 nonusers [76[■],77[■],78[■]]. Modifiable contributors to damage accrual include achieving tight disease control with immunosuppressives and/or biologics aiming for remission targets, such as LLDAS and DORIS in SLE, and CRR in lupus nephritis, initiating hydroxychloroquine, and minimizing steroid exposure.

Mortality trends

National Inpatient Sample (NIS) and population level datasets provide valuable insights into SLE mortality. NIS captures inpatient deaths, reflecting in-hospital survival among more severely ill patients but is biased whereas the CDC Wide-ranging Online Data for Epidemiologic Research (CDC-WONDER) captures population-wide outcomes in real world settings.

Analysis of NIS data (1998–2002) yielded an inpatient mortality of 3.1%, which declined to 2.2% and then 1.5% in consecutive analyses spanning 2006–2016. The highest burden was noted among women, Hispanic and black populations, and those with low socioeconomic status [79,80]. Infections were the leading cause of inpatient deaths, three-fold higher than the general population [81].

Population-level data showed similar overall declines in SLE-related mortality with persistent disparities [82]. Daoud *et al.* [83[■]] in 1999–2020, and Patel *et al.* [84[■]] in 1999–2022 confirmed an overall declining age-adjusted mortality rate (AAMR) 1 to 0.79 per 100 000 from 1999 to 2019, followed by a 21% rise during the COVID-19 pandemic (2019–2021). Huo *et al.* reported that while age-standardized mortality ratio (ASMR) declined over last 20 years, SLE deaths with heart failure increased, underscoring cardiovascular vulnerability despite immunosuppressive therapy [85[■]]. CDC-Wonder analyses (1999–2020) found rising CKD-related AAMR from 0.076 to 0.104 per 100 000, though CKD related to lupus nephritis could not be distinguished from other causes [86[■]]. Within the ESKD subset of patients with lupus nephritis, all-cause mortality improved substantially between 1995 and 2014, as shown in the United States Renal Data System (USRDS) registry, with further survival gains among those receiving kidney transplants [8,87]. Preliminary data from ACR abstracts analyzing lupus nephritis-specific mortality from CDC-WONDER data set suggested a 26% decline in mortality from 1999 to 2019 but increased from 2015 to 2019 [88].

In summary (see Table 5), overall mortality due to SLE has improved over the past two decades,

Table 5. Mortality in systemic lupus erythematosus

Study	Dataset and years	Mortality measure	Trend	Key findings
Daoud <i>et al.</i> [83 [■]], 2025	CDC-WONDER 1999–2020	AAMR per million	Decrease in mortality 4.67–3.29 per million	Higher mortality noted in Black women, greatest burden in southern states
Patel <i>et al.</i> [84 [■]], 2025	CDC-WONDER 1999–2022	AAMR per 100 000	AAMR decreased 1999–2019: decrease from 1 to 0.79, then 21% increase to 0.96 in 2021 (AAPC: – 1.23)	Persistent high mortality in Black race and southern region of United States
Qadri <i>et al.</i> [86 [■]], 2025	CDC-WONDER 1999–2020 Chronic renal failure deaths in SLE	Age-adjusted CKD mortality AAMR per 100 000	Overall AAMR in CKD in SLE increased from 0.076 to 0.104. (APC: 15.06)	Significant rise from 2018 to 2020. Disproportionate impact on Black women
Huo <i>et al.</i> [85 [■]], 2025	CDC-WONDER 1999–2020 SLE deaths related to heart failure	Age standardized mortality rate	Overall ASMR decreased. SLE combined with heart failure deaths increased by 8.2%	Increased mortality in women

SLE, systemic lupus erythematosus.

reflecting early disease recognition, increased awareness, and therapeutic advances. However, organ-specific deaths from CKD, heart failure, and infection continue to rise particularly among women, Hispanic, and black patients and those of low socioeconomic status [79,82,85,86,88].

CONCLUSION

There is no doubt that since the first half of the 1900s, SLE outcomes have improved as evidenced by favorable trends in mortality. In the modern era, the SLE community has witnessed incremental gains in clinical trial outcomes. Although clinical trial endpoints focus on reductions in disease activity, it has long been recognized that disease activity is correlated to damage accrual and mortality. Adoption of treat-to-target strategies is widely recommended, as attainment of either DORIS or LLDAS has been associated with many long-term health benefits. The treatment landscape is expanding beyond B-cell depletion to include more agents that target the innate immune system (TLR7/8, complement), interferon signaling (JAK and TYK inhibitors), and restoring T reg/Th2 balance through low-dose IL2. Emerging cellular therapies, including CAR-T and T-cell engagers, offer the possibility of significant immune modulation and durable remission. As development of SLE immunotherapies continues to progress, equal emphasis on cardiovascular risk reduction, damage prevention, and management of chronic kidney disease will be essential to achieve meaningful long-term improvement in outcomes.

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Conflicts of interest

There are no conflicts of interest.

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How common is vasculitis: what do population-based data tell us?

Anu Pandit, Brian D. Jaros and Anisha B. Dua

Purpose of review

The systemic vasculitides are a group of diseases characterized by vascular inflammation, with varying features and frequencies across the globe. Our review aims to highlight recent epidemiologic data and key findings on these disorders that have been published over the past 18 months.

Recent findings

Advances in imaging techniques, increased disease awareness, and improved diagnostic and therapeutic management has altered the demographic and prognostic landscape of the systemic vasculitides. Updated data driven classification criteria have allowed for better characterization and epidemiologic research in these disease states. The ethno-geographic variability and influence of genetic and environmental factors in the pathogenesis of systemic vasculitis is further highlighted by recent epidemiologic studies, with new trends in certain populations postulated to be secondary to increases in genetic diversity.

Summary

Recent data highlights the geographic, ethnic, and seasonal variability of the systemic vasculitides. The use of advanced imaging techniques and updated classification systems, coupled with new epidemiologic studies from underrepresented populations, shed further light on the burden and characteristics of these diseases globally.

Keywords

antineutrophil cytoplasmic antibody vasculitis, epidemiology, giant cell arteritis, vasculitis

INTRODUCTION

The systemic vasculitides are a group of rare, heterogeneous disorders characterized by inflammation of blood vessel walls. Classification is often based on the size of the predominantly affected vessels – large, medium, small, or variable – according to the revised 2012 Chapel Hill Consensus Conference nomenclature [1]. In this review, we will summarize recent key developments in the incidence, prevalence, morbidity, mortality, environmental/infectious triggers, screening practices, as well as geographic and ethnic variation of the vasculitides.

LARGE VESSEL VASCULITIS

Giant cell arteritis

The reported incidence of giant cell arteritis (GCA) has historically been highest in Northern European countries – particularly Scandinavia – with occurrence typically peaking in the seventh decade of life [2]. While disease incidence in these populations has been well documented in the literature, recent studies have highlighted the cardiovascular impact of GCA. An

analysis from a cohort of 1134 Swedish individuals diagnosed with biopsy-confirmed GCA between 1998–2016 characterized the rate and relative risk of myocardial infarction (MI) in patients with GCA compared to the general population. The authors found an MI incidence rate of 12.8 per 1000 person-years [95% confidence interval (CI) 10.3–15.3] in the GCA cohort and an incident rate ratio of 1.29 (95% CI 1.05–1.59) when considering MI that occurred after GCA diagnosis compared to the general population [3]. A systematic review and meta-analysis of 17 studies evaluating the relationship between GCA and cardiovascular risk factors (type 2 diabetes, hypertension, dyslipidemia, smoking, overweight/obesity, and history of cardiovascular disease) found a significant positive association between a history of cardiovascular disease and risk of

Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA

Correspondence to Anu Pandit, 675 North St. Clair Street, 14th Floor, Suite 100. Chicago, IL 60611, USA. Tel: +1 312 695 8628; e-mail: anu.pandit@nm.org

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KEY POINTS

- Recent data further supports an elevated risk of cardiovascular disease in those with giant cell arteritis.
- Variable vessel vasculitis is estimated to be a presenting manifestation of VEXAS syndrome in up to 25% of patients and supports consideration of genetic screening for UBA1 mutation in males >50 years of age with atypical vasculitic presentations.
- New epidemiologic reports of Kawasaki Disease in Africa, Takayasu Arteritis in Brazil, and Giant Cell Arteritis in Hispanic American populations offer further insights into characteristics and burden of vasculitic disease worldwide.
- The collaborative data reuse project FAIRVASC identified five distinct clinical clusters of ANCA vasculitis, supporting the use of data-driven subtype classification to enhance predictive prognostic models of overall survival and renal outcomes.
- The first epidemiologic assessment of Behçet's Disease in Oslo, Norway identified a rising prevalence of disease from 1999 to 2021, postulated to be related to increased genetic diversification of a previously largely homogenous population.

GCA [odds ratio (OR)=1.28, 95% CI 1.18–1.38] [4]. Further studies are needed to better characterize the underlying pathogenic mechanisms behind these associations.

As the most common form of large vessel vasculitis, GCA frequently leads to inflammation of the aorta and its major branches. A large, retrospective cohort study of patients diagnosed with PMR and GCA from 2000–2024 within the U.S.-based TriNetX database noted the incidence rate of any aortic complication to be 11.69 per 1000 person-years in patients with GCA, compared to 6.78 for patients with PMR (without features of GCA) and 5.09 for the general population [5]. The risk for patients with PMR who later developed GCA was similar to that of patients initially diagnosed with GCA (adjusted hazard ratio 0.85, 95% CI 0.60–1.19). Increased utilization of vascular imaging for the diagnosis and monitoring of large-vessel vasculitis has led to heightened awareness of subclinical GCA in a subset of patients with clinically isolated PMR [6], and has sparked ongoing debate about the risks and benefits of pursuing universal, large vessel screening imaging in PMR patients. Given similar incidence rates of aortic complications between the PMR cohort and the general population, the aforementioned study [5] did not support utilization of routine screening imaging for PMR.

Despite advances in PET technology and previously demonstrated efficacy in diagnosing GCA [8,9]

a recent study in Australia showed a sensitivity of 50% in patients who underwent PET scan for diagnosis when compared to a temporal artery biopsy (TAB) (used as a diagnostic anchor in the same patients) and 41% when compared to clinical diagnosis at 6 months as the diagnostic anchor [7]. The sensitivity of PET/CT as a diagnostic tool in this study was lower than previously reported in the literature [8,9]. Limitations of the study included a small sample size, delayed access to PET/CT (median duration of 11 days of glucocorticoid therapy prior to obtaining PET/CT scan), differences in radiographic interpretation, and subjectivity of clinical evaluation.

As diagnostic modalities for GCA have advanced and become more accessible, recent epidemiologic studies have been undertaken in historically less represented countries allowing for a more comprehensive understanding of disease burden globally. Sun, *et al.* explored rates of GCA in Chinese residents of Shanghai descent >50 years of age and identified a period prevalence of 2.73 cases per 100 000 persons, with mean annual incidence of 1.91 cases per 100 000 persons between 2011 and 2020 [10]. As described in other epidemiologic studies in the literature [11], subgroup analysis revealed an overall lower incidence of GCA in the Asian Shanghaiese population compared to European countries, postulated to be reflective of both variations in genetic susceptibility and differences in diagnostic methods and healthcare tracking systems [10]. In the largest epidemiologic study of GCA in residents of Aotearoa New Zealand, van Dantzig *et al.* noted a mean annual incidence of 14.7 per 100 000 people >50 years of age (95% CI 12.7–16.6), with most cases (93.9%, 201/214) seen in patients of European descent. Their reported incidence of GCA was comparable to prior studies and stable over time from 2014 to 2022 [12]. A retrospective cohort study analyzed the incidence and demographic features of GCA patients diagnosed from 2007 to 2019 at an academic center in Jordan, noting 19 patients with biopsy-proven disease and 41 patients with negative biopsies who were diagnosed clinically, with a mean age of 67.3 (\pm 9.5) years at time of diagnosis [13]. They additionally performed a comprehensive review of all published data on GCA from the listed Arab countries (Algeria, Bahrain, Comoros, Djibouti, Egypt, Iraq, Jordan, Kuwait, Lebanon, Libya, Mauritania, Morocco, Oman, Palestine, Qatar, Saudi Arabia, Somalia, Sudan, Syria, Tunisia, the United Arab Emirates, and Yemen), which yielded only 20 manuscripts (from Saudi Arabia, Lebanon, Egypt, Tunisia, Jordan, Morocco, Bahrain, UAE, and Kuwait), further highlighting both a relatively lower incidence of GCA and dearth of GCA-focused epidemiologic data in populations from this region. In the United States, a single center study sought to compare the

epidemiology and clinical characteristics of GCA between Caucasian and Hispanic patients in southern California – identifying 53 patients (34 Caucasian and 19 Hispanic) [14^{*}]. A higher proportion of Caucasian patients reported visual symptoms and temporal artery pain as initial clinical manifestations compared to headache and jaw claudication in the Hispanic cohort; Caucasians were more likely to relapse compared with Hispanics (65% versus 42%), though the Hispanic cohort tended to relapse earlier (within 0–3 months, 21% of Hispanics versus only 0.6% of the Caucasian cohort). A component of these findings may be attributable to culturally unique healthcare utilization practices and differences in symptomatic description and/or linguistic barriers.

Takayasu arteritis

Although GCA and Takayasu Arteritis (TAK) are both large vessel vasculitides, key epidemiologic differences between diseases have been noted. While the incidence of GCA is highest in Western countries [11], Takayasu's has been reported most frequently in young women of Asian descent and was first noted in Japan [10]. A recent study extracted data from autopsy-confirmed cases of Takayasu's in Japan over a period of three decades (1991–2000, 2001–2010, and 2011–2020), offering insights into epidemiologic trends over time. From the 322 cases evaluated, they noted that while age at onset of disease remained stable, there was a progressive increase in the mean age at time of autopsy (58.5 ± 15.1 years in from 1991–2000 to 66.9 ± 15.3 years in 2011–2020), suggesting an improvement in long-term prognosis [15].

A recent retrospective cohort study from a large Brazilian tertiary center including 203 patients with Takayasu's aimed to better characterize demographics from this region, which has been historically underrepresented in epidemiologic studies in Takayasu's [16]. They noted a mean age at diagnosis of 28 years, with a female predominance. A prior population-based prevalence study of TAK (the only one published to date in Brazil) by Vieira *et al.* from 2023 [17] noted a prevalence rate of 16.9 cases per million but was limited to participants from centers in Rio de Janeiro. Wider population-based studies are needed to accurately capture the burden of disease in this region.

MEDIUM VESSEL VASCULITIS

Kawasaki disease

Kawasaki disease is a medium-vessel vasculitis characterized by persistent fever and a constellation of mucocutaneous and systemic findings, typically affecting children in the first decade of life. Commonly

involving the coronary arteries, it is the leading cause of acquired heart disease in children in developed countries [18].

Since its first reported incidence in Japan in a 1967 case series [19], occurrences of Kawasaki disease have been described globally. In the most comprehensive systematic review on worldwide incidence of Kawasaki to date, the highest incidence (ranging between 50 and >200 per 100 000 children <5 years old) was noted in Japan, Korea, Taiwan, and other regions with large populations of Asian and Pacific Islander descent [18]. A recent retrospective population-based cohort study from the greater Auckland region of New Zealand between 2017 and 2021 noted a disease incidence of 20.4 (95% CI 17.0 to 23.9) cases per 100 000 for children <5 years of age [20], postulated to be related to lower rates of disease incidence in the region during the Covid-19 pandemic, a phenomenon interestingly noted in other populations around the world [21–24]. The first epidemiologic study documenting demographic features of Kawasaki disease in Kenya – and one of the most comprehensive reviews of published data from sub-Saharan Africa – identified 23 inpatients with a discharge diagnosis of Kawasaki disease from two pediatric hospitals in Nairobi over two discrete five-year periods, noting differences such as lower rates of disease-related conjunctivitis compared to studies from North America as well as a longer duration of fever, which was suspected to be related to delayed patient presentation from less disease awareness in the region [25^{*}].

The pathogenesis of Kawasaki disease is not fully understood but is suspected to be a systemic inflammatory response to a variety of environmental, genetic, and infectious triggers. A nationwide population-based study from Taiwan evaluating correlations between disease incidence and viral trends in the region noted a significant correlation between rates of Kawasaki with respiratory and enteric viral activity in infants under one year of age (the age group with highest annual incidence). While there was an overall increase in incidence in patients under 18 years of age (11.78 per 100 000 person-years in 2001 to 22.40 per 100 000 person-years in 2020), there was no association between disease incidence and viral infections in those over one year of age. Multiple studies have described a seasonal association with Kawasaki disease (highest incidence of flares in the Winter/Spring seasons in Northern Hemisphere extra-tropical countries such as the United States, as well as in Japan and Korea; and higher incidence of flares in the Summer/Fall seasons in Taiwan) which was supported by data from this Taiwanese study, and postulated to be related to seasonal variations in viral trends [26]. Recent data has also supported disease association with premature birth [27], and has provided insights

into disease sequelae, such as increased rates of allergic disease [28] and subsequent autoimmune diseases [29] following flares of Kawasaki. The underlying pathogenic mechanism for these phenomena remains unclear, and further studies are needed to better understand these associations.

VARIABLE VESSEL VASCULITIS

The variable vessel vasculitides involve blood vessels of any size and type, without a predominant preference for a specific vessel caliber [1].

Vacuoles, E1-ubiquitin-activating enzyme, X-linked, autoinflammatory, somatic

First described in 2020, VEXAS (vacuoles, E1-ubiquitin-activating enzyme, X-linked, autoinflammatory, somatic) syndrome is an autoinflammatory disorder characterized by an array of rheumatologic and hematologic manifestations secondary to a somatic mutation in the UBA1 gene [30]. Mimicking many other rheumatologic conditions, its prevalence has been estimated to be around 1 in 4269 men and 1 in 26 238 women over 50 years of age [31]. A recent study found that in roughly 25 percentage of patients, VEXAS manifests as a variable vessel vasculitis, with cutaneous small vessels and cutaneous medium vessels being predominantly affected [32^{***}]. Results of this study support the consideration of VEXAS screening in certain populations, particularly males >50 years of age with atypical vasculitic presentations.

Behçet's disease

Behçet's disease is a chronic, relapsing, multisystem inflammatory disorder characterized by recurrent oral aphthous and genital ulcers, cutaneous lesions (such as erythema nodosum and pseudofolliculitis), ocular

involvement (most commonly uveitis), and elevated risk of thrombosis. Affecting both arteries and veins of any size, it has historically been most prevalent in populations along the ancient Silk Road – particularly Turkey – but has a global distribution [33]. A population-based analysis from Oslo, Norway investigated the incidence and prevalence of Behçet's from 1999 to 2021 [34^{***}] and noted a steadily increasing prevalence of disease from 1999 (2.19 cases per 100 000 people) to 2021 (7.14 cases per 100 000 people), suspected to be related to increased genetic diversification of the population over the two decades of the study. Prevalence of Behçet's was found to be lower in those of Norwegian descent compared to non-Norwegians (57% of included cases) in the region.

SMALL VESSEL VASCULITIS

Antineutrophil cytoplasmic antibody-associated vasculitis

The antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are characterized by necrotizing inflammation of the small to medium sized vessels. The three subtypes include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA), with distinct clinical and histopathologic findings. However, there remains ongoing discussion regarding further subclassification of ANCA vasculitis. Utilizing data from 3868 ANCA vasculitis patients (diagnosed between 1966 and 2023) across six registries, the collaborative data reuse project FAIRVASC (Findable, Accessible, Interoperable, Reusable, Vasculitis) identified five disease clusters (Fig. 1), each with a distinct phenotype, biochemical presentation, and disease outcome [35^{***}]. Three clusters were defined by renal involvement and included a severe renal cluster with high

Disease Cluster	MPO	PR ₃	CRP	Renal Disease	Extra-renal disease	Other
SK	X	X	high	XX (high creatinine)		
MPO-K	X			X	limited	
PR ₃ K		X		X	severe	
IMS		X				Inflammatory multisystem
YR			low			ENT involvement young

FIGURE 1. ANCA associated vasculitis disease clusters. *Clusters: SK, severe kidney; MPO-K, myeloperoxidase kidney; PR₃K, proteinase 3 kidney; IMS, inflammatory multisystem.

serum C-reactive protein (CRP), high serum creatinine, and variable ANCA specificity; an MPO-positive renal-involvement cluster with limited extra-renal disease; and a PR3-positive renal-involvement cluster with widespread extra-renal disease. The remaining two clusters were defined by lack of renal involvement and included a predominantly PR3-positive cluster with inflammatory multisystem disease and a cluster of younger patients with predominantly ENT disease and lower serum CRP. The recognition of clusters with distinct trajectories (e.g., severe kidney disease, multisystem inflammation, or ENT-predominant disease) may guide intensity and choice of immunosuppression, monitoring strategies, and patient counseling.

Recent epidemiologic studies describe the burden of ANCA vasculitis around the world. A study in the Native and American Indian populations of Alaska noted a high pooled prevalence of AAV (340 per million adults, 95% CI 230–488), considerably higher than the estimated global pooled prevalence (198 per million adults, 95% CI 187–210) [36] with the most common subtype being GPA (244 per million adults, 95% CI 148–380), a trend towards younger age at presentation, and more clinically severe disease compared to other populations [37]. The first epidemiologic study of GPA in the region, a central Anatolian retrospective cohort study involving 75 adults <65 years of age with GPA revealed seasonal disease variability, with peaks in disease onset in March, November, and April and flares occurring most commonly in the fall [38]. Although seasonal contribution to disease incidence in AAV has been a subject of considerable interest, other reports in the literature have demonstrated varied and inconsistent results.

Within Europe, a study from Southern France estimated the pooled prevalence of AAV to be 103 per million adults >15 years of age (95%CI 84–125) in 2018, higher than prior reports. Prevalence of MPA was also higher in those of non-European descent compared to Europeans in the region [39]. A recent study in Norfolk, United Kingdom noted a steadily increasing incidence of GPA and MPA – but not EGPA – over time since 1988, with the most recent annual incidence of 34.3 per million adults [40]. Data from a recent Swedish study noted a stable annual incidence of GPA, but a significantly increased period prevalence from 2006–2010 (18.7 per 100 000; 95% CI 17.8–19.1) to 2016–2019 (23.9 per 100 000; 95% CI 22.8–25.0), likely secondary to improved prognostic outcomes from advances in diagnostic and therapeutic modalities [41]. A recent Spanish retrospective longitudinal analysis of AAV-related hospital admissions from 2016 to 2022 [42] described significant regional variability between

incidence of AAV, particularly between Northern and Southern Spain, reaffirming prior studies [43]. In contrast to other parts of southern Europe where MPA is more common, there was a higher prevalence of GPA than MPA in Spain. This study also noted a decline in the relative incidence of AAV hospitalizations from 2016 to 2022, possibly related to improved outpatient management practices.

There is limited data on the burden of AAV in populations of Asian descent [36]. A recent study from China noted a high relative incidence of MPO positivity (60–70%) among patients with vasculitis, even those with GPA [44]. A rarer subset of ANCA vasculitis, MPO positive GPA tends towards a milder disease course and improved renal prognosis compared to PR3 positive GPA. With results consistent with other epidemiologic studies of AAV from the country, their findings further highlight significant ethnic and clinicopathologic variability between ANCA subtypes regionally [45]. A nationwide population-based study from South Korea identified patients with GPA and MPA in both the Korean National Health Insurance Service database and the Rare Intractable Disease registry for the entire Korean population [46]. Between 2010 and 2018, they noted an increasing incidence of MPA over time, with no significant change in the incidence of GPA. Studies from Japan have demonstrated an increasing prevalence of EGPA. One study noted an increase from 4.2 per million people in 2005 to 38 cases per million people in 2017, with further increase to 58.6 per million people in 2020 in a more recent study [47,48]. Since 2018, there has been an overall decrease in proportion of patients on prednisolone-equivalent steroid doses >10mg daily, number of disease relapses, and rates of EGPA-related hospitalizations. The trend towards increased prevalence, as well as lower steroid usage and decreased complication rate, is likely reflective of both increased disease awareness and therapeutic advancements – such as the approval of interleukin-5 inhibitor mepolizumab for EGPA in Japan in 2018.

Multiple factors have been theorized to contribute to the development of ANCA vasculitis. In an editorial [49] analyzing results of a recent epidemiologic study on AAV from Southern France [39], the role of genetic predisposition was posited as being a significant contributing factor to higher rates of AAV noted in certain populations – particularly those of North African descent – within the region, considering similar environmental exposures to those of European descent. Only 31 patients of non-European origin were included in the original study, which limits data interpretation. Further data is needed to more accurately capture the role of genetic factors in the development of these diseases.

The relationship between ANCA vasculitis and cardiovascular disease (CVD) is a topic of significant research, with recent studies evaluating the risk of cardiovascular disease prior to diagnosis of vasculitis [50], as well as risk factors for CVD within the ANCA vasculitis patient population [51]. A population-based cohort study from Sweden investigated the incidence rate and predictors of myocardial infarction (MI) in patients with AAV, noting a higher incidence of MI in AAV patients compared to those without the disease and highest incidence in the three months following AAV diagnosis. Age at time of diagnosis was an independent predictor of risk, with an incidence rate of 0.2 (95% CI 0–0.1) per 100 person-years in those <50 years of age and 5.1 (95% CI 2.8–9.2) in those ≥80 years of age [52].

CONCLUSION

Recent epidemiologic data investigating the systemic vasculitides has expanded our understanding of these disorders, and sheds further light on their significant geographic and ethnic variations in incidence, prevalence, and clinical phenotype. Methodologic study differences – such as the use of varying classification criteria, diagnostic tools, and case ascertainment strategies – limits direct comparison of epidemiological data across studies and regions. The lack of standardized definitions and diagnostic criteria remains a major barrier to reliable global epidemiological estimates, as emphasized in recent reviews.

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Conflicts of interest

There are no conflicts of interest.

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Pathogenesis of skin damage in lupus: recent advances and future directions

Qilin Li^{a,b,c} and Qianjin Lu^{a,b,c,d}

Purpose of review

Lupus erythematosus (LE) encompasses a spectrum of autoimmune diseases with significant heterogeneity, ranging from cutaneous lupus erythematosus (CLE), confined to the skin, to systemic lupus erythematosus (SLE), which affects multiple internal organs. The underlying pathogenesis of lupus skin lesions and the heterogeneity among various subtypes remain elusive and require further investigation. This review synthesizes recent progress in elucidating the mechanisms of lupus skin injury, providing novel perspectives on diagnosis and therapeutic strategies, while also outlining promising avenues for future investigation.

Recent findings

Key insights include the active pathogenic role of keratinocytes, essential involvement of neutrophils, the central role of type I interferon (IFN-I) signaling, and a preactivated molecular state in nonlesional skin. Emerging distinctions between CLE and SLE lesions, as well as the role of photosensitivity, are also examined. These findings highlight modifiable environmental factors as critical parts for LE prevention and establish a new paradigm for future precision medicine in LE.

Summary

These novel findings enrich the complex pathogenic network underlying lupus skin injury, accelerating the transition toward precision medicine. Rational prevention, early diagnosis, and targeted treatment represent the core principles and a promising vision for the future evolution of lupus management.

Keywords

cutaneous lupus erythematosus, keratinocyte, precision medicine, systemic lupus erythematosus, type I interferon

INTRODUCTION

Lupus erythematosus (LE) is a constellation of autoimmune disorders influenced by a range of factors including sex, genetic predisposition, epigenetic modifications, microbiota composition, and environmental triggers such as ultraviolet radiation [1]. It is characterized by dysregulated innate immune responses and lymphocyte disturbances as well as the abnormal production of autoantibodies, which contribute to pathological injury to the skin and beyond [2]. Based on clinical manifestations, cutaneous lesions in LE are broadly categorized as acute (ACLE), subacute (SCLE), or discoid (DLE) lupus erythematosus [3]. Among these, ACLE is most closely linked to systemic disease and is often viewed as the characteristic skin manifestation of systemic lupus erythematosus (SLE) [4]. Both DLE and SCLE are classified under cutaneous lupus erythematosus (CLE) [3]. DLE represents the most prevalent subtype of CLE, accounting for more than 80% of all cases [3]. Collectively, cutaneous lesions represent a hallmark clinical feature of LE and exert a detrimental effect on quality of life, underscoring the critical need for

effective, targeted dermatological therapies within comprehensive LE management [5].

The pathogenesis of LE is multifactorial, with factors such as genetic predisposition, epigenetic regulation, sex bias, metabolic disturbances, and immune dysregulation, which has been extensively reviewed in previous literature [1,6,7,8*,9]. Here, we synthesizes some key molecular players and cellular interactions in the pathogenesis of lupus skin lesions, highlighting

^aHospital for Skin Diseases, Institute of Dermatology, Chinese Academy of Medical Sciences and Peking Union Medical College, ^bKey Laboratory of Basic and Translational Research on Immune-Mediated Skin Diseases, Chinese Academy of Medical Sciences, ^cJiangsu Provincial Key Laboratory of Dermatology, Nanjing and ^dDepartment of Dermatology, Second Xiangya Hospital, Central South University, Hunan Key Laboratory of Medical Epigenomics, Changsha, Hunan Province, China

Correspondence to Qianjin Lu, Hospital for Skin Diseases, Institute of Dermatology, Chinese Academy of Medical Sciences and Peking Union Medical College, 210042 Nanjing, China.
E-mail: qianlu5860@pumcdern.cams.cn

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KEY POINTS

- Keratinocytes can play an active pathogenic role in initiating lupus skin lesions.
- Neutrophils mediate crosstalk between cutaneous and systemic inflammation in lupus.
- The type I interferon response represents a core pathogenic mechanism in lupus skin lesions.
- Multiomics analyses support distinct pathogenic mechanisms between systemic and cutaneous lupus erythematosus.
- Elucidating the pathogenesis of lupus skin lesions accelerates the development of targeted therapies and precision medicine.

recent advances beyond classical frameworks and outlining promising directions for future investigation.

Keratinocytes: active pathogenicity of nonimmune cells

The pivotal role of keratinocytes (KC) in the pathogenesis of LE has been extensively established [10,11]. In brief, the ultraviolet (UV)-induced KC–type I interferon (IFN-I) axis serves as an initial driver, promoting the release of multiple inflammatory mediators that recruit and activate diverse immune cells, ultimately establishing a self-sustaining inflammatory circuit in the skin (see Fig. 1).

Ultraviolet radiation (UVR) is a well established trigger of keratinocyte damage, thereby liberating endogenous damage-associated molecular patterns (DAMPs), which notably include cellular DNA and DNA-binding proteins such as high mobility group box 1 (HMGB1) [3]. These DAMPs not only activate the cytosolic cGAS–STING axis which triggering nuclear translocation of transcription factors IRF3 and nuclear factor (NF)- κ B, but also engage endosomal Toll-like receptor (TLR) 3 and retinoic acid-inducible gene I (RIG-I) pathways (Fig. 1) [1,12,13]. Consequently, keratinocytes secrete large quantities of interferon (IFN)-I (IFN- $\alpha/\beta/\kappa$), type III interferons (IFN- λ), chemokines, and proinflammatory cytokines [interleukin-6 (IL-6), tumor necrosis factor alpha (TNF- α), IL-1 β , etc.], which form a communicative bridge between keratinocytes and immune cells, amplifying inflammatory feedback loops [1,12–16,17[¶]]. For instance, CXCL9, CXCL10, and CXCL11 recruit autoreactive T cells (Th1 and CD8⁺ T cells) via CXCR3, exacerbating keratinocyte death and contributing to interfacial dermatitis (Fig. 1) [15,18]. IFN-I signaling

promotes the differentiation and skin residency of CD16⁺ dendritic cells (DC) [19]. As antigen-presenting cells (APCs), DCs activate naïve T cells, leading to their differentiation into effector T cells that subsequently promote the maturation of autoreactive B cells into plasma cells, ultimately driving the production of copious autoantibodies (Fig. 1) [1]. Cytokines including IL-6 and B-cell activating factor (BAFF) support B cell survival, proliferation, and differentiation, while IFN-I lowers the activation threshold of B cells, facilitating B cell infiltration into skin lesions and promoting autoantibodies production and deposition [17[¶]]. The resulting immune complexes (ICs) re-enter the inflammatory circuit as positive stimuli, further amplifying the immune response (Fig. 1). These autoantibodies function as both cause and effect – a concept supported by previous studies demonstrating that serum IgG from lupus-prone mice or SLE patients can promote skin inflammation via the TNF α –TNFR1 pathway and enhance monocyte differentiation into dendritic cells [20].

Recent studies have established that keratinocyte-specific dysregulation of IFN-I signaling can induce systemic autoimmunity in mice, underscoring the active pathogenic role of keratinocytes in lupus [10]. For instance, epidermal overexpression of VGLL3 – a transcriptional cofactor enriched in female skin – drives SLE-like cutaneous and systemic autoinflammatory phenotypes [21]. Similarly, KC-specific PPAR γ deletion in mice replicated SLE-like features [22^{¶¶}]. Mechanistically, PPAR γ directly binds with IRF3 to block its nuclear translocation, thus suppressing downstream IFN-I production and preventing dendritic cell activation in the skin [22^{¶¶}].

Nevertheless, further evidence is required to determine whether these keratinocyte-driven mechanisms of local and systemic immune activation are conserved in humans and whether they can be therapeutically targeted for lupus treatment.

Neutrophils: key contributors

Beyond KC, neutrophils orchestrate lupus immunodysregulation through multiple mechanisms, encompassing the release of proinflammatory cytokines, antimicrobial peptides (including LL-37), reactive oxygen species (ROS), and the formation of neutrophil extracellular traps (NETs) [23]. Composed of extracellular structures like chromatin, histones, and granular proteins, NETs function as a self-defense mechanism to capture and eliminate pathogens. However, dysregulation of this process can drive autoimmune pathology [23]. Accumulations of neutrophils with NETs have been observed near the dermo-epidermal junction in both SLE and

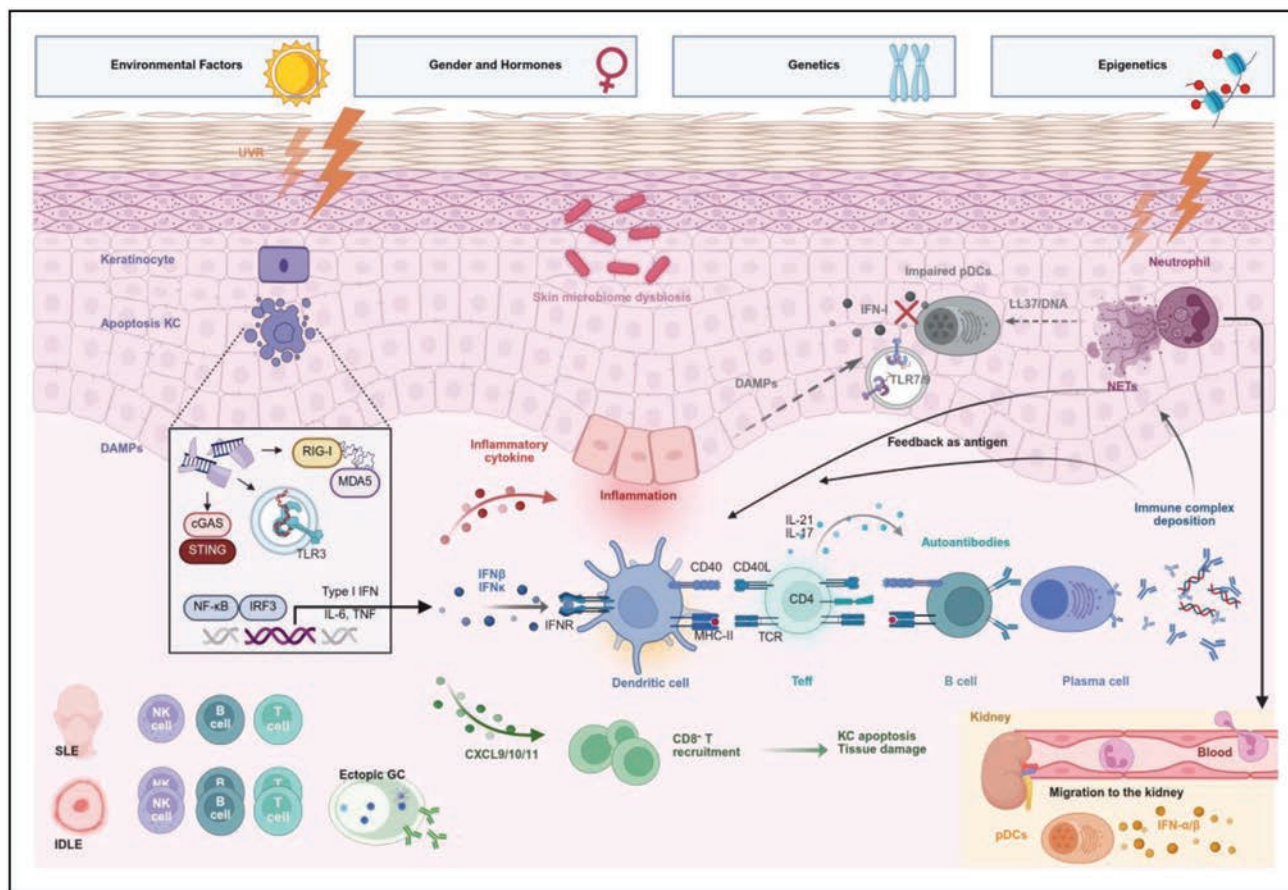


FIGURE 1. Pathogenesis of skin damage in lupus. The pathogenesis of LE skin lesions is complex and involves genetic, epigenetic, gender, hormonal, and environmental factors. UVR induces KC damage, leading to the release of DAMPs, which activate KC to produce IFN-I, various inflammatory cytokines, and chemokines. Among them, IFN-I acts as a critical driving force by promoting DC activation, effector T cell differentiation, B cell maturation, excessive autoantibody production, and immune complex deposition. Chemokines such as CXCL9, CXCL10, and CXCL11 recruit CD8⁺ T cells, which further damage KC and exacerbate skin lesions. Multiple inflammatory cytokines, including IL-6 and TNF, sustain the inflammatory state in the skin. UVR also enhances the release of NETs by neutrophils and promotes their migration to the kidneys, thereby aggravating systemic symptoms. Unlike in the kidneys, pDCs in lupus skin may exist in a dysfunctional state, unable to produce significant amounts of IFN-I in response to TLR signaling. Compared to SLE lesions, IDLE lesions exhibit more extensive infiltration of T cells, B cells, and NK cells, along with germinal center-like structures that facilitate in situ production of large quantities of autoantibodies. Immune complexes produced by B cells can either promote NETosis or directly act as antigens to activate DC, forming an amplified positive feedback loop. Additionally, lupus patients exhibit perturbations in their cutaneous microbiome. DAMPs, damage associated molecular patterns; DC, dendritic cell; IDLE, isolated discoid lupus erythematosus; IFN-I, type I interferons; KC, keratinocyte; LE, lupus erythematosus; NETs, neutrophil extracellular traps; pDCs, plasmacytoid dendritic cells; SLE, systemic lupus erythematosus; TLR, Toll-like receptor; UVR, ultraviolet radiation.

various CLE subtypes – such as lupus panniculitis, ACLE, and DLE – but not in healthy skin [23,24].

Low-density granulocytes (LDGs), a distinct neutrophil subset characteristically elevated in lupus, exhibit enhanced NET formation. These NETs contain oxidized mitochondrial DNA and serve as potent inducers of interferon-stimulated genes (ISGs) in epithelial cells, a process that can lead to clinical manifestations such as cutaneous vasculitis and nephritis [8[¶]]. Mechanistically, IFN-I stimulate neutrophils to release NETs containing LL-37/dsDNA complexes or oxidized

mtDNA/TFAM complexes. After internalized by plasmacytoid dendritic cells (pDCs), they trigger TLR9 activation and further IFN-I production, thereby establishing a self-amplifying loop [25]. Similarly, LL-37/DNA complexes within NETs can also function as autoantigens that trigger memory B cells to produce autoantibodies, and then ICs derived from B cells promote NETs formation in return, creating another positive feedback loop (Fig. 1) [26]. Evidence suggests that anti-galectin-3 antibody-positive sera from SLE patients have been shown to accelerate NETs formation,

contributing to the development of cutaneous lupus vasculitis [27].

Of note, the infiltration of neutrophils into the skin precedes the clinical onset of disease in CLE mouse models, suggesting their potential role in the initiation or preactivation of cutaneous lesions [26]. UVR also triggers NETosis [28], promotes neutrophil migration and sustained skin infiltration, and facilitates reverse transmigration of neutrophils to the kidneys, contributing to renal injury (Fig. 1) [29]. Collectively, these data position neutrophil trafficking as a candidate mechanism bridging cutaneous and systemic lupus, yet future work is needed to directly establish this causal relationship.

Type I interferon signaling: a preprimed state in nonlesional skin

The central role of IFN-I in lupus pathogenesis is well established and has been extensively reviewed [25]. Herein, we focus on emerging evidence regarding the cellular sources of IFN-I and the preprimed state in nonlesional skin of lupus patients and susceptible individuals, offering insights into the feasibility of targeting this pathway therapeutically.

Conventional models posit pDCs as the primary producers of IFN-I in LE [3]. However, this view has recently been challenged [25]. Emerging data suggest that noncirculating, nonhematopoietic sources may dominate IFN-I production during the preclinical stages [12]. Studies have shown that individuals at high risk for SLE reveal an interferon signature in clinically unaffected skin without immune infiltration, which driven primarily by KC-derived IFN- κ [12]. In contrast, pDCs in these contexts display transcriptional signatures of cellular stress and senescence, coupled with accelerated telomere attrition (Fig. 1) [12]. Spatial and single-cell RNA sequencing analyses further demonstrate that nonlesional skin of CLE patients characterized by high IFN-I levels microenvironment educates myeloid cells, such as CD16⁺ dendritic cells (DC), to initiate cutaneous inflammation [19]. Conversely, pDCs appear infrequent and relatively quiescent in these samples [19].

Additional evidence argues against pDCs as the dominant IFN-I producers in either SLE or CLE. Peripheral blood mononuclear cells (PBMCs) from SLE patients produce less IFN- α than HC when stimulated with SLE serum or herpes simplex virus-1 (HSV-1). Consistent with this, skin-derived and circulating pDCs from CLE patients express significantly less IFN- α upon TLR7 stimulation *ex vivo* [30^{***}]. This impaired pDCs are observed across multiple lupus mouse models as the disease progressed [31], may result from TLR tolerance, analogous to pDCs exhaustion in chronic viral infection [32], or could be associated with

regulatory effects of cytokines such as TNF- α , resembling pDCs reprogramming during senescence [33].

Paradoxically, pDC depletion ameliorates disease symptoms in lupus mice models [34], and clinical targeting of pDCs with anti-BDCA2 antibodies alleviates skin lesions in CLE patients [35], complicating the role of pDCs in lupus pathogenesis. A recent study have implicated that *PLD4* mutation-driven pDCs expansion and aberrant IFN-I activation in initiating renal immune infiltration in lupus nephritis [36], but the role of pDCs in cutaneous autoimmunity requires further investigation.

In summary, a preprimed microenvironment enriched IFN-I is present in the nonlesional skin of lupus patients or high-risk population. Further evidence is required to identify the precise “switch” that triggers this preactivated state in future research, enhancing the understanding of lupus initiation and recurrence.

Photosensitivity: linking cutaneous and systemic inflammation

Up to 80% of lupus patients demonstrate photosensitivity to UVR [29,37]. UVR plays a central role in the initiation, exacerbation, and recurrence of LE skin lesions, as well as in photosensitivity, and can even contribute to systemic manifestations such as renal injury [17^{*},29]. The minimal erythema dose for UVB (UVB-MED), a quantifiable indicator of photosensitivity, is not only an independent risk factor for SLE but also shows an inverse association with SLEDAI scores [38].

Current evidence indicates that lupus photosensitivity and subsequent systemic inflammation are primarily driven by epidermal-derived IFN-I responses, primarily from keratinocyte-produced IFN- κ [39]. A recent investigation identified TRIM21 as a negative regulator that constrains UVB-induced local and systemic IFN-I inflammation by suppressing cGAS-STING pathway [40^{*}]. Another study implicates Z-DNA and Z-DNA-binding protein 1 (ZBP1) as drivers of UVB-induced photosensitivity and inflammation [41^{**}]. Notably, UV exposure upregulates ISGs in skin, blood as well as kidney [29]. Integrated transcriptomic analyses reveal more pronounced dysregulation of UVB-response genes (UVBRGs) in skin than in blood [38]. Among 14 lupus-associated UVBRGs, eight are IFN-I-stimulated genes (e.g., IRF7, ISG15, ISG20, IFI44, IFITM1, MX1, LY6E, OASL), which are dysregulated across multiple tissues and organs [38]. A recent study revealed that signals originating from the skin can be directly communicated to the immune system via lymphatic vessels [42^{*}].

Together, these findings elucidate part of the mechanism underlying the systemic symptoms associated

with photosensitivity in lupus and highlight the crucial role of UV-induced skin dysfunction in the initiation and progression of systemic damage in LE.

Heterogeneity between cutaneous lupus erythematosus and systemic lupus erythematosus: are they the same disease?

Historically, CLE and SLE have been regarded as opposing ends of the lupus disease spectrum, differing in skin lesion morphology, autoantibody profiles, histopathological patterns, treatment approaches, and immunopathogenic mechanisms [43²²]. However, significant clinical and immunologic overlap exists between these entities. On the one hand, over 75% of SLE patients develop cutaneous manifestations, which 20% presenting at disease onset [44]. On the other hand, less than 5% of DLE and 10–15% of SCLE may progress to involve other organs and evolve into SLE [43²²]. This raises a fundamental question: are CLE and SLE interchangeable clinical subtypes of the same disorder, or are they distinct entities with different etiologies?

Over 90% of isolated DLE (IDLE) show positive lupus band test (LBT) findings confined to the skin, typically without elevated serum IgG autoantibodies – suggesting that antibodies in CLE skin may not originate from the bloodstream [3]. scRNA-seq and immunohistochemistry confirmed a higher proportion of T cells, B cells, and NK cells in DLE lesions compared to SLE patients or HC [45]. A recent comprehensive study integrating immune repertoire (IR) sequencing, high-resolution HLA allele mapping, and multispectral histopathology revealed distinct immune pathogenic mechanisms in the skin lesions of SLE versus IDLE [43²²]. The study demonstrates that SLE represents a systemic B cell-driven disorder characterized by a dysregulated circulating IR, whereas IDLE presents as a skin-confined autoimmune condition with no significant peripheral repertoire disturbance. Notably, IDLE skin lesions exhibited higher V-J recombination diversity, elevated somatic hypermutation (SHM) frequency, and enhanced class-switch recombination (CSR) compared to SLE lesions, reflecting greater diversity of local IR. Interestingly, structures resembling ectopic germinal centers (GCs) were identified in IDLE via multiplex immunohistochemistry, populated with Tfh cells and Bcl-6⁺ B cells – indicative of localized clonal expansion and in-situ antibody production. In contrast, SLE skin showed reduced SHM/CSR and fewer IgG⁺ cells accumulation, consistent with passive deposition from circulation rather than active local immune activity [43²²].

These findings provide novel insights into the distinct pathogenic mechanisms underlying SLE and

CLE, highlighting implications for subtype-specific diagnostics and targeted therapeutic strategies.

Prevention and treatment of lupus skin lesions: toward precision medicine

Conventional management of LE includes antimalarials, glucocorticoids, calcineurin inhibitors, and various immunomodulatory or immunosuppressive agents [1,11]. Recently, the emergence of targeted therapies offered new prospects for LE treatment. These include T-cell-targeted approaches (e.g., anti-S1PR1 or anti-CD40L), B-cell-targeted therapies (e.g., anti-CD19/CD20/CD22/CD38/BAFF/APRIL/BTK), and targeting IFN-I axis (including targeting IFN- α , IFNAR, JAK-STAT signaling, pDCs, or TLR) [11,17²³]. Other promising strategies comprise cytokine blockade (e.g., anti-IL-6), chimeric antigen receptor cell immunotherapy (e.g., CAR T/NK cells), and immunometabolic interventions (e.g., mTOR inhibition) [6,11].

Notably, skin microbiome profiling has identified several bacterial species – particularly *Staphylococcus aureus* and *Staphylococcus epidermidis* – as potential biomarkers in SLE skin lesions (Fig. 1) [46]. ACLE lesions show high colonization rates of *S. aureus* (approximately 50%) [47], and topical antibiotics like mupirocin can reduce staphylococcal load, thereby alleviating cutaneous inflammation and IFN-I responses in CLE lesions [48²⁴]. Alterations in the skin microbiota of lupus patients suggest a role for dysbiosis in disease pathogenesis, thereby implicating the microbiome as a potential biomarker and therapeutic target.

Beyond pharmacological interventions, health education and avoidance of modifiable risk factors are essential components of lupus prevention – particularly in high-risk individuals and for mitigating flares. Key recommendations include sun protection, smoking cessation, avoidance of estrogen-containing medications, adequate sleep, stress management, and dietary modifications such as low-carbohydrate or ketogenic diets and obesity prevention [17²³].

In the foreseeable future, the integration of artificial intelligence (AI) and big data analytics into clinical decision support systems (CDSS) may empower physicians to enhance diagnostic efficiency and precision. Indeed, a multimodal deep learning system (MMDLS) has been developed to facilitate human–AI collaboration in differential diagnosis of LE, demonstrating significant advantages in telemedicine [49²⁵]. A comprehensive stratification strategy incorporating genetic susceptibility, epigenetic profiles, immune phenotyping, and multiparameter laboratory markers has been proposed to enable refined patient classification and personalized targeted therapy [50].

CONCLUSION

The rapid advancement of multiomics technologies has significantly enhanced our ability to elucidate the connections and distinctions between CLE and SLE skin lesions. Beyond immune cells, nonimmune cells such as keratinocytes also play crucial roles, at times acting as active initiators rather than passive targets. Dysregulated innate defense mechanisms in neutrophils can hyperactivate autoimmune responses and potentially mediate crosstalk between cutaneous and systemic immunity (such as during photosensitivity reactions). IFN-I continues to occupy a central position in the inflammatory network, not only driving local skin inflammation and coordinating systemic immune reactions but also establishing a preactivated “time bomb” in nonlesional skin. Targeting the IFN-I axis remains a cornerstone of therapeutic strategies for lupus skin disease; anti-IFNAR antibodies such as anifrolumab have shown promising yet still unsatisfactory efficacy in refractory cutaneous lupus.

A pressing and unresolved challenge in clinical practice is the early stratification of lupus patients into subtypes at the initial lesion stage to enable precision interventions. This underscores the critical need to dissect the distinct pathogenic mechanisms of CLE and SLE. Finally, The establishment of an integrated healthcare model spanning the entire disease course – from preemptive education and screening of high-risk populations, through multiomics subtyping and personalized treatment, to long-term follow-up and rehabilitation – will require deep collaboration across clinical medicine, basic research, biotechnology, data science, and public policy.

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Conflicts of interest

There are no conflicts of interest.

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Pathophysiology of glomerulonephritis in autoimmune diseases

Kayaho Maeda

Purpose of review

Autoimmune glomerulonephritis (GN) emerges when self-reactive humoral and cellular immunity converge in the kidney. Combined immunofluorescence and electron microscopy aids in classifying GN; however, more stratification strategies are required for personalized therapy. We aimed to review biopsy-anchored clinicopathologic classification and pathophysiology of GN-associated disorders based on immunofluorescence and electron microscopy. Additionally, we sought to integrate mechanistic insights from multiomics and spatial profiling that resolve the composition and spatial organization of the cellular “neighborhoods” that drive injury and repair across IgA vasculitis/nephropathy, lupus nephritis, antiglomerular basement membrane disease, and antineutrophil cytoplasmic antibody-associated vasculitis.

Recent findings

Although inciting antigens, immune complexes, and deposition patterns vary among entities, downstream injury pathways overlap. The convergent programs include complement activation, including locally produced renal complement, Fc receptor-driven myeloid effector functions, neutrophil extracellular traps with nucleic-acid sensing, the reprogramming of monocytes/macrophages, interleukin (IL)-23/IL-17, and type 1 interferon-primed cytotoxicity of T cells, and epithelial stress responses in podocytes and parietal epithelial cells.

Summary

Despite diverse triggers, autoimmune GNs share targetable injury pathways. Integrating biopsy-defined immune deposits and the accompanying inflammatory context with spatial, single-cell, and proteomic readouts enables mechanistic subtyping and pathway-aligned therapy. Tailoring treatment to individual dominant injury programs may improve renal outcomes and reduce adverse effects.

Keywords

antineutrophil cytoplasmic antibody-associated vasculitis, antiglomerular basement membrane disease, immunoglobulin A vasculitis, immune-complex-mediated glomerulonephritis, lupus nephritis

INTRODUCTION

Autoimmune glomerulonephritis (GN) comprises disorders characterized by the convergence of self-reactive humoral and cellular immune responses in the kidney, producing proliferative and/or necrotizing lesions. Although the inciting antigens, immune complexes, and deposition patterns differ among diseases, the downstream injury pathways – complement activation, Fc receptor-mediated effector functions of myeloid cells, cytotoxicity of lymphocytes, and stress responses of intrinsic glomerular cells – are shared [1]. Defining the deposit nature and location requires combining the immunofluorescence (IF) staining and electron microscopy (EM) of kidney biopsies, a vital strategy for classifying GN; however, further disease stratification and mechanistic understanding are crucial for personalized therapy. Recent advances in multiomics, spatial transcriptomics, and

multiplex immunofluorescence imaging are elucidating the mechanisms defined by the “composition and spatial organization” of constituent cells within renal inflammation. In this review, we aimed to summarize the common pathophysiological mechanisms of GN in rheumatology, including immunoglobulin A (IgA) vasculitis, lupus nephritis (LN), antiglomerular basement membrane (anti-GBM)

Department of Nephrology, Nagoya University Graduate School of Medicine, Nagoya, Japan

Correspondence to Kayaho Maeda, Department of Nephrology, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan. Tel: +81 52 744 2185; fax: +81 52 744 2209; e-mail: maeda15@med.nagoya-u.ac.jp

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KEY POINTS

- Glomerulonephritis-associated disorders share similar downstream injury pathways.
- Integrating immunofluorescence/electron microscopy with spatial, single-cell, and proteomic readouts improves the classification of glomerulonephritis.
- Focusing therapy on the dominant pathway in each glomerulonephritis-associated disorder may improve outcomes and reduce adverse effects.

disease, and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV).

ETIOLOGICAL CLASSIFICATION OF GLOMERULONEPHRITIS

A diagnostic kidney biopsy distinguishes GN from other renal diseases. It identifies the injured glomerular compartments, enabling light-microscopic categorization as “minimal mesangial GN,” “mesangial proliferative GN,” “active proliferative GN,” “necrotizing GN,” “crescentic GN,” “membranoproliferative GN (MPGN),” “exudative GN,” or “sclerosing GN”

[2]. However, for entities such as immune-complex GN (ICGN), pauci-immune GN, and C3-associated GN, light microscopic patterns are nonspecific; therefore, IF-based inference of the underlying immune mechanism is essential. The histological signs of immune activity – the deposition of complement components (C1q, C3c, and C4) and immune complexes and their isotypes and clonality – as well as ultrastructural changes on EM, inform the underlying etiology of GN. For example, in IgA vasculitis/nephropathy and anti-GBM disease, IF findings directly establish the final diagnosis. In many ICGNs, the combination of the predominant antibody/complement staining and a characteristic deposition pattern facilitates diagnosis (Fig. 1).

MECHANISMS OF THE ONSET AND PROGRESSION OF GLOMERULONEPHRITIS

In autoimmune diseases, most deposits comprise autoantibodies and immune complexes. Deposits occur in diverse renal compartments, such as the glomeruli, tubulointerstitium, and vessels; however, the glomeruli predominate owing to their structural properties. Three deposition modes exist, namely (1) circulating immune complexes form in the bloodstream and deposit in the kidney; (2) extrinsic antigens first deposit in the kidney and subsequently

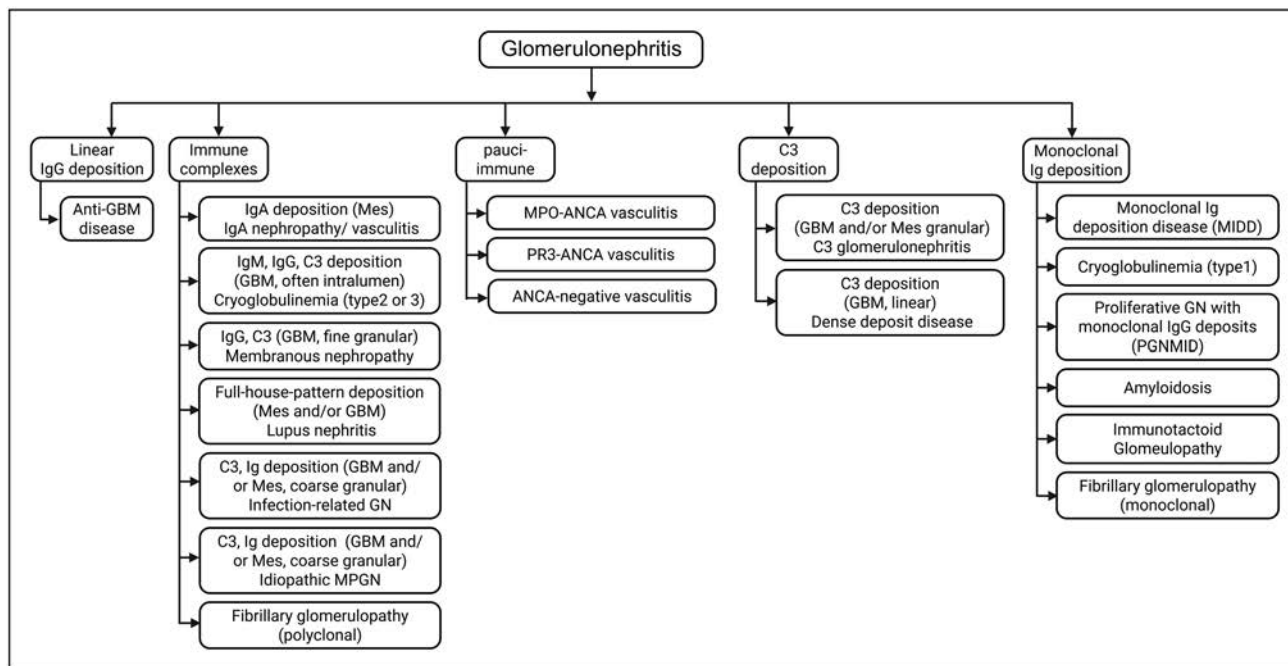


FIGURE 1. Immunofluorescence-based classification of the glomerulonephritis. Representative immunofluorescence patterns distinguishing anti-GBM, immune complex-mediated, pauci-immune, complement-dominant, monoclonal immunoglobulin-mediated glomerulonephritides, classified by dominant immunoreactants, deposition site (mesangial/capillary wall), and staining intensity. ANCA, antineutrophil cytoplasmic antibody; GBM, glomerular basement membrane; GN, glomerulonephritis; Ig, immunoglobulin; Mes, mesangium; MPO, myeloperoxidase; PR3, proteinase 3.

react *in situ* with circulating autoantibodies to form immune complexes; and (3) autoantibodies react *in situ* with intrinsic renal components to form immune complexes [3]. Systemic lupus erythematosus (SLE) exemplifies Modes (1) and (2). Anti-GBM antibody-mediated nephritis and membranous nephropathy exemplify Mode (3). Subendothelial and mesangial deposits provoke multiple inflammatory processes – complement activation, pro-coagulant activity, the release of cytokines and growth factors, and the generation of chemotactic factors. Although antibody deposition is usually substantial in autoimmune or infection-related GN, it is not strictly required for severe inflammation, as demonstrated by ANCA-associated GN (pauci-immune GN) and C3 glomerulopathies. Similarly, subepithelial immune complexes are sequestered from the circulation by the GBM; therefore, they may not trigger robust inflammation [3]. The major mediators and effector cells in the initiation and progression of GN are summarized subsequently.

Complement

Initiation via C1q (classical pathway), amplification through the alternative pathway, and the generation of the anaphylatoxins C3a/C5a drive leukocyte chemotaxis to the glomeruli [3]. The chemoattractant C5a, a fragment released from complement component C5, is particularly crucial in antibody-induced glomerular inflammation [4]. C5a promotes the recruitment of inflammatory cells – neutrophils, eosinophils, monocytes, and T lymphocytes – activates phagocytes, and induces the release of granule enzymes and the production of oxidants, contributing to tissue injury. In ANCA-induced GN, neutrophil activation and GN are mediated through the C5a receptor [5]. Consistent with this, the C5a receptor inhibitor avacopan improves GN in ANCA vasculitis and is recommended as a steroid-sparing alternative to high-dose glucocorticoid [6]. In IgA nephropathy/vasculitis, the alternative and lectin pathways are particularly relevant, and the intensity of C3 deposition correlates with disease severity [7]. Moreover, a multicenter proteome-wide Mendelian randomization and co-localization study demonstrated complement regulators (complement factor H related 1 and complement factor H) as putative causal factors for IgA nephropathy. The terminal complement complex (C5b-9) mediates injuries to the mesangial (e.g., in IgA nephropathy/vasculitis and LN) and endothelial (e.g., in LN) cells [8]. These observations underscore the significance of complement regulation in these diseases and suggest complement inhibition as a promising therapeutic approach. Indeed, the factor B inhibitor iptacopan,

which regulates the alternative complement pathway, significantly reduced proteinuria in a phase 3 trial of IgA nephropathy [9] and has been approved by the U.S. FDA. In addition, ravulizumab, a monoclonal antibody against C5, produced a significant reduction in proteinuria in a combined phase 2 study of IgA nephropathy and LN [10], and a phase 3 trial is now underway (NCT06291376). Pegcetacoplan, a C3-targeting peptide drug, is currently undergoing phase 3 trials for C3 glomerulopathy and immune complex-mediated MPGN (NCT05809531).

Beyond liver-derived circulating complements, injured renal parenchymal cells – particularly proximal tubules – produce C3 locally, contributing to inflammation and kidney fibrosis [11]. Injured proximal tubules segregate into successful- and failed-repair states. Failed-repair tubules participate in renal fibrogenesis and exhibit sustained C3 upregulation, increased vascular cell adhesion protein 1 (VCAM1) expression, and activated transforming growth factor- β and nuclear factor (NF)- κ B pathways. In LN, spatial analyses revealed a cortex-restricted niche characterized by the co-localization of VCAM1⁺ proximal tubules, myofibroblasts, and immune cells (CD163⁺ M2 and integrin α X⁺ macrophages, CD8⁺ T cells, and plasma cells). This niche exhibited increased expression of complement (C3 and C15), chemokines (CCL5 and CCL19), and collagens (COL3A1 and COL4A1), suggesting that local complement upregulation accompanies concurrent inflammation and extracellular matrix remodeling [12^{*}]. Thus, locally produced complement may represent a therapeutic target to halt renal disease progression, including autoimmune GN.

Neutrophils

Neutrophils were evident in kidney biopsies from patients with IgA vasculitis, LN, AAV, and anti-GBM disease [13]. At sites of immune-complex formation, the neutrophil phagocytosis of immune aggregates triggers activation, generating reactive oxygen species and releasing enzymes (such as elastase) that mediate glomerular injury. In some GNs – notably ANCA-associated GN and LN – neutrophils form neutrophil extracellular traps (NETs), web-like structures of histones comprising proteases, peptides, and enzymes [14]. Subsequently, extracellular DNA (ecDNA) acts as an intrarenal damage-associated molecular pattern (DAMP) to amplify inflammation via toll-like receptor (TLR)9–NF- κ B/Type 1 interferon (IFN) and cyclic GMP–AMP synthase-stimulator of IFN gene pathways [15,16]. In the kidney biopsies of patients with AAV, ecDNA was increased, whereas its degrading enzyme, DNase I, was downregulated. In an MPO-AAV mouse model, intravenous recombinant human (rh) DNase I

reduced ecDNA deposition, NETs, necrotizing changes, and inflammatory gene expression. Adeno-associated virus-vector-mediated DNase I delivery outperformed repeated rhDNase I dosing, lowering MPO-ANCA titers and proteinuria [17]. These findings support NET-targeted therapy as a feasible strategy. Recent studies have shown that the myeloid inhibitory C-type lectin-like receptor (MICAL) directly recognizes NETs as a pattern-recognition receptor, suppressing excessive neutrophil activation and secondary NET formation. During MICAL deficiency, NET formation increases via reactive oxygen species-dependent and peptidylarginine deiminase 4-related pathways, exacerbating inflammation [18[¶]]. This MICAL-mediated pathway limits tissue injury in conditions such as autoimmune arthritis; hence, a protective role in autoimmune GN is anticipated. However, further investigation is required.

Monocytes and macrophages

Monocytes and macrophages are major constituents of glomerular and tubulointerstitial lesions in autoimmune GN [19,20]. They localize to the glomeruli through interactions with deposited immunoglobulins via Fc receptors and multiple chemokines, including macrophage chemoattractant protein-1 (MCP-1) [21] and granulocyte macrophage colony-stimulating factor (GM-CSF) [22]. During inflammation, patrolling monocytes that express MHC class II localize within glomerular capillaries and aggravate acute glomerular inflammation by presenting antigen to effector T cells and activating neutrophils as they traverse inflamed glomeruli. Depleting these monocytes reduced T-cell-mediated inflammation and neutrophil activation, alleviating glomerular injury [23,24]. Recent integrated single-cell RNA-sequencing (RNA-seq) and spatial transcriptomics in human and murine LN revealed that in an active Class III/IV disease, *CD9/SPP1/APOE/FABP5/GPNMB/TREM2*-expressing monocytes (classic monocyte 2; C2) derived from CCR2⁺ classic monocyte 1 (C1), preferentially infiltrated the glomeruli. C2 cells displayed enhanced phagocytic activity and increased immune-complex uptake. The extent of C2 infiltration correlated with the LN activity index, implicating these cells in immune-complex-driven intraglomerular inflammation [25[¶]].

The significance of macrophages is supported by the beneficial effects observed in interventions that inhibited MCP-1, GM-CSF, or macrophage migration inhibitory factor [21,22,26]. Macrophages are highly plastic and polarize into distinct phenotypes in response to environmental cues, broadly categorized as M1 (pro-inflammatory) and M2

(anti-inflammatory) [27]. Spatial proteomics indicated that LN is characterized by the infiltration of CD163⁺ M2 macrophages [28], aligning with the utility of urinary soluble CD163 as an excellent diagnostic and activity marker in LN [20]. Lupus flares have been linked to imbalanced M1/M2 ratios [29]. M1 macrophages were associated with active SLE [30], whereas polarization toward M2 was observed in LN amelioration [31]. Single-cell analyses of LN kidneys have delineated trajectories from inflammatory M1-like monocytes to M2 macrophages, with stepwise downregulation of pro-inflammatory cytokine genes, suggesting a shift from pro-inflammatory to alternatively activated phenotypes over the disease course [32]. These M2 macrophages possibly contribute to resolution and tissue repair during the later stages of LN.

T cells

Although T cells are less conspicuous within glomerular lesions, they are detectable, particularly in diseases such as crescentic GN that are largely macrophage-mediated [3,13]. T-cell-mediated injury occurs primarily via chemokine release and subsequent macrophage recruitment, with the macrophages serving as effector cells [33]. The roles of T helper 17 (Th17) cells in certain morphologic GN forms are being delineated [34]. Th17 expansion is promoted by interleukin (IL)-23, and the IL-23/Th17 axis is critical across multiple experimental GN models [35,36], augmenting intrarenal inflammation [37]. Additionally, preclinical data suggest that resident CD4⁺ T cells – particularly Th17 cells via IL-17 production – drive the progression of ANCA-associated GN [38], highlighting the IL-23/IL-17 axis as a therapeutic target (Fig. 2). Spatial and single-cell transcriptomics further demonstrated that intrarenal Th1/Type 1 CD8⁺ T cell (Tc1) and Th17/IL-17-secreting CD8⁺ T cell (Tc17) populations drive local inflammation in ANCA-associated GN. Guided by such data, IL-12/23 blockade (ustekinumab) was identified as an optimal target and produced favorable short-term responses in relapsing ANCA-associated nephritis [39[¶]]. The other combined spatial transcriptomics and scRNA-seq have been used to elucidate how the cytotoxicity of T cells is acquired. In human LN and ANCA-GN, IFN-stimulated gene–high T cells (ISG-T) cluster near intrarenal plasmacytoid dendritic cells (pDCs). Locally produced IFN-1 acts on T cells to induce IFN regulatory factor (IRF)7 and potentiates a granzyme B-centered cytotoxic program via an ISG-T “intermediate state.” In mice, IFN-alpha/beta receptor blockade reduced IRF7/granzyme B and ameliorated nephritis, supporting a causal pathway in LN and ANCA-GN progression [40[¶]].

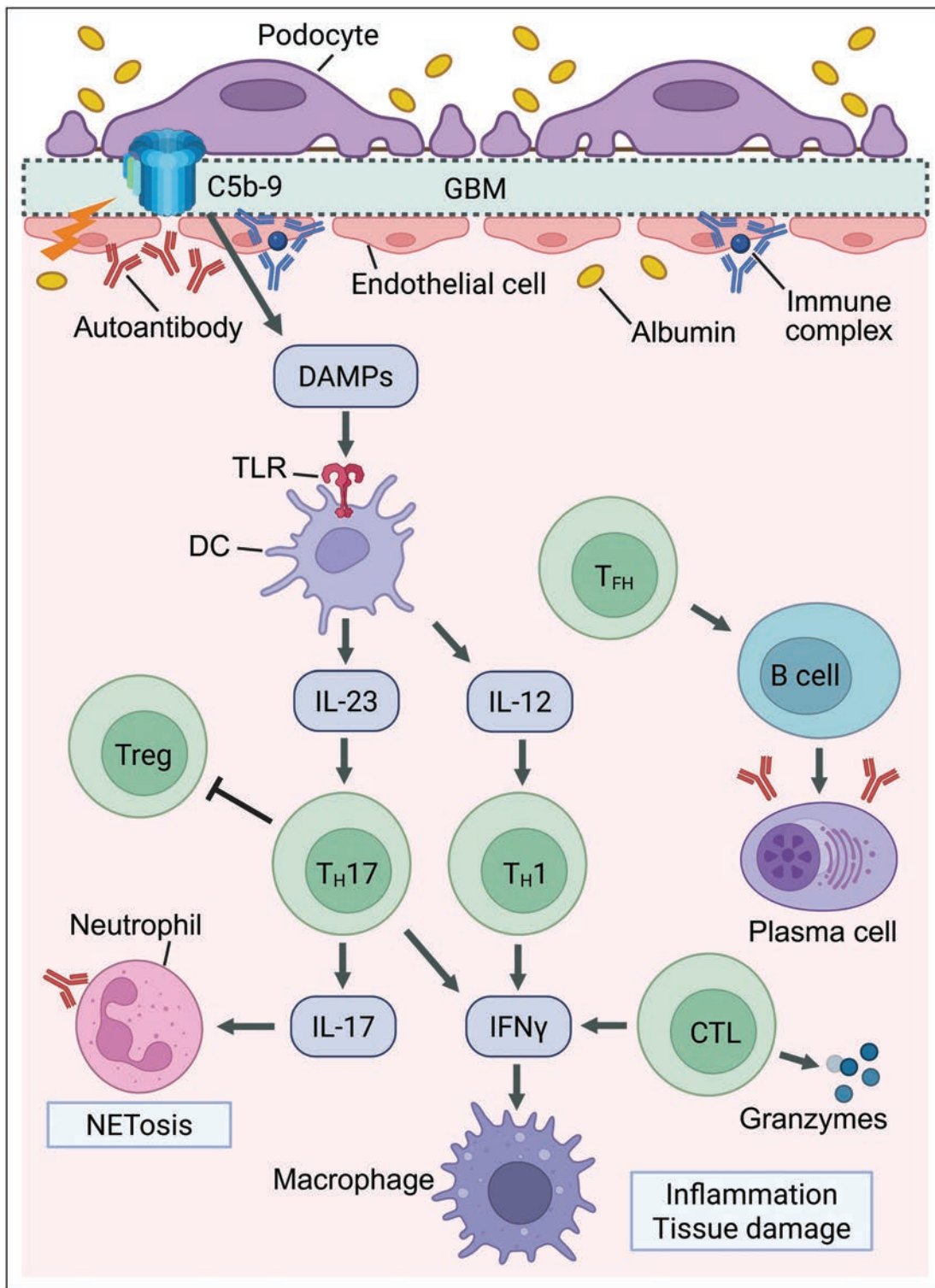


FIGURE 2. Immune triggers-to-tissue injury cascade in autoimmune nephritis. Immune complexes and complement deposit along the glomerular basement membrane, breach the barrier, and release DAMPs sensed by dendritic and kidney resident cells. These signals drive IL-23– T_H17 polarization, IL-17 production, and neutrophil influx, while T_{FH} / T_H17 cells license B cells to make antibodies. IFN- γ from CTLs, T_H1 , and T_H17 cells recruits macrophages. T cells then orchestrate together with neutrophils and macrophages a cytokine/chemokine cascade, B-cell expansion, and activation of intrinsic kidney cells, leading to persistent dysfunction and irreversible kidney damage. CTL, cytotoxic T lymphocytes; DAMPs, damage-associated molecular patterns; IFN γ , interferon γ ; T_{FH} , T follicular helper cells; T_H17 , T-helper (T_H) type 17 cells; TLR, Toll-like receptor.

Mesangial cells

Mesangial cell injury – usually accompanying mesangial immune-complex deposition – is a hallmark of IgA nephropathy/vasculitis and LN [41]. A multihit model has been proposed for IgA nephropathy: (Hit 1) overproduction of galactose-deficient IgA1 (Gd-IgA1); (Hit 2) induction of antibodies (primarily IgG, sometimes IgA) that recognize aberrant Gd-IgA1 glycans; (Hit 3) immune-complex formation between Gd-IgA1 and antiglycan antibodies; and (Hit 4) mesangial deposition that activates mesangial cells and complement to drive glomerular inflammation [42]. Activated mesangial cells produce cytokines such as IL-6 and chemokines that act on mesangial cells, other resident glomerular cells, and leukocytes. Consequently, these cells secrete mediators that feed back on mesangial cells, creating paracrine loops [41,43]. In murine SLE models, mesangial IL-6 secretion independently accelerated GN [44]. In patients with LN and LN mouse models, Ca^{2+} /calmodulin-dependent kinase IV (CaMK4) – a serine/threonine kinase required for mesangial proliferation and IL-6 production – was overexpressed; however, CaMK4 deficiency ameliorated GN. Notably, the mesangial cells from CaMK4-deficient lupus-prone MRL/lpr mice failed to proliferate or produce IL-6 in response to platelet-derived growth factor [45].

Podocytes and parietal epithelial cells

Inflammation-mediated podocyte injury exhibits multifaceted mechanisms, including disordered cytoskeletal dynamics and eventual dedifferentiation and detachment [46]. Podocyte damage is the principal driver of proteinuria in GN, and excessive podocyte loss causes irreversible glomerular injury. Beyond being a target, podocytes express numerous molecules linked to innate and adaptive immunity, participating in GN pathogenesis. Podocytes are vulnerable to complement-mediated injury and actively contribute to complement production [47]. Primary and conditionally immortalized podocytes express complement genes under basal conditions; puromycin-induced podocyte damage increases C3 expression [48]. In addition to driving LN, TLRs are crucial in the onset and progression of other renal diseases, such as ischemia–reperfusion injury, acute kidney injury, and diabetic kidney disease [49]. Podocytes express TLRs and recognize pathogen-associated molecular patterns and DAMP, leading to the induction of chemokines and cytokines that promote glomerular injury via downstream mediators such as NF- κ B, MyD88, IRAK, and TRAF6 [50]. Furthermore, podocytes express MHC class II and CD86 required for T-cell activation [51,52]. Mice with

podocyte-specific MHC II deficiency showed attenuated responses to nephrotoxic serum-induced nephritis [51]. Moreover, signal-regulatory protein- α (SIRP α), a transmembrane protein with anti-inflammatory functions in macrophages, is expressed by podocytes. Marked downregulation of SIRP α in podocytes from patients with LN and lupus-prone mice enhanced podocyte antigen presentation, T-cell activation, and pro-inflammatory cytokine production, creating a harmful feedback loop [53].

Parietal epithelial cells (PECs), together with podocytes, contribute to crescent formation. Mouse models targeting initial injury to the glomerular endothelial cells and/or GBM showed subsequent PEC proliferation that markedly increased cellularity within crescents [54]. In addition, glomerular cells may promote crescents by releasing soluble factors. In murine and human crescentic GN, heparin-binding EGF-like growth factor (HB-EGF) was upregulated in glomerular cells, enhancing the phosphorylation of the EGFR/ErbB1 receptor in mice. HB-EGF-deficient mice lack glomerular EGFR activation and exhibit improved disease. Even after GN induction, podocyte-specific EGFR deletion or pharmacologic inhibition mitigated injury [55]. Furthermore, counter-regulatory mechanisms enhance glomerular resilience. Nuclear factor erythroid 2-related factor (NRF2) induced podocyte-specific PPAR γ expression, protecting against podocyte injury; however, NRF2 deficiency markedly worsened crescentic GN [56]. The downregulation of Krüppel-like factor 4 – a zinc-finger transcription factor essential for podocyte homeostasis and PEC quiescence – may promote PEC proliferation and crescent formation following podocyte injury [57,58]. In patients with LN, CaMK4 expression is increased in mesangial cells and podocytes. Moreover, in lupus-prone mice, the targeted delivery of a CaMK4 inhibitor to podocytes preserved podocyte ultrastructure despite ongoing systemic autoimmunity, prevented immune-complex deposition and crescent formation, and suppressed proteinuria [59]. Thus, CaMK4 and the calcium signaling required for its activation suggest a connection between immune-mediated glomerulonephritis and podocyte injury.

CONCLUSION

Autoimmune GNs have diverse triggers but share similar injury programs, including complement activation, Fc-receptor–driven myeloid responses, cytotoxicity of T cells, and epithelial (podocyte/PEC) stress. Biopsy with IF and EM remains the diagnostic anchor, while single-cell and spatial omics reveal cellular “neighborhoods” that sustain inflammation and fibrosis. These insights point to targeted, steroid-

sparing strategies – complement inhibition, NET modulation, IL-23/IL-17 and Type I IFN blockade, macrophage reprogramming, and epithelial protection. Aligning therapy to the dominant pathway in each patient promises improved outcomes with reduced adverse effects.

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Conflicts of interest

There are no conflicts of interest.

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Neuropsychiatric systemic lupus erythematosus – current and novel treatments

Rohan Gupta^{a,*}, Maeva Agapoff^{b,*} and Betty Diamond^b

Purpose of review

Here, we provide a broad overview of the current treatment landscape of neuropsychiatric systemic lupus erythematosus (NPSLE) focusing on diffuse central nervous system manifestations and potential new treatments based on studies of murine models and neuroimaging studies of patients.

Recent findings

The therapeutic landscape focuses on three approaches: modulation of B cell activity and circulating autoantibodies (CAR-T cell and BTK inhibitor therapies), reduction of systemic inflammation (JAK, TYK2, and anti-IFN inhibitors), and direct neuroprotection (ACE inhibitors and ARBs).

Summary

These findings broaden the therapeutic landscape for NPSLE beyond general immunosuppression. Future research must prioritize clinical trials inclusive of NPSLE patients to validate these promising strategies.

Keywords

blood–brain barrier, cognitive impairment, microglial activation, neuropsychiatric lupus

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease defined by the presence of antinuclear antibodies (ANAs), and an increase in circulating inflammatory cytokines, which cause damage to multiple organ systems, commonly including the kidney, skin, and the central nervous system (CNS) [1]. The involvement of the CNS, present in up to 80% of patients [2], is specifically referred to as neuropsychiatric SLE (NPSLE). NPSLE includes peripheral, central focal, and central diffuse manifestations. Peripheral manifestations such as neuropathies are often treated with anti-inflammatory medications. Central focal manifestations such as stroke and epilepsy are treated symptomatically. However, there are unmet needs for treatment for central diffuse manifestations such as fatigue, cognitive dysfunction (colloquially referred to as “brain fog”), mood disorders, and psychosis, which greatly affect quality of life [3]. Etiologies for central diffuse NPSLE are presumed to be increased levels of serum cytokines, alterations in the ratio of kynurenic acid (K, an NMDA receptor antagonist) to quinolinic acid (Q, an NMDA receptor agonist) and brain-reactive antibodies. For the latter to cause brain injury there must be a breach in blood–brain barrier (BBB) integrity to allow immunoglobulins to penetrate brain parenchyma.

CURRENT THERAPEUTIC LANDSCAPE

Figure 1 provides an overview of the current and novel therapeutic strategies targeting the systemic and central mechanisms of NPSLE. Current therapies for NPSLE affecting the CNS are designed to modulate an inflammatory pathogenic process. For acute cases the standard approach is high-dose glucocorticoids, which may be combined with the immunosuppressive drug cyclophosphamide [4]. Rituximab, a B cell depleting monoclonal antibody, intravenous immunoglobulins (IVIGs), or therapeutic plasma exchange are sometimes considered if first round therapies do not achieve an adequate response [4].

^aBarbara and Donald Zucker School of Medicine, Hempstead and

^bInstitute of Molecular Medicine, Feinstein Institutes for Medical Research, Manhasset, New York, USA

Correspondence to Betty Diamond, MD, Institute of Molecular Medicine, Feinstein Institutes for Medical Research, 350 Community Drive, Manhasset, NY 11030, USA. Tel: +1 516 562 3830; fax: +1 516 562 2953; e-mail: bdiamond@northwell.edu

*Co-first authors.

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KEY POINTS

- There is no current approved treatment uniquely targeting neuropsychiatric manifestations of systemic lupus erythematosus (SLE).
- Neuropsychiatric manifestations are frequently an exclusion criterion in clinical trials for (SLE) leading to a lack of knowledge on the effectiveness of novel therapeutics for patients with SLE experiencing neuropsychiatric symptoms.
- The current available treatments and ongoing trials are targeting microglial activation (with the use of ACE inhibitors), reducing systemic inflammation, targeting B cells and circulating cytokines, and restoring the blood-brain barrier integrity (notably via the gut-brain axis).

Hydroxychloroquine is an antimalaria drug that reduces disease flares and is used continuously in a high percentage of patients [5]. It is thought to protect against thrombosis including intracerebral thrombosis [6].

Biologic therapies have transformed the treatment landscape for many autoimmune diseases, including SLE, but their effectiveness in NPSLE is largely untested. This evidence gap is a direct consequence of the design of clinical trials, which, for safety reasons and difficulties in assessing CNS-specific outcomes, have systematically excluded patients with severe, active CNS lupus, thereby leading to a critical knowledge gap.

Among the therapies in use for other SLE manifestations are those designed to decrease circulating autoantibodies, which would include anti-brain antibodies. Studies of patient serum have revealed numerous anti-brain antibodies and investigations of some of these in mice have demonstrated their ability to alter cognition or mood [7,8]. For example, SLE is characterized by the presence of a subset of anti-DNA antibodies, which also cross-react with the NMDA receptor present on glutamatergic neurons, termed DNRAbs. [9]. When these antibodies access brain parenchyma in the mouse hippocampus, a region often involved in NPSLE based on neuroimaging studies, the interaction of these antibodies with

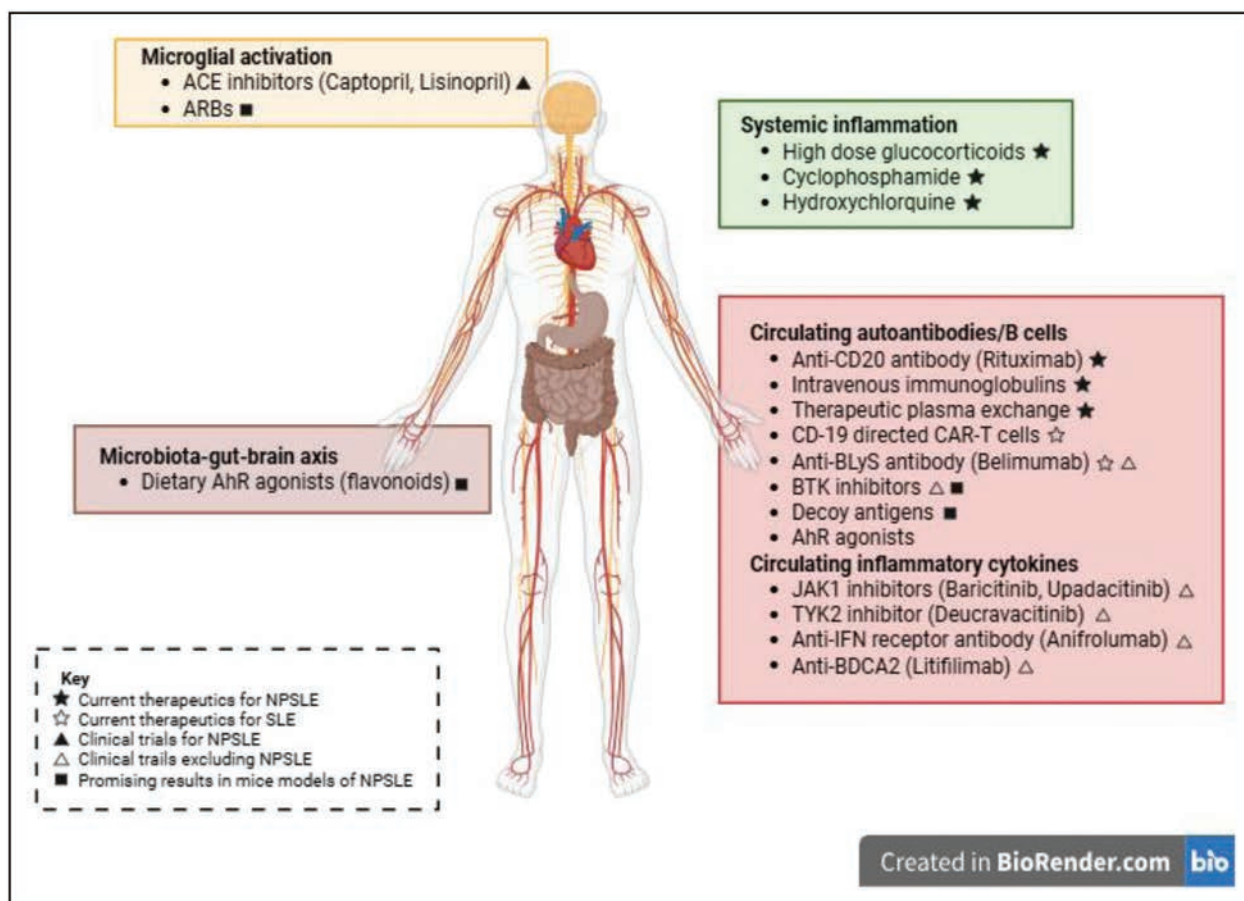


FIGURE 1. Current and emerging therapeutic targets for neuropsychiatric systemic lupus erythematosus (NPSLE). This diagram illustrates the therapeutic interventions for NPSLE, categorized by their mechanism of action.

the NMDA receptor causes immediate excitotoxic neuronal death and the pathology progresses to microglial activation, loss of neuronal dendritic arborization, and cognitive impairment [10¹¹].

Anti-P antibodies, which cross-react with neuronal surface P antigen, also cause direct excitotoxic neuronal death followed by cognitive impairment in a mouse model. There are, no doubt, many other antibodies that are neurotoxic once they cross the BBB [11].

THERAPIES TO REDUCE ANTIBODY TITERS

Current and future therapies that provide neuroprotection by targeting the production of antibodies and autoantibodies will reduce by the engagement of endosomal toll-like receptors by nuclear acid antigens potential exposure of the brain to neurotoxic antibodies. They will also decrease systemic inflammation by limiting the formation of nucleic acid containing immune complexes which can activate endosomal toll-like receptors and induce production of inflammatory cytokines and interferon (IFN). Decreased systemic inflammation will, in turn, help maintain BBB integrity.

Rituximab (Rituxan), a B-cell depleting antibody, is used off-label for severe, refractory SLE, despite the fact that two major clinical trials in nonrenal (EXPLORER) and renal (LUNAR) lupus failed to meet their primary endpoints. Evidence from open-label studies and large, prospective observational cohorts, such as the British Isles Lupus Assessment Group Biologics Register (BILAG-BR), suggest that rituximab can be effective for severe inflammatory NPSLE, however, no large-scale clinical trials have been conducted for subacute central nonfocal NPSLE.

CD19-directed chimeric antigen receptor (CAR) T cell therapy leverages the patient's adaptive immune system by genetically modifying T cells to kill B cells expressing the CD19 protein, thus preventing the production of autoantibodies by B cells. CAR-T cell therapy has been dramatically beneficial in SLE leading to long-term drug-free remissions in many patients. One of the most serious and common side effects of CAR-T cell therapies is Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS). This reaction can lead to disorientation, confusion, delirium, impairments in motor function, and can also lead to cerebral edema [12]. However, CAR-T cell therapy was used as a compassionate treatment for a male patient with severe NPSLE. The treatment has improved the patient's neurological symptoms, reduced inflammatory lesions throughout the CNS, and resulted in no sign of ICANS [13]. The depletion of B cells in patients with SLE by CAR-T cells will mitigate autoantibody-induced damage that contributes to NPSLE [14].

Belimumab (Benlysta), a monoclonal antibody that inhibits the B-cell survival factor BAFF is approved for active, autoantibody-positive SLE and lupus nephritis. However, the BLISS trials explicitly excluded patients with severe active NPSLE and did not specifically address chronic manifestations of CNS lupus. Posthoc analyses have suggested a possible reduction in headache incidence, but this finding is exploratory.

BTK is essential for B cell survival and activation. Treatment with a BTK inhibitor in MRL/lpr lupus-prone mice significantly improved cognitive dysfunction and depression-like behavior, as well as reduced the infiltration of T cells, B cells, and macrophages into the choroid plexus [15]. Clinical trials with two BTK inhibitors, evobrotinib and orelabrutinib have had different outcomes. The Phase 2 clinical trial for evobrutinib in SLE (NCT02975336) failed to meet its primary efficacy endpoints, leading to the termination of its development for SLE. In contrast, orelabrutinib has shown more encouraging results. The Phase 1b/2a study demonstrated a positive trend in efficacy, with a dose-dependent increase in the SLE Responder Index (SRI-4) response rate and a decrease in circulating antidsDNA antibodies compared to placebo. Based on these findings, a larger Phase 2b clinical trial (NCT05688696) is ongoing. To be effective in NPSLE, these therapies would need to reduce autoantibody titers and symptoms of central diffuse NPSLE would need to be assessed.

Emerging therapeutics for SLE include other intracellular kinase inhibitors which target the signaling pathways of inflammatory cytokine receptors and are designed to decrease systemic inflammation and especially interferon. These therapies have potential to decrease BBB permeability and to decrease exposure of brain parenchyma to toxic levels of cytokines. Baricitinib is a JAK1/2 inhibitor that has shown promise in treating SLE, as it reached the primary endpoint of increasing the chance of a patient reaching Systemic Lupus Erythematosus Responder Index 4 (SRI-4) [16]. While clinical trials for baricitinib have been discontinued for failing to reach secondary endpoints, such as glucocorticoid sparing, upadacitinib is a promising JAK 1 inhibitor that is currently undergoing a Phase 3 clinical trial for SLE (NCT05843643) [16,17]

There are additional therapies not currently in the clinic that might be neuroprotective by neutralizing pathogenic antibodies or decreasing plasma cell differentiation. Another potential therapeutic approach is to prevent tissue damage by using decoy antigens to block the interaction between the autoantibody and its target. Thus, preventing tissue damage is a potential therapeutic approach. FISLE-412

binds the subset of autoantibodies that cross-reacts with the NMDA receptor and DNA. In NZB/W F1 mice, a common model for lupus, FISLE-412 was well tolerated, reduced IgG deposition in the glomeruli, delayed the onset of SLE [18], and decreased antibody-mediated neurotoxicity [19].

Another actor in B cell differentiation into antibody producing cells is the aryl hydrocarbon receptor (AHR). The AHR is a transcription factor expressed in all immune cells and in barrier tissues (gut, lung, skin, liver) that can be activated by dietary ligands. AHR activation by one of its ligands, TCDD, has been shown to reduce B cell differentiation and to induce interleukin (IL)-10 secretion [20,21]. Although IL-10 is an anti-inflammatory cytokine in many situations, IL-10 secretion in the CNS may be harmful in NPSLE as it decreases LAIR1-expression in microglia, with LAIR-1 being essential for the downregulation of microglial activation [10**].

THERAPIES TO REDUCE CYTOKINE LEVELS

Type 1 IFN is commonly elevated in the serum of patients with SLE [22]. Injection of an adeno-associated virus expressing type 1 IFN leads to an increase of neurological symptoms in a mouse model of NPSLE [23]. Moreover, IFN therapies used in hematology and oncology are reported have various neurological side effects including deficits in memory retrieval and psychosis [24]. Blocking the interferon signaling pathway remains a potential beneficial approach to managing some NPSLE manifestation.

Deucravacitinib is a selective allosteric TYK2 inhibitor, a member of the JAK family involved in the type I IFN signaling pathway [25]. Deucravacitinib has demonstrated significant efficacy in a Phase 2 trial and has since advanced to a Phase 3 clinical trial [26]. Deucravacitinib is unlikely to cross the BBB; it would be interesting to investigate the effect of a BBB permeable selective TYK2 inhibitor in NPSLE [27].

Anifrolumab and litifilimab are two therapeutics that target the IFN pathway. Anifrolumab is a monoclonal antibody that blocks the type I IFN receptor (IFNAR1) and has been approved for moderate-to-severe SLE, but the trials excluded patients with active, severe NPSLE. Similarly, litifilimab (BIIB059), which targets BDCA2 on plasmacytoid dendritic cells (the main producers of type I IFN), is also in development, but clinical trials have also excluded the population with NPSLE. The exclusion of these patients is debatable as high interferon levels, whether from disease or therapeutic administration, can cause neuropsychiatric side effects, including a condition known as “interferon psychosis” [28]. Patients with

high IFN levels may benefit the most from type IFN blockade as IFN activates the kynurenine (K) pathway, leading to quinolinic acid (Q) synthesis. An added benefit of blocking IFN is that it will increase the K/Q ratio, decreasing NMDA receptor activation, thus decreasing excitotoxic neuronal death.

THERAPIES TO MAINTAIN BLOOD–BRAIN BARRIER INTEGRITY

BBB disruption is necessary for antibodies to penetrate the brain parenchyma. Historically, MRIs using gadolinium-based contrast agents have been used to assess BBB permeability in patients with SLE; this technique has shown that individuals with SLE have a more permeable BBB than healthy controls [29]. However, gadolinium is contraindicated for people with kidney disease, a common symptom of SLE. To overcome this hurdle, new diagnostic technologies are analyzing expanded perivascular spaces/, which are fluid filled cavities around blood vessels in the brain, as a marker of BBB integrity. For example, expanded perivascular spaces (ePVS) are assessed with T1/T2 contrast MRIs. Patients with NPSLE have a significant higher number of ePVS compared to healthy controls, and ePVS are linked to BBB impairment [29,30]. Another method used to characterize the BBB is diffusion tensor imaging along the perivascular space (DTI-ALPS) [31]. Lifestyle factors, such as tobacco use and stress, can compromise BBB integrity, lifestyle interventions may then be a potential strategy for maintaining BBB integrity [32,33]. However, it is important to note that BBB disruption is often a consequence of the inflammatory processes in SLE that can lead to increased cytokine levels, such as TNF, IL-1, IL-6, IFN, and complement activation products, such as C5a.

It has been proposed that an abnormal gut microbiota may contribute to SLE pathogenesis through the AHR pathway, which has a role in maintaining the gut barrier and the BBB [34]. For example, patients with SLE have an altered ratio of *Lactobacillus* and *Bifidobacterium*, specifically a decrease in *Lactobacillus* [35,36]. These bacteria help maintain gut and immune health. A healthy gut microbiome, rich in these beneficial bacteria, is crucial for producing short-chain fatty acids (SCFAs), which have potent anti-inflammatory effects and help to maintain the integrity of the gut barrier and the BBB. When this ratio is skewed, a condition known as dysbiosis occurs, which can lead to a “leaky” gut where antigens can cross into the bloodstream, triggering systemic inflammation exacerbating autoimmune symptoms and decreasing BBB integrity [37]. For example, intestinal commensal *E. gallinarum* can translocate to the liver and cause

autoimmune hepatitis in patients with SLE. *R. gnavus* can increase serum anti-dsDNA antibody and LPS levels [36].

Specific dietary components, such as flavonoids, may be a promising therapeutic avenue for managing SLE by restoring a healthy gut-immune axis. Indole-3-carbinol (I3C) is a flavonoid, which has shown promise in a mouse model of lupus [38]. However, it is worth noting that I3C acts as an AHR ligand that upregulates the production of anti-inflammatory cytokines such as IL-22 and importantly IL-10 [39,40]. While generally considered beneficial, metabolites of I3C, such as 3,3'-diindolylmethane (DIM), can cross the BBB and thus might induce IL-10 production in the brain, possibly promoting microglia-mediated neuronal damage in the DNRAb model of lupus by decreasing the inhibitory receptor LAIR-1 on microglia [10¹¹,41].

THERAPIES TARGETING MICROGLIAL ACTIVATION

One of the lessons from mouse models is that inflammation in the brain does not resolve spontaneously. Treatment may be needed to resolve brain inflammation even in the absence of systemic inflammation.

Centrally acting angiotensin-converting enzyme inhibitors (ACEi) were identified as promising candidate therapeutics due to their ability to suppress microglial activation. They have shown efficacy in Alzheimer's disease (a neurodegenerative disorder accompanied by neuroinflammation) [42]. Moreover, in the mouse model of NPSLE, induced by DNA–NMDA receptor cross reactive antibodies (DNRAb), the brain-penetrant ACE inhibitor captopril, had a protective effect in the CNS, preserving memory and neuronal structure, whereas the non-brain-penetrant ACEi enalapril had no effect. These findings led to the use of Lisinopril, a centrally acting ACEi in a currently active clinical trial in patients with NPSLE [43¹¹]. The mechanism of protection by ACE inhibition is an active area of research. ACE inhibition can protect through several mechanisms. One mechanism is preventing the conversion of angiotensin I into angiotensin II, which can bind to and activate microglia [44]. In the DNRAb mouse model, ACE inhibition certainly provides benefit, at least in part, through this mechanism as angiotensin receptor blockers are also efficacious. Another mechanism of ACE inhibition is preventing ACE from inactivating bradykinin. Bradykinin can quell microglial activation by binding to the B1 receptor (B1R), which is more prominent in activated microglia, and reduces the release of pro-inflammatory cytokines [45–47] and type 1 IFN. Whether this mechanism is operative in the model is not known. Preclinical

studies have shown that IFN can activate microglia and induce neuronal pruning, which can be reversed by blocking IFN [48]. This led to a Phase 2 clinical trial (NCT04486118) to test the efficacy of the centrally acting ACE inhibitor lisinopril patients with lupus displaying cognitive impairment. The trial compares lisinopril to a noncentrally acting ACE inhibitor, benazepril, and assesses changes in resting brain metabolism, cognitive testing, and microglial cell activation to test the hypothesis that brain penetration is key to treatment success.

A mechanistic insight from a mouse model led to a novel therapeutic undergoing clinical trial. Understanding disease mechanisms in the DNRAb model expands future options for therapeutics interventions NPSLE. Other models will similarly inform therapeutics in SLE.

CONCLUSION

Despite the complexity of the disease and the exclusion of NPSLE from clinical trials, the therapeutic landscape for NPSLE is promising. The broader SLE treatment pipeline offers biologics that target cytokines and intracellular kinases involved in inflammation, as well as CAR-T cell therapy, which targets autoantibody-producing B cells. In parallel, insights from studies in DNRAb mice have resulted in a clinical trial for ACEi in patients with NPSLE, investigations into decoy antigens that block the binding of autoantibodies, and the exploration of therapeutics that target the AHR pathway. The multipronged development of therapeutics provides hope for more effective treatments for NPSLE in the future.

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Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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Environmental and occupational contributors to autoimmune, inflammatory, and musculoskeletal rheumatic disease: a review of emerging evidence and clinical implications

Nicole K. Ward^a and Richard S. Panush^b

Purpose of review

Autoimmune and inflammatory rheumatic diseases as well as certain musculoskeletal diseases treated by rheumatologists result from a complex interplay between genetic predisposition and environmental factors.

Recent findings

Accumulating research has examined the possible roles of physical trauma, psychological stress, pollutants, and occupational exposures as triggers or influencers of disease. We review and summarize existing evidence for these contributors for conditions including rheumatoid arthritis, systemic lupus erythematosus, psoriatic arthritis, spondyloarthritis, systemic sclerosis, Sjogren's syndrome, vasculitis, myositis and fibromyalgia. We highlight findings from case-control, cohort, and twin studies that associate trauma, chronic stress and environmental exposure with immune dysregulation and increased disease risk. We apply the GRADE framework to assess the strength of evidence and identify key research gaps. Summary tables are included to guide clinical assessment which could also support interdisciplinary communication in medico-legal contexts.

Summary

These data have implications for disease etiopathogenesis; management; historical appreciation; public health, policy and safety; and legal considerations.

Keywords

autoimmune disease, environment exposures, occupational risk, rheumatology, trauma

INTRODUCTION

Autoimmune and inflammatory rheumatic diseases (AIRDs) such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), psoriatic arthritis (PsA), spondyloarthritis (SpA), systemic sclerosis (SSc), Sjogren's syndrome, myositis, and vasculitis are complex disorders that are influenced by an interplay between genetic and environmental influences [1–11]. While genetic predisposition is fundamental to disease vulnerability, increasing observations explore the role of environmental and psychosocial exposures as significant contributors to disease onset, progression, or expression. Separately, fibromyalgia syndrome (FMS), while not generally considered autoimmune, shares many clinical overlapping clinical features with AIRDs and has also been linked to environmental factors [12–14]. These exposures include inhaled agents (e.g. silica, solvents, cigarette smoke, air pollution, and industrial gases); metals, solvents and industrial coatings such

as lacquers; physical trauma (defined here as significant tissue injury, repetitive biomechanical strain, or musculoskeletal insult), and psychological trauma (e.g. posttraumatic and chronic stress) [4,15^a,16–19].

Environmental factors such as proximity to traffic and industrial zones may also impact exposure to

^aDivision of Rheumatology, Department of Medicine Cedars Sinai Medical Center, Los Angeles, California and ^bDivision of Rheumatology, Department of Medicine, Keck Medical School, University of Southern California, Los Angeles, California, USA

Correspondence to Nicole K. Ward, DO, MPH, Cedars-Sinai Medical Center, Los Angeles, CA 90048, USA.

E-mail: Nicole.Zagelbaum@cshs.org

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KEY POINTS

- This review provides a framework for clinicians to assess environmental and occupational exposures related to the onset, expression, and progression of autoimmune and inflammatory rheumatic conditions.
- It highlights the importance of considering factors such as trauma, stress, silica, solvents, and mechanical factors in the pathogenesis of these diseases.
- The article offers valuable guidance for counseling patients regarding disability, workplace accommodations, and injury-related claims stemming from environmental and occupational exposures.

air quality, stress, and socioeconomic influences. Although causal relationships are difficult to establish, emerging data suggest these exposures may perturb host immune and neuroendocrine pathways and affect disease in susceptible individuals. Observational research includes epidemiologic reports, cohort studies, and case-control analyses [6,20–24].

Although causality is difficult to establish, claims of association arise frequently in disability evaluations, workers' compensation, and tort litigation. Literature relating to occupational medicine also summarizes those recognized and suspected environmental risk factors for autoimmune and other rheumatic diseases [25] including some that are relevant to medicolegal contexts [26].

We therefore reviewed and summarized the pertinent available literature regarding possible relationships of environmental, occupational, physical, and psycho-social contributions to rheumatoid arthritis, systemic lupus erythematosus, psoriatic arthritis, spondyloarthritis, systemic sclerosis, Sjogren's syndrome, vasculitis, myositis, and fibromyalgia. We highlighted findings from case-control, cohort, and twin studies that associate trauma, chronic stress and environmental exposure with immune dysregulation and increased disease risk. We applied the American College of Rheumatology GRADE framework to assess the strength of evidence and identify key research gaps. We discuss the implications of these observations for disease etiopathogenesis; management; historical appreciation; public health, policy and safety; and legal considerations.

ENVIRONMENTAL EXPOSURE AND AUTOIMMUNE AND INFLAMMATORY RHEUMATIC DISEASES

We performed a literature review using PubMed, focusing on human studies published in English

between January 1990 and May 2025. Observational and interventional studies were screened at the title-and-abstract stage. Additional references were identified from article bibliographies and relevant reviews. Eligible studies included exploration of an association between at least one environmental or psychosocial exposure and the incidence or clinical course of one of the diseases of interest.

Studies were grouped into five exposure categories: physical trauma or biomechanical stress; psychological stress or trauma; inhaled pollutants and particulates (e.g. silica, air pollution, cigarette smoke); metals, solvents, and industrial chemicals; and animal and domestic exposures.

For each study, data were extracted including design, population characteristics, comparator definition, follow-up duration, primary outcome, and reported effect estimates. Key data extracted included study design, population, comparator groups, duration, primary outcome, and strength of association. When available, findings were integrated into summary evidence tables.

Exposures related to diet, allergens, and drug-induced autoimmune syndromes were excluded and considered beyond the scope of this review. Pet ownership or animal contact were also excluded unless they were explicitly assessed in human epidemiologic studies. Non-English studies were excluded unless full-text translation was available.

For each observational study we applied the American College of Rheumatology adaptation of the GRADE framework and rated the certainty of each exposure-disease association as high, moderate, low, or very low considering study design, risk of bias, result consistency, evidence of a dose-response gradient, and biological plausibility (see Table 1). Findings were summarized by exposure category (see Tables 2–4). Tables 2–4 present detailed data from primary studies reporting associations between specific exposures and rheumatic diseases. For each entry, we summarized study design, participant numbers, duration, comparator groups, and primary outcomes to provide a structured and comparative overview of the literature.

Physical trauma and biomechanical stress (see Tables 1–4 for additional details and GRADEs)

In RA, observational and case-based data suggest a possible link between injury and disease onset although the data were limited. Early case series and historical reports, including a three-patient series of RA or PsA-like disease following finger joint trauma, a case of seronegative monoarticular arthritis of the elbow after a radial head fracture with persistent synovitis for over seven years, and a 2024 case of

Table 1. Observational evidence outlining occupational risks and rheumatic disease

Disease	Occupation or risk factor	Increased risk?	Grade level of evidence*	Comments
RA (Wallace <i>et al.</i>) [112]	Emotional or physical trauma	Possibly (aggravation more than causation)	Low	Several studies suggest stress and trauma can exacerbate existing disease Weak support for initiating disease
RA (Karlson <i>et al.</i>) [6]	Smoking Silica	Yes	Low	Smoking: Most consistently demonstrated environmental risk factor stronger association in ACPA+ RA; dose-response relationship present Silica: Multiple cohort and case-control studies show consistent dose-response relationship
RA (Anaya <i>et al.</i>) [4]	Smoking, silica, mineral oil	Yes	Low	Smoking interacts with HLA-DRB1 shared epitope Silica linked to Caplan's syndrome
RA (Di Giuseppe <i>et al.</i>) [67]	Smoking	Yes	Moderate	Meta-analysis (10 studies) found dose-response relationship, with risk plateauing beyond 20 pack-years Stronger for RF-positive RA (RR 2.47)
RA (Tobon <i>et al.</i>) [19]	Smoking	Yes	Moderate	Strong, consistent evidence from cohort and case-control studies
RA (Sigaux <i>et al.</i>) [113]	Silica	Yes	Moderate	Dust Exposure Life-Course Questionnaire used
RA (Aleganova <i>et al.</i>) [157]	Fine particulate matter PM2.5, coarse particles (PM10), other gases including sulfur dioxide (SO2), carbon monoxide (CO), nitrogen oxides (NOx)	Yes	Moderate	Fire smoke-related PM2.5 exposure is associated with increased risk of incident RA Exposure to fossil fuel-related NOx was most strongly associated with RA overall and with seronegative RA Associations persisted even among never-smokers
RA, SLE (Barragan-Martinez <i>et al.</i>) [5]	Smoking, Silica, solvents	Yes	Low	Meta-analysis with subgroup analysis showed consistent association Supported by additional case-control studies; heterogeneity noted
SLE (Edwards <i>et al.</i>) [114]	Silica, silicone, aromatic amines, hydrazines, vinyl chloride, solvents, metals, smoking, infections	Yes	Low	Theoretical mechanisms outlined
SLE (Goldshen <i>et al.</i>) [547]	PTSD	Yes	Moderate	Prospective cohort studies and large epidemiologic database Behavioral factors including smoking may be related
SLE (Parks <i>et al.</i>) [22]	Silica	Likely	Moderate	Association noted but smaller and less consistent than for SSC
SLE (Barbhaiya <i>et al.</i>) [16]	Smoking, silica	Yes	Moderate	Smoking remains a key modifiable risk factor in SLE
SLE (Parperis <i>et al.</i>) [11577]	PTSD (including from combat, 9/11 exposure, childhood trauma, military service)	Yes	Moderate	All included studies reported positive association
SLE (Gardner <i>et al.</i>) [91]	Mercury exposure in gold mining	Yes	Low	Mercury-exposed Brazilian gold miners had higher ANA, and pro-inflammatory cytokines vs. nonexposed miners Cross-sectional field study
PsA (Stober <i>et al.</i>) [116]	Trauma, biomechanical stress, obesity	Yes	Low	Promotes biomechanical stress at entheses Increasing risk of transition from Psoriasis to PsA; dose-dependent risk

Table 1 (Continued)

Disease	Occupation or risk factor	Increased risk?	Grade level of evidence*	Comments
PsA (Hseih <i>et al.</i>) [36]	Physical trauma	Possible	Moderate	~9% PsA patients report trauma prior to onset vs. 1–2% in RA/SpA Supported by retrospective case series and case–control studies
SSc (Keitnanah <i>et al.</i>) [76]	Organic solvents	Yes	Moderate	Meta-analysis of 11 studies (n = 1,291 SSc, 3,435 controls) found OR 2.4 [95% CI 1.7–3.4], higher risk in men (OR 3.0) than women (OR 1.8) Heterogeneity and publication bias noted
SSc (Aryal <i>et al.</i>) [93]	Organic solvents	Yes	Moderate	Meta-analysis of eight studies (7 case–control, 1 cohort) identified increased relative risk with solvents and disease (RR = 2.9, 95% CI 1.6–5.3) Limitations included heterogeneity
SSc (Mora <i>et al.</i>) [77]	Silica, aromatic hydrocarbons	Possible	Low	Occupational silica exposure a known risk; solvent evidence growing
SSc (Garabrant <i>et al.</i>) [104]	Organic solvents Paint thinners and removers	Possibly (weak association)	Low	Some studies show increased risk, mostly in men Associations inconsistent
SSc (Rubio <i>et al.</i>) [81]	Silica	Yes	Moderate	13 case–control studies with data from 2,107 patients
Myositis (Costa) [1]	Environmental exposures (e.g., birds, mold, feather pillows)	Yes	Low	Retrospective observational study; 59% of patients reported exposures, 74% among those with pulmonary onset Suggests link between environmental antigens and disease phenotype
FMS (Wolfe <i>et al.</i>) [117]	Physical trauma: motor vehicle accidents, surgery, work injury, whiplash	Not clear	Low	Most of the supporting studies are low-quality, with selection, recall, or measurement bias
FMS (White <i>et al.</i>) [118]	Physical trauma	Possibly	Low	More high quality research needed including prospective design, psychological profile, long term follow up and litigation must be addressed

* Evidence grading: the quality of evidence for each exposure–disease relationship was assessed using the GRADE framework. Studies were classified as high, moderate, low, or very low quality based on judgement about study design, consistency of findings, presence of dose–response, risk of bias, and biological plausibility. Prospective cohort studies with consistent findings and mechanistic support were graded higher than single case–control or retrospective studies.

Table 2. Summary of trials surrounding rheumatologic disease and environmental exposure (trauma)

Study	Design	Participants	Duration	Comparator groups	Primary outcome
Trauma: RA					
A case-control study examining the role of physical trauma and the onset of rheumatoid arthritis [29]	Multicenter retrospective case-control	262 RA	N/A	262 controls	55/262 (21%) RA patients reported physical trauma within six months prior to onset
Trauma: PsA					
Interplay between environmental factors, articular involvement, and HLA-b27 in patients with psoriatic arthritis [35]	Retrospective case-control	138 PsA	N/A	138 RA	12/138 (9%) PsA reported preceding acute medical disorder < 10 days prior vs. 2/138 RA
Clinical, laboratory and immunogenetic aspects of posttraumatic psoriatic arthritis: a study of 25 patients [33]	Case series with a comparison cohort	300 PsA	1-7 years	300 RA 100 SpA	25/300 PsA with preceding trauma < 3 months prior to disease onset
Association between environmental factors and onset of psoriatic arthritis in patients with psoriasis [37]	Case-control	159 PsA	N/A	159 Psoriasis	PsA associated with heavy lifting (OR ~2.9) and infections requiring antibiotics (OR ~1.7) Injuries showed a borderline association, smoking was protective (OR ~0.5)
Physical trauma recorded in primary care is associated with the onset of psoriatic arthritis among patients with psoriasis [34]	Matched cohort	15,416 PsA with trauma	N/A	55,230 controls without trauma	Multivariate HR 1.32 (95% CI 1.13-1.54); joint trauma HR 1.50 (1.19-1.90); bone trauma HR 1.46 (1.04-2.04)
Trauma: SpA					
Seronegative spondyloarthropathy initiated by physical trauma [40]	Cross-sectional	288 SpA	N/A	N/A	12 patients identified with physical trauma 1 month prior to SpA
Trauma: SSc					
Scleroderma and occupational exposure to hand-transmitted vibration [43]	Case-control	76 Ssc	> 6 months of job exposure	213 controls	SSc men more likely than controls to have had exposure to hand-transmitted vibration (OR ~1.5) or silica (OR ~5.2) but the association was not statistically significant
Trauma: FMS					
Role of road traffic accidents and other traumatic events in the onset of chronic widespread pain: results from a population based prospective study [48]	Case-control	241 with chronic widespread pain	4 years	N/A	Road traffic accidents associated with higher risk of chronic widespread pain (OR 1.84), but association lost significance after adjusting for psychological and sleep factors (OR 1.50)

Table 2 (Continued)

Study	Design	Participants	Duration	Comparator groups	Primary outcome
Mechanical injury and psychosocial factors in the workplace predict the onset of widespread body pain: a 2 year prospective study among cohorts of newly employed workers [49]	Prospective cohort	1,081 respondents	2 years	896 free of pain	New widespread pain associated with: lifting >15 pounds 1 hand, >24 pounds 2 hands, pulling >56 pounds, squatting and prolonged work with hands Psychosocial factors include job satisfaction
A case-control study examining the role of physical trauma and the onset of fibromyalgia syndrome [12]	Retrospective case-control	136 FMS	N/A	152 controls	53/136 (39%) FMS patients reported trauma 6 months prior to onset 22/102 adults with neck injury developed FMS 1 year after injury compared to 1/59 adults with lower extremity fractures
Increased rates of fibromyalgia following cervical spine injury. A controlled study of 161 cases of traumatic injury [45]	Cohort	102 adults neck injuries	Mean 3.2 months post injury	59 lower extremity fractures	FMS diagnosed in 21.6% of neck injury patients vs. 1.7% of controls (P = 0.001), FMS 13 × more frequent after neck injury
Does physical trauma lead to an increase in the risk of new onset widespread pain? [47]	Prospective cohort	376 crash-exposed	6 months	114 non-crash controls	New onset widespread pain at 6 months: 8% in crash group vs 4% in non-crash Association not statistically significant after adjustment for psychological factors
The role of workplace low-level mechanical trauma, posture and environment in the onset of chronic widespread pain [14]	Prospective cohort	1,658 adults	Baseline, 12 month, and 36 month follow-up	Exposed vs unexposed to workplace mechanical, postural, and psychosocial risk factors	Mechanical risk factors: Pushing/pulling heavy weights (RR 1.5) Repetitive wrist movements (RR 1.8) Kneeling (RR 1.7)

Table 3. Summary of trials surrounding rheumatologic disease and environmental exposure (stress)

Study	Design	Participants	Duration	Comparator groups	Primary outcome
Environment: stress RA					
A twin study of the association between PTSD symptoms and rheumatoid arthritis [53]	Prospective observational	3,143 twin pairs	4 years	PTSD symptom quartiles; within-pair twin analyses controlling for familial/genetic factors	Highest PTSD symptom quartile had 3.8× higher odds of RA (95% CI 2.1–6.1) vs. lowest quartile Association persisted within twin pairs
Elevated risk for autoimmune disorders in Iraq and Afghanistan veterans with posttraumatic stress disorder [52]	Cohort	666,269 Veterans	Median follow up 4.1 years	Veterans with no psychiatric disorders	PTSD doubled risk of autoimmune disorders overall (ARR 2.0 vs. no psychiatric diagnoses), with elevated risk for RA and SLE
Post-traumatic stress disorder and risk for incident rheumatoid arthritis [51]	Prospective cohort	54,224 female nurses	22 years	N/A	Higher PTSD symptoms associated with increased RA risk (HR 1.76, 95% CI 1.16–2.67) Risk rose with number of PTSD symptoms ($P = 0.01$)
Role of stress in the development of rheumatoid arthritis: a case-control study [50]	Case-control	76 RA	N/A	76 controls	RA patients had higher stress scores (167 vs 83, $p < 0.001$) RA patients reported more stressful life events (5.4 vs 2.7, $p < 0.001$)
Environment: Stress SLE					
Elevated risk for autoimmune disorders in Iraq and Afghanistan veterans with posttraumatic stress disorder [52]	Retrospective cohort	666,269 Veterans	Median follow-up: 4.9 years	PTSD vs. No psychiatric diagnosis	Veterans with PTSD had a 58% increased risk of developing AIRDs (adjusted HR 1.58; 95% CI 1.47–1.69)
Association of trauma and posttraumatic stress disorder with incident systemic lupus erythematosus (SLE) in a longitudinal cohort of women [32]	Longitudinal	54,763 female nurses	24 years	N/A	73 women developed SLE Probable PTSD (4–7 symptoms) was significantly associated with an almost three-fold increased risk of SLE (HR 2.94, 95% CI: 1.19–7.26, $p < 0.05$)
The association of trauma with self-reported flares and disease activity in systemic lupus erythematosus (SLE) [31]	Cross-sectional	252 SLE	N/A	N/A	Any traumatic event (excluding illness) was associated with more than double the odds of a self-reported flare in SLE (OR 2.27, 95% CI 1.24–4.17)

Table 3 (Continued)

Study	Design	Participants	Duration	Comparator groups	Primary outcome
Association of stress-related disorders with subsequent autoimmune disease [55]	Cohort	1,064,640 patients with stress related disorders	10 years	Matched 1,064,640 unexposed persons 126,652 full siblings	Patients with stress-related disorders had an increased risk of autoimmune disease (HR = 1.36) PTSD: autoimmune disease was higher (HR = 1.46) This risk more pronounced for multiple (≥ 3) AIRDs (HR = 2.29)
Perceived stress independently predicts worse disease activity and symptoms in a multi-racial/ethnic systemic lupus cohort [56***]	Prospective longitudinal cohort	260 SLE	3 years	N/A	Perceived stress independently associated with greater physician-assessed disease activity ($p = 0.015$), greater self-reported disease activity ($p < 0.001$), more pain ($p = 0.019$), and more fatigue ($p < 0.001$)
Environment: Stress SpA					
Influence of environmental factors on disease activity in spondyloarthritis: a prospective cohort study [58]	Prospective cohort	272 SpA	3 years	N/A	Significant temporal relationship between stressful life events and increased SpA disease activity (95% CI 0.4–0.7)
Infection and work stress are potential triggers of ankylosing spondylitis [8]	Retrospective population survey	1,080 SpA	N/A	102 patients with chronic back pain	SpA patients were more likely to report workplace stress in the 12 months before symptom onset compared to the prior year (OR 1.51, 95% CI 1.07–2.14)
Posttraumatic stress disorder prior to diagnosis is as rare in spondyloarthritis as in non-inflammatory rheumatic conditions and rheumatoid arthritis [7]	Observational cohort	510 SpA (167 ankylosing spondylitis, 140 PsA, 130 non-radiographic axSpA, and 51 peripheral SpA)	N/A	365 patients with non-inflammatory rheumatic control diagnoses 514 RA	PTSD prevalence prior to diagnosis: SpA: 4.9% RA: 6.6% Non-inflammatory controls: 6.0% Differences not statistically significant
Environment: Stress Sjogren's Syndrome					
Stress, coping strategies and social support in patients with primary Sjogren's syndrome prior to disease onset: a retrospective case-control study [60]	Case-control	47 Sjogren's	N/A	35 patients with lymphoma 120 healthy controls	Experiencing more than one negative stressful life event increased the risk of disease onset fourfold when compared to healthy controls (OR = 4.25, 95% CI: 1.57 to 11.49)

Table 3 (Continued)

Study	Design	Participants	Duration	Comparator groups	Primary outcome
Association between stressful life events and female primary Sjogren's syndrome and their role in disease activity [59]	Case-control	67 Sjogren's	N/A	67 controls	Negative-event score associated with increased risk (OR 1.31, 95% CI 1.19–1.43); negative events correlated with disease activity ($p < 0.05$)
Environment: Stress FMS					
Traumatic experiences, major life stressors, and self-reporting a physician-given fibromyalgia diagnosis [63]	Cross-sectional	10,424 adults	N/A	Trauma-exposed vs non-trauma-exposed	FMS significantly associated with lifetime physical (OR 1.38) and sexual abuse (OR 1.41), even after adjustment for age, sex, race, and education.
Vulnerability to traumatic stress in fibromyalgia patients: 19 month follow-up after the great East Japan disaster [46]	Prospective observational	60 FMS	19 months	23 RA 26 healthy controls	FMS patients had significantly higher trauma scores than RA or controls with more depression symptoms
Posttraumatic stress disorder, tenderness, and fibromyalgia syndrome: are they different entities? [64]	Cross-sectional	124 men (55 PTSD, 20 depression, 49 healthy controls)	N/A	49 healthy controls	49% of PTSD patients met ACR criteria for FMS vs. 5% with depression and 0% controls Strong correlation between PTSD severity and tender point burden

Table 4. Summary of trials surrounding rheumatologic disease and environmental exposure (pollution, solvents, and pets)

Study	Design	Participants	Duration	Comparator groups	Primary outcome
Environment: RA					
Occupational exposure to respirable silica and risk of autoimmune rheumatic disease: a nationwide cohort study [68]	Cohort	1,541,505 men and 1,470,769 women (12,268 RA)	1979–2015	Non-exposed workers	Men exposed to high levels of respirable crystalline silica had an increased incidence rate ratio (IRR) for RA of 1.57 (95% CI 1.41–1.75)
Rheumatoid arthritis among women in the agricultural health study: risk associated with farming activities and exposures [87]	Case-control	135 RA	10 years	675 controls	Pesticides: no strong associations Any welding activity, whether on or off the farm, was associated with a 2.1-fold increased risk of RA (OR = 2.1, 95% CI: 0.8–5.4)
Exposure to traffic pollution and increased risk of rheumatoid arthritis [23]	Cohort	90,297 female nurses	28 years	Exposure to high vs. low long-term PM _{2.5} levels (air pollution)	Women living <50 meters of major road had a 31% higher risk of RA compared to controls (HR 1.31, 95% CI: 0.98–1.74)
Silica exposure among male current smokers is associated with a high risk of developing ACPA positive rheumatoid arthritis [21]	Case-control	1,419 RA	10 years	1,674 controls	Particularly pronounced among nonsmokers, 62% increased risk of RA (HR 1.62, 95% CI: 1.04–2.52) Increased risk of developing RA (HR 1.31) associated with traffic-related air pollution
Association between occupational exposure to mineral oil and rheumatoid arthritis: results from the Swedish ERA case-control study [10,119]	Case-control	1,598 RA	N/A	2,514 controls	Association of silica exposure with RA risk, especially in ACPA-positive men Mineral oil exposure associated with increased risk of RF+ RA in men (OR up to 2.1); no association in women
Insecticide use and risk of rheumatoid arthritis and systemic lupus erythematosus in the women's health initiative observational study [89]	Cohort	76,861 postmenopausal women	Mean follow up 7.6 years	Never vs. personal insecticide use; frequent vs. infrequent exposure, with/without farm history	Personal and residential insecticide use associated with increased RA/SLE risk; strongest effect with frequent use (HR 2.04) and among farm-exposed women (HR 2.73)
Genetic susceptibility and the link between cat exposure and rheumatoid arthritis [98]	Case-control	98 RA	N/A	77 controls	Increased RA risk in those with DRB1 0401, *0404, or *1501 and intimate cat exposure (OR up to 8.4)
Rheumatoid arthritis: are pets implicated in its etiology? [97]	Case-control	132 RA	N/A	Cat ownership vs. none 132 matched controls	Non-significant trend toward increased RA risk with cat exposure; supports hypothesis of microbial antigen role but not conclusive
Occupation, occupational exposure to chemicals and rheumatological disease: a register-based cohort study [86]	Cohort	515,174 Swedish workers (375,035 men, 140,139 women), aged 35–74 in 1980, with ≥10 years in same occupation	1981-1983	Occupational exposures based on a job-exposure matrix (e.g. organic solvents, mineral oils) vs. unexposed	Exposure to organic solvents was associated with an odds ratio (OR) of 2.3 for developing RA

Table 4 (Continued)

Study	Design	Participants	Duration	Comparator groups	Primary outcome
Occupations and exposures in the work environment as determinants for rheumatoid arthritis [30]	Case-control	293 RA	20 year latency	Population control	OR for RA by exposure: Male conductors OR 17.8 (95% CI 1.5–207.8) Farmers OR 2.4 (1.1–5.2) Asbestos exposure OR 2.5 (1.0–6.8) Vibrations OR 2.0 (0.9–4.4)
Silica dust exposure increases risk for rheumatoid arthritis [120]	Case-control	141 RA	2007–2016 (after 2-year washout)	549 controls	Among men with high cumulative exposure to solvents, OR for ACPA-positive RA was 1.54 (95% CI 1.10 to 2.16).
Are cleaning activities a source of exposure to crystalline silica in women with rheumatoid arthritis? A case-control study [120]	Case-control	31,139 RA	N/A	Matched controls smoking, age, sex	RA had significantly higher occupational exposure scores for cleaning activities (p=0.02) and dusty work clothes (p=0.01)
Air pollution exposure increases the risk of rheumatoid arthritis: a longitudinal and nationwide study [121]	Cohort	97 RA	10 years	Quartiles of yearly averages	High exposure to silica exposure associated with ILD (OR 6.5, 95% CI 1.3–32.6) Increased risk of RA in participants exposed to nitrogen dioxide (NO2) (HR 1.07, 1.63, 1.49)
Air pollution as a potential determinant of rheumatoid arthritis: a population based cohort study in Taiwan [71]	Cohort	3,895 RA	10 years	Compared with entire cohort 322,301	Long-term PM _{2.5} exposure showed no clear increase in RA
Occupational exposure to respirable silica and risk of autoimmune rheumatic disease: a nationwide cohort study [68]	Cohort	1,541,505 men (3,490 RA) 1,470,769 women (9,190 RA)	1979-2015	No exposure	Individuals in the highest NO ₂ quartiles had ~50% higher adjusted risk of developing RA. Incidence rate RA: Men: RR 1.57 (95% CI 1.41–1.75) Women: RR 1.42 (95% CI 1.29–1.56)
Associations of fire smoke and other pollutants with incident rheumatoid arthritis and rheumatoid arthritis-associated interstitial lung disease [70a]	Case-control	9,701 RA (531 with RA-ILD)	5–9 years of exposure data	68,851 controls	Fire smoke-related PM _{2.5} associated with increased risk of RA/ILD (OR = 1.98) NO associated with increased risk of RA overall
Occupational exposure to organic dusts and risk of developing rheumatoid arthritis: findings from a Swedish population-based case-control study [69]	Case-control	12,582 RA	Exposure estimates by job history	129,335 controls	Seropositive RA: OR 1.2 (95% CI: 1.1–1.4) Seronegative RA: OR 1.3 (95% CI: 1.1–1.5) Dose-response relationship animal dust OR 1.4 (95% CI: 1.1–1.8)
Systemic autoimmune disease mortality and occupational exposures [85]	Mortality-based case-control	36,178 RA 7,241 SLE 5,642 SSc 4,270 other	N/A Death certificate data	Occupational groups (e.g., farming, animal contact, industrial work) vs. general population	Farming: increased risk death AIRDs (OR 1.3, 95% CI 1.2–1.4) Mining machine operators: increased risk of death AIRDs (OR 1.3, 95% CI 1.1–1.5) Hand painting, hand coating and hand decorating: increased risk of death AIRDs (OR 1.8, 95% CI 1.0–2.9)

Table 4 (Continued)

Study	Design	Participants	Duration	Comparator groups	Primary outcome
Predicting the impact of air quality index on rheumatoid arthritis disease activity [72]	Retrospective observational study	1,185 female 341 male	Variable	N/A	NO: significantly linked with DAS28 (Disease Activity Score assessing 28 joints) (P = 0.0024) PM ₁₀ : negative coefficient and was significantly linked with DAS28 (P=0.0098) O ₃ : significantly linked with DAS28 (P = 0.0057)
Environment: SLE					
Occupational and environmental exposures and risk of systemic lupus erythematosus: silica, sunlight, solvents [20]	Case-control	258 SLE	N/A	263 controls	Silica and SLE: OR 2.1 (95% CI 1.1-4.0)
Associations between ambient fine particulate levels and disease activity in patients with systemic lupus erythematosus (SLE) [73]	Cohort	237 SLE	7 years	N/A	No significant association between PM _{2.5} exposure and overall disease activity (SLEDAI-2K). Short-term increases in PM _{2.5} were significantly associated with presence of anti-dsDNA antibodies (OR 1.34, 95% CI 1.02-1.77)
Acute effects of air pollution on lupus nephritis in patients with systemic lupus erythematosus: a multicenter panel study in China [74]	Cohort	8,552 SLE	4 years	N/A	PM _{2.5} : OR 1.16 (95% CI 1.08-1.19) NO ₂ : OR 1.19 (95% CI 1.12-1.26) SO ₂ : OR < 1 (protective) CO, O ₃ : no significant association
Cluster of systemic lupus erythematosus (SLE) associated with an oil field waste site: a cross sectional study [90]	Cross-sectional	Residents of a subdivision exposed to petroleum products and mercury	N/A	Community comparison	Increased prevalence of SLE and other rheumatic diseases in the exposed community (OR 19.33, 95% CI 1.96-190.72 for SLE and OR 10.78, 95% CI 4.14-28.12 for rheumatic diseases)
Association of systemic lupus erythematosus with uranium exposure in a community living near a uranium-processing plant [88]	Case-control	25 SLE	18 years	99 controls 150 RA	High uranium exposure including occupational linked to nearly a fourfold increased risk of SLE (OR 3.92) Not found in RA
Association of perfluoroalkyl and polyfluoroalkyl substances (PFASs) exposures and the risk of systemic lupus erythematosus: a case-control study in China [75]	Case-control	100 SLE	N/A	100 controls	PFASs are risk factors for SLE and PFASs exposures are associated with SLE risk in a dose-response manner Lifetime exposure assessed
Occupational exposure to crystalline silica and risk of systemic lupus erythematosus [92]	Case-control	265 SLE	N/A	355 controls	Silica: increased risk medium exposure (OR 2.1, 95% CI 1.1-4.0), high exposure (OR 4.6, 95% CI 1.4-15.4)
Fine particulate air pollution and systemic autoimmune rheumatic disease in two Canadian provinces [65]	Population based	Approximate total population of around 7,977,960 residents	Alberta (1993-2007) Quebec (1996-2011)	Within group comparison	Positive relationship between PM _{2.5} exposure and AIRDs including SLE
Environment: SSC					
Systemic sclerosis and occupational risk factors: role of solvents and cleaning products [44]	Case-control	93 SSC	N/A	206 controls	Higher PM _{2.5} levels associated with increased risk
Prospective study to evaluate the association between systemic sclerosis and occupational exposure and review of the literature [18]	Case-control	100 SSC	N/A	300 controls	Organic solvents associated with increased risk of SSC (OR ~2.0)

Table 4 (Continued)

Study	Design	Participants	Duration	Comparator groups	Primary outcome
Occupational silica exposure in an Australian systemic sclerosis cohort [78]	Prospective cohort	1,640 SSc (126 reported silica exposure)	12 years	SSc without exposure	Silica exposure associated with increased odds of SSc (adjusted OR = 1.65; 95% CI: 1.17–2.32); association stronger in men (OR = 2.61)
Occupational quantitative exposure to crystalline silica, solvents and pesticides and risk of clinical forms of systemic sclerosis [79]	Cross-sectional	228 SSc	N/A	N/A	Silica and pesticide exposures underestimated; job-exposure matrices revealed higher prevalence. Non-significant trends toward increased risk in pulmonary fibrotic phenotype (OR 3.12) and vascular phenotype (OR 2.89)
What is the contribution of occupational environmental factors to the occurrence of scleroderma in men? [122]	Case-control	56 SSc	N/A	41 controls	No significant association between SSc and occupational exposure to silica, solvents, or epoxy resins
Prospective risk of rheumatologic disease associated with occupational exposure in a cohort of male construction workers [83]	Prospective cohort	240,983 male construction workers	13 years	Unexposed workers	In combined group (SSc, SLE, RA, dermatomyositis); Silica exposure: RR 1.39 (95% CI 1.17–1.64); Other inorganic dusts: RR 1.31 (95% CI 1.11–1.53)
Environment: Sjogrens Syndrome					
Primary Sjogren's syndrome and occupational risk factors: a case-control study [17]	Case-control	175 Sjogren's	4 years	350 matched controls	Exposure to any type of solvent was associated with increased risk (OR 2.76, 95% CI 1.70–4.47)
Systemic autoimmune rheumatic disease risk is associated with long-term exposure to fine particulate matter [66▪▪]	Population-based cohort	7,482,397 adults	19 years	N/A	Overall: PM _{2.5} linked to increased incidence (HR 1.036, 95% CI 1.002–1.070, per IQR; HR 1.012, 95% CI 1.002–1.021, per decile increase in mixture) Sjogren's syndrome: Stronger effect (HR 1.41, 95% CI 1.00–1.99, per IQR)
Environment: Myositis					
Occupational exposure in patients with the antisynthetase syndrome [11]	Case-control	32 patients with antisynthetase syndrome	N/A	32 patients with myositis without antisynthetase antibodies	High exposure to dusts, gases, or fumes: 16/32 (50%) antisynthetase syndrome vs 7/32 (22%) myositis controls (<i>p</i> < 0.05)
Environment: Vasculitis					
Impact of exposure to environmental particulate matter on the onset of giant cell arteritis [96▪▪]	Case-crossover study	232 GCA	Mean follow-up 38 months	Each patient served as own control	PM ₁₀ exposure: Odds of GCA increased by 27.1% (95% CI 5.8–52.6) per 10µg/m ³ rise within 60 days; in patients ≥70 years, risk increased by 38.8% at a 60-day lag

monoarticular RA in the knee following injury, offered anecdotal support [9,27,28]. A multicenter case-control study reported that recent musculoskeletal trauma was more common in RA patients than controls [29]. Another case-control study found that long term exposure to vibration was associated with increased risk of RA [odds ratio (OR) 2.2, 95% confidence interval (CI): 1.3–3.8] with the highest risks observed in farming, freight/transport, and print-making [30]. While not an acute traumatic event, vibration may result in repetitive mechanical strain and micro-injury, supporting its inclusion in the trauma category.

The role of physical trauma in SLE is not well defined. Some studies assessing trauma exposures in SLE included both physical and psychological domains, complicating categorization. In cross sectional cohort data, higher lifetime exposures including serious accidents, physical assaults, and early life adversity was associated with significantly increased disease flares (OR 2.27, 95% CI 1.24–4.17) and disease activity [31]. Longitudinal cohort data that included both physical and psychological events (e.g., car accidents, assaults, natural disasters), found that exposure was associated with a significantly increased risk of developing SLE [hazard ratio (HR) = 2.87; 95% CI: 1.31–6.28] [32]. However, because these studies did not isolate physical trauma as an independent exposure – and the observed associations likely reflected psychological stress mechanisms – they were not included in the physical trauma exposure summary tables.

In PsA, case series suggested that a higher proportion of patients had a history of trauma preceding symptom onset when compared with RA or SpA populations [33–36]. In one series, 25 of 300 PsA patients reported preonset trauma compared to RA or SpA controls [33] while another found only three of 138 PsA patients with prior articular trauma [35]. More robust evidence from a large population-based cohort study found that psoriasis patients who experienced physical trauma had an increased risk of developing PsA, particularly after joint trauma and bone trauma [34]. A case-control study of psoriasis patients, PsA was independently associated with lifting heavy loads (OR 2.8) and physical injuries (OR 2.1) [37].

In SpA, small studies and case series reported preceding physical trauma [38–42] with new-onset seronegative spondyloarthritis, Reiter's syndrome (the now-discarded term found in the older literature), or peripheral arthritis development within weeks of injuries such as falls, car crashes or joint trauma. Inflammatory symptoms often localized to the site of injury, suggesting a potential role for biomechanical triggers in disease expression

[39,40,42]. Although patient numbers were small, findings were consistent across SpA subtypes. A separate case series described trauma-related complications in ankylosing spondylitis but did not establish trauma as an initiating factor and was therefore excluded from the summary table [41].

SSc data was sparse. In a case-control study of male construction workers, hand-arm vibration from power tools was linked to a higher risk of Raynaud's phenomenon, but not SSc and was difficult to separate from concurrent silica exposure [43]. Another case-control study reported an OR of 3.9 (0.8–19) for vibration and SSc, which was nonsignificant due to the limited number of cases [44].

We were not aware of eligible studies linking physical trauma to the onset of Sjogren's syndrome, myositis, or vasculitis.

In FMS, case-control and prospective studies have found increased risk of chronic widespread pain following motor vehicle accidents and other physical injuries, particularly when accompanied by psychological distress [12,13,45–49]. A case-control study found increased number of FMS patients reported significant physical trauma in the 6 months prior to disease onset, compared to controls [12]. This provided low to moderate-quality evidence, limited by retrospective self-report and modest sample size. A cross-sectional study found FMS in 21.6% of 102 patients with cervical spine injury vs. 1.7% of and 59 leg fracture controls. This provided moderate-quality evidence for a trauma-associated FMS subset [13]. In contrast, another study found low incidence of chronic widespread pain following motor vehicle accidents (MVA) attributing modest associations to psychological distress [47].

Psychological trauma and stress

Psychological trauma, including posttraumatic stress disorder (PTSD), early life adversity, and chronic emotional stress, has been investigated as a potential contributor to autoimmune disease onset, flare activity and symptom severity [50].

In RA, several large epidemiologic studies have reported an increased risk associated with PTSD and early life adversity. Women with PTSD had a significantly higher risk of developing RA over a 24-year follow-up period after adjusting for smoking and other confounders [51]. This relationship has been confirmed in cohort data when compared to veterans with no psychiatric history [52]. A retrospective twin-control study found a dose-dependent relationship between PTSD symptom burden and adult-onset RA [53]. This represented moderate quality evidence due to large sample sizes and prospective design.

Multiple prospective and cohort studies have demonstrated trauma exposure to SLE risk [32,54²²,55,56²³]. One study found a three-fold increased risk of subsequent incident SLE compared with women without trauma exposure when controlling for confounders [32]. Another study of 666 000 post9/11 veterans linked PTSD to SLE [risk ratio (RR)=1.65; 95% CI: 1.14–2.40; $P=0.008$] [52]. In the California Lupus Epidemiology Study (CLUES) cohort a rise in perceived stress over three years correlated with higher disease activity, pain, and fatigue [56²⁴]. This was moderate quality evidence although reliance on self-reported stress was a limitation.

In a case–control study initially discussed in the physical trauma section linking mechanical exposures and PsA onset, emotional stressors such as bereavement, divorce, job changes, unemployment, and treatment for depression or anxiety were assessed but none were significantly associated suggesting discrete life events may not independently trigger PsA onset [37].

A large nationwide cohort study of over 3.7 million individuals found that stress was associated with AIRDs including psoriasis (HR 1.42, 95% CI: 1.37–1.47) [7]. A separate cross-sectional report found psoriasis patients were more likely than dermatology controls to report emotional abuse, substance exposure, and traumatic experiences across lifespan, although PsA was not assessed [57].

In SpA, a prospective cohort of 272 patients found that stressful life events were associated with disease activity ($P<0.005$) [58]. A population survey of 1080 patients reported more physical stress, work problems, and infections in the year prior to symptom onset [8]. In contrast, a cohort study comparing 510 SpA patients with 514 RA and 365 non-inflammatory controls found no significant differences in PTSD provenance prior to diagnosis [7].

We were not aware of evidence linking stress to SSc.

For Sjogren's syndrome, limited but consistent evidence suggested higher frequency of stress prior to disease onset compared to controls. Case–control studies reported more negative stressful life events in the year preceding disease onset among Chinese women with primary Sjogren's syndrome compared to controls (OR=2.59; 95% CI: 1.87–3.58) [59] and more major negative life events compared with healthy and lymphoma controls [60]. This provided low quality due to recall bias and absence of large sample size.

Limited evidence suggested an association between emotional stress and increased risk for AIRDs, with some datasets potentially including vasculitis among the outcomes, although it was not

reported as a distinct category. However, for myositis, we did not identify direct data linking emotional trauma or stress to disease onset or activity.

Multiple studies indicated a significant association between FMS and psychological stress, emotional trauma, and PTSD [61,62]. A large population-based sample found that individuals with a history of physical or sexual abuse had significantly higher odds of reporting a fibromyalgia diagnosis [63]. Following a national disaster, acute stress was associated with disease onset [46] and in a male veteran cohort, nearly half of those with PTSD met fibromyalgia criteria [64]. A 2018 systematic review of 31 studies reported consistent associations between FMS and early-life trauma, particularly sexual and physical abuse. Because it did not examine occupational exposures, it was excluded from Table 1, which is restricted to observational and pooled analyses of occupational risk factors [61]. This represented low quality evidence as these cases are observational in nature.

Environmental and chemical exposures (see Tables 1–4 for additional details and GRADEs)

To clarify the diverse environmental factors implicated in AIRDs, we classified them into three categories: inhaled pollutants and particulates, including both ambient air pollution (e.g., PM_{2.5}, NO₂, and wildfire smoke), occupational dusts (e.g., silica, asbestos, and textile fibers), and indoor air contaminants (e.g., mold and secondhand smoke); metals, solvents, pesticides and industrial chemicals, capturing systemic toxins such as organic solvents, metals, pesticides, and epoxy resins that may be absorbed through inhalation, skin contact, or ingestion; and animal and domestic exposures, including pet ownership, farm animal contact, and household or hobby-related exposures which may influence immune dysregulation and disease onset. We excluded behavioral exposures (e.g., alcohol use), drug-induced syndromes (e.g., hydralazine, procainamide, and penicillamine), and dietary triggers (e.g., allergens and specific food antigens).

Inhaled pollutants and particulates (see Tables 1–4 for additional details and GRADEs)

Emerging evidence suggested that ambient air pollution may contribute to the development of AIRDs [65,66²⁵]. In a population-based cohort of over 7.4 million adults, long-term exposure to fine particulate matter (PM_{2.5}) was associated with a small but significant increased risk of AIRDs including SLE, Sjogren's, and SSc (HR 95% CI: 1.00–1.02) [66²⁵]. This represented high-quality evidence due to the

large cohort, robust exposure modeling, and outcome validation.

In RA, a meta-analysis of ten studies (seven case-control and three cohorts) identified a dose-response relationship to smoking [67]. A nationwide cohort of over 3 million workers found an association between high cumulative silica exposure with increased risk [68] linked silica to ACPA-positive disease (OR 1.67; 95% CI: 1.13–2.48) [21]. In >12 000 RA cases and 129 000 controls, animal and textile dust exposure increased risk for RA (OR 1.6) [69]. Mineral dust (OR 2.5) and asbestos exposure (OR 1.6) were also associated to RA as well as vibration exposure (see trauma section) [30].

Air pollution studies showed consistent associations: a U.S. veteran case-control study [9701 RA, 531 RA interstitial lung disease (ILD)] found NO_x, ozone, and PM₁₀ was associated with higher risk, while fire smoke-related PM_{2.5} increased RA-ILD risk (OR 1.98) [70[■]]. In a Nurses' Health Study (>90 000) traffic related air pollution increased risk of developing RA (HR 1.31), particularly among nonsmokers (HR 1.62) [23]. A Taiwanese cohort study (>322 000) linked CO (HR 1.17), NO₂ (HR 1.54), and O₃ (HR 1.37) to new RA with no significant PM₁₀, and modest SO₂ association (HR 1.02) [71]. Recently, a retrospective observational study in Kuwait found NO₂ and O₃ exposure to be linked to disease activity [72[■]]. These findings represented moderate quality evidence supported by large sample sizes, prospective design, and consistency across cohorts.

In SLE, a multicenter case-control study (258 cases) found that outdoor work, silica exposure, and use of art-related chemicals were associated with increased risk [20]. From the same Canadian cohort, one study found no link between short-term PM_{2.5} exposure and total SLEDAI-2K scores [16] while another reported increased antidsDNA positivity and renal casts following higher PM_{2.5} levels, suggesting subclinical immune activation [73]. A multicenter longitudinal (>8500) found short-term increases in PM_{2.5} and NO₂ associated with increased lupus nephritis risk [74]. A separate case-control study linked five PFASs compounds to SLE with a dose-response relationship [75]. These findings represented moderate-quality evidence supported by large sample size, although limitations included potential regional confounding and reliance on ambient exposure estimates [74].

We were not aware of studies linking inhaled pollutants to SpA or PsA.

For SSc, silica was a well established environmental risk factor [44,76–79]. A meta-analysis of >20 studies found strong associations (ORs 2–37) as well as with solvents (OR ~2) [80]. Another pooled data analysis of 15 case-control studies (OR 2.81,

95% CI: 1.86–4.23) and 4 cohort studies (RR 17.52, 95% CI: 5.98–51.37) confirmed this relationship [81,82]. A case-control study (80 cases, 160 controls) found that silica occupational exposure significantly increased disease risk (OR 4.0, 95% CI: 1.6–9.9) [18]. In the Australian Scleroderma Cohort Study (*n*=1670) silica exposure was linked to earlier disease onset, more joint contractures (OR 1.8), anti-Scl-70 positivity, and worse disability (OR 1.4) [78]. One UK case-control study did not find associations with silica, solvents, or epoxy resins [83].

For Sjogren's syndrome, a cohort in Quebec assessed the impact of PM_{2.5} and AIRD's and found 3268 incident cases as well as increased risk (HR 1.41, 95% CI: 1.00–1.99) [66[■]]. Another study (175 cases, 350 controls) found associations between dichloromethane (OR 9.28), toluene (OR 4.18), white spirit (OR 3.60), and chlorinated solvents (OR 2.95) [17].

For myositis, a case-control study of 32 patients with antisynthetase syndrome (ASS) and 32 myositis controls without antisynthetase antibodies found high exposure to dust, gases, or fumes in 50% of ASS patients vs. 22% of controls (*P*<0.05). This provided low quality evidence, limited by small sample size but supported by antibody-defined subtyping [11]. Isolated case series also suggested links between silica and solvent exposure to myositis, although these were limited by small sample size [84].

In vasculitis, a meta-analysis (33 studies) found a significant association between solvent exposure and AIRDs, including primary systemic vasculitis (OR 1.54; 95% CI: 1.25–1.92) [5]

We were not aware of direct or specific evidence linking pollution to FMS.

Metals, solvents, and industrial chemicals (see Tables 1–4 for additional details and GRADEs)

Industrial occupations surrounding solvent, metal and machinery exposure have been associated with increased risk of systemic autoimmune diseases. A national mortality study identified elevated risk of death from RA, SLE, and SSc among workers in occupations such as machine operation (RA OR 1.5), textile processing, and hand painting or coating (SSc OR 4.4) [85].

For RA, a case-control study (715 cases, >2200 controls) linked farming, freight/transport work, and printmaking with increased risk [30]. In a Swedish cohort (>500 000 workers) organic solvents exposures were associated with increased RA risk (RR=1.2), particularly among spray-painters, lacquer workers, and machinery repairmen [86]. In 76 000 postmenopausal women, self-reported insecticide use was associated with increased risk of RA and

SLE (HR 2.04 for frequency, HR 1.97 duration ≥ 20 years) [22]. The Agricultural Health Study found no overall pesticide association but elevated risk for lindane and welding [87]. Others found no relationship between RA and uranium exposure [88]. A large case-control study (12 582 RA cases, 129 335 controls) found associations with animal dust (OR 1.2–1.3) and textile dust ($P=0.014$) [69]. This represented moderate grade evidence due to large sample size, multiple high-quality cohorts, and dose-response evidence despite some exposure classification limitations.

Insecticide use has been linked to increased risk of SLE [22,89]. A case-control study of 258 patients with SLE and 263 controls found occupational exposures including outdoor work, use of paints or dyes, nail polish application, metals and pottery was associated with increased risk [20]. A prospective study of nurses found dose-dependent increase in SLE risk with occupational solvent exposure (HR 1.59, 95% CI 1.05–2.42) [16]. A community comparison study found increased SLE prevalence in the petroleum and mercury-exposed community compared to controls [90]. In Brazilian miners, mercury exposure in gold mining was associated with increased ANA titers and pro-inflammatory cytokines [interleukin (IL)-1 β , tumor necrosis factor alpha (TNF- α), interferon gamma (IFN- γ)] compared to diamond and emerald miners [91]. SLE development was found to be almost four-fold higher in uranium exposures [88]. Higher SLE prevalence has also been reported in silica-exposed occupations, including uranium miners, scouring powder factory workers, and silicosis patients, with one Swedish registry study noting a more than 20-fold increased hospitalization risk in those with silicosis [92]. However, other studies have found no association between SLE and pesticides [85].

For PsA and SpA current evidence did not establish a consistent or causal association with specific environmental or occupational exposures.

In SSc, a 2001 meta-analysis of 8 studies found increased risk of solvent exposure and disease (RR 2.9) [93]. A 2008 meta-analysis of 11 studies confirmed this relationship in an occupational setting [76]. A larger systematic review and meta-analysis of 33 studies reported that exposure to organic solvents was significantly associated with increased AIRDs (OR 1.54; 95% CI: 1.25–1.92), including SSc and vasculitis [5]. A case-control study of 93 patients with SSc and 206 controls found occupational exposure to solvents was significantly associated with increased risk (OR=3.23; 95% CI: 1.58–6.63) [44]. Additional case-control and observational studies have identified similar associations for epoxy resins, pesticides, and welding fumes [81,85]. Overall this

represented moderate to high-quality evidence, supported by pooled estimates, sensitivity analyses, and minimal publication bias, although heterogeneity in exposure assessment remained a limitation.

A case-control study investigated the association between Sjogren's syndrome and solvent exposure and demonstrated significantly elevated odds ratios for multiple solvents, including dichloromethane (OR 9.28), perchloroethylene (OR 2.64), benzene (OR 3.30), and toluene (OR 4.18). Overall exposure to any solvent (OR 2.76) and to chlorinated or aromatic solvents was associated with higher risk [17]. There was no significant association with pesticide exposure.

A case of polymyositis with antihistidyl-t-RNA synthetase (Jo-1) antibody syndrome was reported following extensive vinyl chloride exposure [94].

Two case reports described systemic vasculitis following prolonged exposure to organic solvents in male workers (electrician and painter), suggesting a possible temporal association [95]. A questionnaire-based study comparing 53 patients with granulomatosis with polyangiitis (GPA) to controls reported possible links between mercury and lead exposure, as well as allergy history, although findings were limited by small sample size [2]. A case cross-over study of 232 patients with giant cell arteritis (GCA) revealed increased odds of disease onset with PM10 particulate exposure, and this effect was stronger in individuals aged ≥ 70 years and in chronically exposed individuals [96*].

For FMS the overall body of research was limited, inconsistent, or inconclusive for these factors.

Animal and domestic exposures (see Tables 1–4 for additional details and GRADEs)

Animal and domestic exposures have been proposed as potential triggers for systemic autoimmune diseases. A national mortality study found that occupational animal exposure was associated with increased risk of death from all AIRDs, with the most consistent association with RA [85]. In a case-control study of 122 RA patients, prepubertal exposure to cats was significantly associated with increased risk (OR 4.9; 95% CI: 2.7–9.0), with a reported dose-response effect [97]. A follow-up genetic analysis found that exposure was strongly associated with RA risk (OR 4.2; 95% CI: 2.1–8.5) [98].

We were not aware of data regarding epidemiological data on human exposure to animals and the development of PsA, SpA, SSc, vasculitis, or FMS.

One hundred eighteen patients with polymyositis, dermatomyositis, or ASS, were studied with exposure to household exposures to mold, birds, and feather pillows using questionnaires. However,

specific results regarding animal-related exposures were not reported, and therefore no conclusions can be drawn from this study regarding animal exposure and myositis risk [11].

DISCUSSION

This review summarized the environmental and occupational exposures to autoimmune, inflammatory and musculoskeletal disease. It covered a broad scope of exposures, including physical trauma, psychological stress, and various chemical agents like silica and solvents. We applied the GRADE framework (Table 1) to evaluate the strength of the evidence and address the clinical and legal implications of these findings, providing a comprehensive review for clinicians to consider when assessing exposure history and injury related claims. The review intentionally excluded several areas of study to maintain focus. We did not cover the potential roles of diet, nutrition, or complementary and alternative medicine, nor historical perspectives of environmental or occupation exposures. For more information on these topics, please see the provided references [25,99–101].

Our review found several key patterns relating environmental exposures to rheumatic disease (Tables 2–4). Certain exposures, such as physical stress, psychological stress, silica, solvents and airborne pollutants had consistent associations with disease onset or exacerbation, although the strength of evidence varied. The evidence for physical trauma and psychological stress was mixed and often depended on the specific disease and context [4,54²²,102]. Psychological stress has been identified in large populations as associated with SLE and other autoimmune diseases, with moderate-level evidence from prospective cohorts and epidemiologic databases [32,54²²,56²²]. The link between silica exposure and diseases including RA [4,15²,16] and SSc [4–6,18,21,76,77,81,82,103,104] was particularly strong and well documented. Overall, the findings suggested a nuanced relationship where environmental factors can act as triggers in presumably genetically susceptible individuals.

These observations highlight how rheumatic disease may develop in predisposed individuals. For example, the increased prevalence of RA after the industrial revolution, associated with increased availability of sugar, perhaps associated with periodontal disease and a trigger like *Porphyromonas gingivalis* perhaps leading to disease, supports the concept that new environmental exposures may contribute importantly to disease [105]. This underscores the importance of gene-environment interactions and the historical search for infectious or environmental triggers. The concept of “therapeutic windows” in

preclinical disease is also relevant, suggesting that understanding these triggers may allow for earlier intervention [106]. Further insight could help guide intervention strategies, including workplace modifications and providing preventive counseling for patients in high-risk occupations. This knowledge also supports targeted screening in exposed populations, potentially leading to earlier diagnosis and treatment.

This review also contributes to the historical understanding of rheumatic diseases, which have long been understood as complex and multifactorial. Certain diseases have not been thought to have been recognized in antiquity, supporting the notion that recent and environmental factors may contribute to their etiology. Nor do we really know what causes (most) rheumatic diseases. We have seen thoughts over the years about humors, infections, food and diets, viruses, amoebae, mycoplasma, other microbes, immune dysregulation, the microbiome, even space aliens!, and now the environment [99,105,107]. This perspective is particularly relevant today as our understanding of complex environmental contributions to disease pathogenesis continues to evolve.

The implications from these findings extend to public health and policy. There is a clear need for stricter occupational safety standards and environmental regulations to protect workers and the general population. Recognizing links between exposure and disease can support a more equitable approach to compensation systems for those affected.

LEGAL IMPLICATIONS

Question of relationships of environmental factors, occupation, trauma, and physical and psycho-social stress frequently arise in disability and legal contexts. While scientific evidence is evolving, legal standards require substantiated proof as well as preponderance of medical evidence when addressing issues of causation and aggravation.

From a medicolegal standpoint, physicians must navigate standards of causation and apportionment. Courts have emphasized that apportionment requires medical evidence and explanation (e.g. Escobedo [108], Gonzales [109]), that aggravation of preexisting conditions may be compensable (Sweat [109]), and that misapplication of psychiatric vs. physical injury standards can undermine physician opinions (Villa [110]). Selected illustrative cases are summarized in Table 5.

CONCLUSION

Environmental exposures are important, although variably supported, contributors to AIRDs and rheumatic disease. Understanding these exposures

Table 5. Legal implications

Legal/jurisdiction principle	Illustrative cases	Outcome and specific rationale	Medical evidence used
Aggravation of preexisting conditions	<i>Sweat v. Superior Industries, Inc.</i> [109]	The Tennessee Supreme Court found a preexisting, asymptomatic disease compensable when employment activities caused an "actual progression" of the disease. The court placed the burden of proving the nonindustrial portion of the progression on the employer, noting the "inability to precisely quantify" the allocation.	Physician testified that in PsA repetitive, strenuous, weight-bearing activities resulted in permanent joint injury.
Apportionment to causation	<i>Gonzales v. Team Infinity, Inc</i> [108]	The court confirmed that apportionment must be based on a physician's analysis of causation. "Vocational apportionment" by nonphysicians cannot negate a valid medical opinion.	Medical experts provided opinions that a preexisting arthritic condition was a contributing cause of disability.
Causation standard for stress related vs. physical injury	<i>Villa v. Calavo Growers, Inc.</i> [110]	The court determined the physician incorrectly applied the stricter psychiatric injury standard to a physical injury (FMS) caused by stress.	The case involved a rheumatologist's opinion that the employee's symptoms were best explained by a preexisting psychiatric condition and did not sufficiently explain the causation related to the physical injury.
Burden of proof and substantial medical evidence	<i>Brophy v. WCAB</i> [123]	The court emphasized that the defendant has the burden of proving a valid basis for apportionment. A physician must adequately explain "how and why" a nonindustrial factor caused a portion of the disability.	Physician determined that heavy smoking and obesity caused 80% of a pulmonary condition. The report was found to be inadequate when the physician could not explain the apportionment between two injuries beyond stating they were close in time.
Medical treatment vs. causation	<i>County of Santa Clara v. WCAB</i> [124]	The court clarified that the employer is not responsible for disability without apportionment if medical treatment is not the sole cause of permanent disability. Apportionment is required if other factors, like a preexisting condition, contribute to the disability.	Diagnostic studies showing preexisting severe osteoarthritis, which led to the need for surgery, served as the basis for a 50% nonindustrial apportionment.
Requirement for substantive apportionment analysis	<i>Linda Becerra v. Conifer Health Solution</i> [125]	The court ruled that the doctor's apportionment analyses did not meet standard for substantial evidence because they failed to provide a detailed explanation of "how and why" the disability was causally related to specific nonindustrial factors or prior injuries.	In the apportionment analysis, the physician noted contribution including multiple factors, such as work stresses and orthopedic injuries, without a specific and individualized assessment of how and why each factor is at present contributing.

provides a critical framework in the evolving understanding of disease pathogenesis and has implications for management, public health and safety, historical perspectives about our diseases, and too considerations in our legal system. Despite growing interest, key gaps remain. Future research should prioritize objective and detailed exposure assessment and outline clear temporal relationships to disease onset [111[¶]]. This may inform public health policy, refine workplace protections, and support intervention in high-risk individuals. In

the meantime, clinicians should maintain vigilance for environmental and psychosocial contributors as part of comprehensive rheumatologic care [126[¶], 127^{¶¶}, 128[¶], 129^{¶¶}].

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Conflicts of interest

The authors do not have financial interests that are directly or indirectly related to the work submitted for publication.

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Spatial transcriptomics: challenges and future directions in musculoskeletal diseases

Keemo Delos Santos^{a,b}, Jason S. Rockel^a and Mohit Kapoor^{a,b,c}

Purpose of review

This review examines recent advancements in spatial transcriptomics and its current and potential use to advance musculoskeletal (MSK) research. These insights will be vital to address the complexity of MSK diseases and will pave the way for future therapeutic developments.

Recent findings

The advent of next-generation sequencing has significantly improved our understanding of the cellular and transcriptomic heterogeneity in the MSK system. Spatial transcriptomics has revolutionized research allowing in-situ gene expression analyses directly from intact histological sections. Understanding spatial transcriptomes of cells within tissues will shed light into the biological complexity of MSK diseases. Here, we summarize the role of spatial transcriptomics in unveiling molecular mechanisms underlying MSK diseases and the challenges prohibiting its widespread application in MSK research, and opportunities to overcome these challenges.

Summary

We provide a summary of emerging techniques in spatial transcriptomic field and its use in advancing MSK research. Furthermore, challenges in its application in MSK tissues are discussed as well as potential future considerations to improve spatial transcriptomics insights.

Keywords

musculoskeletal diseases, next-generation sequencing, spatial transcriptomics

INTRODUCTION

Musculoskeletal (MSK) diseases comprise various forms of disorders affecting bones, muscles, connective tissues, and whole joints, and include wide variety of diseases such as osteoarthritis, rheumatoid arthritis (RA), psoriatic arthritis (PsA), among others [1]. These MSK diseases burden individuals with chronic pain, stiffness, and loss of function leading to poor quality of life and are a major source of disability worldwide. As such, MSK diseases represent a significant global public health and economic concern, which is projected to rise due to an increasing elderly population [2].

The advent of transcriptomic technologies, techniques to study the transcriptome or the sum of all RNA transcripts from an organism, has greatly advanced our understanding of the biological complexity in both physiological and pathological conditions [3–5]. Notably, the emergence of single cell RNA-sequencing (scRNA-seq) and single nucleus RNA-sequencing (snRNA-seq) technologies has considerably increased insights into cellular heterogeneity underlying MSK diseases and broadened our understanding of many aspects of disease pathologies. RNA sequencing has revolutionized the field by giving researchers the ability to assess contributions of single cells in homeostatic and disease states. In the past decade, there have been

notable findings using scRNA-seq and snRNA-seq that have been instrumental in dissecting cellular heterogeneity in MSK tissues affected by osteoarthritis, RA, and PsA [6–8]. However, such methods require intact cells to be dissociated from their native environments and may preclude successful isolation from dense MSK tissues. Most cell dissociation methods can induce transcriptome-wide changes, such as ectopic cell death, stress and/or aggregation [9]. Importantly, these methods cannot retain the spatial organization of cell types within tissues and fall short of capturing tissue architecture complexities, including that of MSK tissues. The location of cells and their position relative to their

^aSchroeder Arthritis Institute, University Health Network, ^bDepartment of Laboratory Medicine and Pathobiology and ^cDepartment of Surgery, University of Toronto, Toronto, Ontario, Canada

Correspondence to Mohit Kapoor, 60 Leonard Avenue, Toronto, ON M5T 2S8, Canada. Tel: +1 416 603 5800 x4796; e-mail: mohit.kapoor@uhn.ca

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KEY POINTS

- Spatial transcriptomics has revolutionized biomedical research by providing a spatial context to cellular transcriptomic profiles.
- In MSK diseases, ST has been used to investigate cellular subtypes in OA, treatment response and inflammatory signals in RA, and inflammation and immune signals in PsA.
- Technical challenges, mainly associated with samples processing of MSK tissues, have precluded wide-spread adoption of spatial transcriptomics in MSK research.
- Emerging spatial protocols for MSK tissues and other -omics technologies will provide critical insights into MSK biology and clinical research.

neighbours can better inform cell and tissue functions [10]. Within the MSK field, the ability to obtain transcriptomic information from dense MSK tissues can give a better understanding of the unique niches within affected tissues, providing useful information on cellular states and phenotypes regulating diseases. Hence, the need to perform transcriptomics on intact tissue has been a prime motivator in advancements of spatial transcriptomics.

Spatial transcriptomics, named Method of the Year 2020 by Nature Methods [11], is a cutting-edge technology allowing in-situ gene expression analysis from intact histological sections [12]. This emerging technology has the power to transform our understanding of cellular heterogeneity within tissues. Using bioinformatic approaches, cell heterogeneity within tissues can be evaluated, enabling deeper insights into cell organization, cell-cell interactions, and their functions within intact healthy and diseased tissues [13]. Transcriptomic information within diseased microenvironments, such as regions of inflamed synovium, within degenerated cartilage, or bone marrow lesions, will be useful to gain a deeper understanding of disease pathologies. Here, we provide a discussion of recent advances in spatial transcriptomics technologies and briefly discuss their use in some studies of MSK diseases such as osteoarthritis, RA, and PsA. We also discuss the challenges and opportunities related to the application of spatial transcriptomics in MSK diseases.

SPATIAL TRANSCRIPTOMICS: SEQUENCING AND IMAGING-BASED TECHNOLOGIES OVERVIEW

ST refers to a diverse array of tools that can quantify and localize RNA expression within the spatial context of tissues and cells [12,14–16]. While methods

such as in-situ hybridization (ISH) have been used for decades to interrogate spatial gene expression, it is limited to a small number of genes and needs to be manually performed [17]. Rapid advancements in spatial transcriptomics technologies coupled with decreasing costs of next-generation sequencing (NGS) over the past decade have led to significant progress in the field. Multiple technologies have emerged in the past few years, with ever increasing resolution and throughput. Broadly, they can be categorized into (1) NGS-based approaches wherein spatial information is encoded onto RNA transcripts prior to sequencing, or (2) imaging-based approaches whereby mRNAs are imaged *in situ* via microscopy (Table 1) [12,14]. Several recent reviews have comprehensively summarized current spatial transcriptomics technologies, their technical features, and avenues for advanced bioinformatics analyses [12,13,15,16].

Sequencing-based spatial platforms provide up to whole-transcriptome coverage and thus, are well suited for hypothesis-generating studies and/or differential gene expression analyses. Additionally, sequencing-based spatial transcriptomics (herein termed NGS-ST) technologies allow for larger capture areas, which is particularly beneficial to study MSK diseases with defined and compartmentalized pathology, such as in the joints of osteoarthritis and RA. Spatial transcriptomics analysis of joint tissues, such as complete capture of full-thickness cartilage, can reveal unprecedented insights underlying disease heterogeneity within discrete spaces. Notably, NGS-ST tools have higher throughput compared to imaging-based strategies. Importantly, adoption of NGS-ST techniques is more straightforward to implement as most tools do not require specialized imaging instruments nor lengthy imaging processes. Conversely, imaging-based spatial transcriptomics technologies benefit from higher sensitivity and resolution, with some techniques achieving transcriptomic profiles at a subcellular level [12]. The trade-off of this higher spatial resolution is lower throughput in transcript detection; however, its targeted profiling is apt for hypothesis-testing or clinical studies.

SPATIAL TRANSCRIPTOMICS TECHNOLOGIES: LIMITATIONS AND CHALLENGES

Despite the wide range of commercially available spatial transcriptomics technologies and their rapid evolution, no single method can address all desired parameters, namely the ability to profile at a single cell level and provide efficient mRNA recovery. Each of the available tools described above has unique capabilities and trade-offs.

Table 1. Overview and comparisons of spatial transcriptomics methods

Type	Method	Spatial resolution	Coverage	Sample compatibility	References
In-situ Capture	Stahl method of ST	Visium HD 2 µm resolution (Single Cell to Subcellular)	Gene Panel (18 000+) or Transcriptome-wide (via polyT-capture)	Fresh Frozen, Fixed, Frozen, FFPE	[18,19]
		Visium, 55 µm resolution (Multicellular)	Transcriptome-wide	Fresh Frozen, Fixed Frozen, FFPE	
In-situ Capture	Stereo-seq	200–500 nm resolution (Subcellular)	Transcriptome-wide	Fresh Frozen, FFPE	[20]
In-situ Capture	High-definition spatial transcriptomics for in situ tissue profiling	2 µm resolution (Single Cell)	Transcriptome-wide	Fresh Frozen	[21]
In-situ Capture	Slide-seq	10 µm (Single Cell)	Transcriptome-wide	Fresh Frozen	[22]
In-situ Capture	Slide-seqv2	10 µm (Single Cell)	Transcriptome-wide	Fresh Frozen	[23]
In-situ Capture	Pixel-seq	1 µm (Subcellular)	Transcriptome-wide	Fresh Frozen	[24]
Imaging-based/ISH	smFish	Subcellular	Gene Panel (18 000+)	Fresh Frozen, FFPE	[25,26]
Imaging-based/ISH	CosMx SMI	10 µm (Single Cell)	1K–6K	Fresh Frozen, FFPE	[27]
Imaging-based/ISH	RNAscope	Single molecule	up to 50K	Fresh Frozen, Fixed, Frozen, FFPE	[28]
ROI selection/In-situ microdissection	GeoMx DSP	10 µm (Single Cell within ROI)	Gene Panel (18 000+)	Fresh Frozen, Fixed, Frozen, FFPE	[29,30]
LCM and scRNA-seq	Geo-seq	Multicellular	Transcriptome-wide	Fresh Frozen	[31]
In-situ Microdissection	Tomo-seq	Multicellular	Transcriptome-wide	Fresh Frozen	[32]

DSP, digital spatial profiler; FFPE, formalin-fixed paraffin-embedded; Geo-seq, geographical position sequencing; ISH, in-situ hybridization; LCM, laser capture microdissection; Pixel-seq, Polony-indexed library-sequencing; ROI, region of interest; scRNA-seq, single-cell RNA sequencing; smFISH, single-molecule fluorescent in-situ hybridization; SMI, single-molecule imaging; ST, spatial transcriptomics; Stereo-seq, spatial enhanced resolution omics-sequencing.

(1) Single-cell resolution – The prevailing issue with spatial transcriptomics approaches is they lack the ability to capture transcripts at a true single-cell resolution. There is considerable work being done to improve spatial resolution either by increasing density of spatial probes on glass slides, like with Visium HD NGS-ST platform, or through decreasing bead diameter, as with Slide-seq v2 NGS-ST (Table 1). On a practical level, however, these emerging NGS-ST tools capture mRNA from single cell-sized areas, as cells often straddle multiple barcoded arrays or pixels. Refining the resolution down to a ‘true’ single cell level is necessary to gain deeper insights into the spatial gene regulation inside single cells. However, high resolution techniques are analytically challenging, as increasing resolution introduces issues such as noise, data sparsity, and difficulty inferring cell boundaries, while requiring more computational power for analyses [33]. As such, integration of spatial transcriptomics data with community driven

cell segmentation tools is crucial to create a comprehensive map of cell types *in situ* and accurately quantify cell type composition [34]. The most widely used deconvolution method is based on unsupervised clustering and is derived from scRNA-seq analyses [35]. However, this does not consider mixed data from multiple cell types. There is a thriving ecosystem of community-based tools and other methods that have been developed to pare out cell types from mixed transcriptomic data from overlapping cells that are continuously evolving alongside spatial transcriptomics developments [36,37]. Moreover, commercially available spatial transcriptomics tools, such as Visium HD NGS-ST and Stereo-seq NGS-ST, provide H&E-based cell segmentation as part of their analytical pipelines [38,39]. An alternative strategy is to integrate spatial transcriptomics data with scRNA-seq to maximize resolution while preserving spatial information [40]. ScRNA-seq data compensates for lower resolution and depth in

current spatial transcriptomics methods and enables further analyses, such as cell-cell interactions and pseudo-time trajectory, to deeply characterize single cells in tissue.

- (2) Species compatibility – Stereo-seq and Visium 3' gene expression assays perform spatial mapping through polyadenylated RNA transcripts offering an unbiased approach. These may be useful for the discovery of novel gene expression patterns and cellular states that targeted approaches may miss. This RNA capture approach is also well suited across a wide range of species, including humans, animals, and plants. Visium, Stereo-seq and Pixel-seq have similar mRNA recovery rates with differences in tissue size compatibility (Table 1). However, Visium 3' HD NGS-ST approach is limited to fresh-frozen tissue sections due to more stringent RNA quality requirements, which may not be compatible with hardened MSK tissues.
- (3) Sample compatibility – While formalin-fixed paraffin-embedded (FFPE) tissue preservation is a widely adopted practice in pathology for long-term storage, most spatial transcriptomics methods are currently only compatible with fresh, flash-frozen tissue. This is likely due to RNA degradation during the FFPE preservation process, which impedes RNA capture [41]. Consequently, RNA detection is lower in FFPE tissue sections compared to fresh tissues due to crosslinking and RNA fragmentation during formalin fixation. Fresh, flash-frozen tissues have inherently higher RNA quality and thus can provide a more comprehensive RNA profile. This presents a challenge with MSK tissues, such as bone and cartilage, which necessitates decalcification and FFPE processing. Visium v1 and HD probe assays, in addition to Stereo-seq technology, support a myriad of sample preparations, including flash-frozen and FFPE samples [18,42]. Another challenge for nearly all spatial transcriptomics methods is the susceptibility of certain tissue sections, particularly hardened tissues like cartilage and bone, or less adherent tissues such as skin, to tearing when placed on a slide or array for spatial profiling, leading to RNA loss and lower RNA detection efficiency. Optimizing section thickness or incorporating replicates is recommended.
- (4) Resolution – Overall, NGS-ST approaches have lower resolution and gene-detection efficiency than imaging-based tools [16]. Due to the limited capture size of arrays, some complex structures and lower abundant genes pose a challenge via NGS-ST methods. Depending on the efficacy of cell segmentation, study of rare cells can be

difficult as they cannot be profiled individually even at a single-cell scale. It is likely that the transcriptome from these rare cells is captured and mixed with its surrounding neighbours. Of note, lower abundance transcripts, as well as noncoding and small RNAs, may not be captured without added sequencing costs. Additionally, lowly transcribed genes, such as certain transcription factors, may be difficult to detect with the relatively low detection efficiency of current era spatial transcriptomics tools. Furthermore, poly-A based capture chemistries are more inclined to detect highly expressed genes. Therefore, it is recommended to perform experiments, such as immunohistochemistry or in-situ hybridization, in parallel with spatial profiling if rare cell types or lowly expressed genes are the area of study.

- (5) Tissue size – The capture area or the field-of-view dictates the tissue size and type that is feasible for study. Larger tissue sections remain a challenge, with size constraints of current spatial transcriptomics tools. Out of all NGS-ST technologies, Stereo-seq is well suited for larger tissues with capture areas of 10x10 or 20x30mm [42]. However, underpinning this improvement is increasing sequencing and computational costs. The larger tissue sections and increasing cellular resolution require more data points, and thus more sequencing depth and higher computational power are required to visualize and interpret the data.

A comprehensive technical comparison was performed by Fu *et al.* [43] whereby current era NGS-ST technologies were evaluated based on sequencing resolution, depth, and molecular diffusion rates. They developed a benchmarking pipeline, termed *cadastre*, for cross-comparison of 11 sequencing-based spatial transcriptomics methods. Their analysis showed that different spatial transcriptomics technologies have varying capabilities with respect to capture efficiency, with Stereo-seq showing the highest capturing capability with its large array size. Notably, their analyses demonstrated the stringent requirement to mitigate blood contamination during sample preparation and tissue sectioning.

SPATIAL TRANSCRIPTOMICS OF OSTEOARTHRITIS, RHEUMATOID ARTHRITIS, AND PSORIATIC ARTHRITIS TISSUES

While spatial transcriptomics is an emergent technique, many fields in biomedical research have readily adopted spatial transcriptomics tools [13,44].

Notably, spatial transcriptomics has been used to identify spatial gene patterns involved in mechanisms of cancer, where tissue structure is significantly altered [45] or where the disease is known to be significantly heterogeneous [46]. By the same token, spatial transcriptomics is particularly useful for studying knee osteoarthritis joint tissues, whose etiology is multifactorial in nature [47]. Its heterogeneous pathology results in a wide range of clinical characteristics influencing disease progression and treatment response. Thus, effective interventions need to be curated according to disease subgroups (endotypes). Recent review articles have comprehensively summarized applications of spatial profiling to osteoarthritis [48²²], RA [49], and PsA [50] tissues, and their attempts to further refine the molecular complexity of these MSK diseases. Briefly, in the field of osteoarthritis, spatial transcriptomics has deepened our understanding of a number of knee joint tissues, including novel insights into chondrocyte subtypes and their organization within knee articular cartilage [51²³]. Spatial transcriptomics has also been utilized in RA research, primarily to understand distributions of immune cells in afflicted tissues including synovium, but also in a clinical context for the prediction of treatment response or resistance to two commonly used biological therapies for RA: rituximab (RTX) and tocilizumab (TCZ) [52]. Additionally, this technology has been used to elucidate differences in cellular niches and molecular mediators in PsA skin and synovium, providing insights into the immunopathogenesis of PsA [53]. Table 2 outlines significant findings in key spatial transcriptomics studies of osteoarthritis, RA, and PsA. Overall, these studies underscore the utility of spatial transcriptomics technologies in understanding spatial changes associated with MSK diseases for future improved diagnostic and therapeutic modalities.

To date, spatial transcriptomics has been readily applied to study mouse and early embryonic MSK tissues, but its use in adult tissues has been limited. The paucity of groups using spatial transcriptomics may be due, in part, to the technical challenges associated with MSK tissues, namely difficulties in obtaining high-quality sections. Optimization of tissue preparation is required to preserve high quality RNA. MSK tissues, such as bone, cartilage, and other joint tissues, contain dense, extracellular matrix-rich tissues, which may even be mineralized, with relatively lower cellularity, placing constraints on RNA detection rates [76]. Furthermore, in contrast to soft tissues, an extra decalcification step is often required due to the hardened nature of these samples [77]. However, this extra sample processing step often utilizes strong acids, such as hydrochloric or nitric acid, that lead to RNA degradation.

Decalcification with milder reagents, such as EDTA significantly minimizes degradation of RNA quality and increases RNA recovery [78]. Of note, RNA degradation is significantly increased in cartilage samples obtained from osteoarthritis and RA patients, underlying the importance of preserving RNA quality during tissue processing [79]. Additionally, as mentioned in the previous section, these tissues are prone to detaching from slides, due to high proteoglycan content and tissue swelling [79]. FFPE tissue preservation improves tissue adhesion to slides compared to flash-frozen samples [80]. However, this widely used histological technique minimizes recovery of good quality RNA due to increased RNA cross-linking [81]. Comprehensive protocols for preparing FFPE samples from murine MSK tissues [82] and human osteochondral tissues [83] have recently been developed, and may be a transformative development for wider implementation of spatial transcriptomics in MSK research [76,82,84]. Thus, spatial transcriptomics technologies that are compatible with FFPE samples is a critical prerequisite for MSK research. Additionally, species compatibility is a consideration with some spatial transcriptomics platforms that are currently restricted to human and mouse samples, or evolutionarily similar species. Technologies which allow for species-agnostic spatial profiling, such as those that use poly-A based mRNA capture chemistry, allow for greater flexibility in research using model organisms. Another challenge is the limited capture area of current spatial transcriptomics technologies, which restricts the ability to spatially profile the entire human joint tissue. These technical constraints and the relative novelty of spatial transcriptomics tools limit a more widespread adoption of spatial transcriptomics to study MSK tissues. Adoption of modified techniques that have been successful in other challenging tissues, such as skin lesions [52,85], may also provide solutions for MSK tissues.

THE FUTURE OF SPATIAL TECHNOLOGIES FOR MUSCULOSKELETAL RESEARCH

Emergent spatial transcriptomics tools offer another layer to understand how gene expression is linked to tissue structure and unveils complexity inherent in organisms (Fig. 1). Despite the remarkable evolution in these tools, there remain avenues for growth.

- (1) The ability to perform simultaneous analysis of multiple modalities, such as transcriptome, proteome, epigenome, and metabolome, using the same tissue sections or in adjacent sections, will improve our understanding of cellular structure

Table 2. Summary of spatial transcriptomics technologies used in osteoarthritis, rheumatoid arthritis, and psoriatic arthritis studies

ST type	Tissue	MSK disease	Species	Sample preparation	Key findings	References
In-situ capture; Visium	Healthy and degenerated ACL	OA	Human	FFPE	Reported 10 fibroblast subclusters in ACL in spatial proximity to endothelial and immune cells	[54]
Re-annotation (RA synovial membrane spatial profile and spatric for single cell projection)	Knee Synovium	OA	Human	Imported Database	Identified increased immune myeloid and lymphoid cells in OA synovial lining	[55]
Imaged-based Spatial Capture (Geo-seq) with (LCM coupled with scRNA-seq)	Knee articular cartilage	OA	Human	Fresh frozen; OCT blocks	Identified 2 novel chondrocyte populations (pre-inflammatory and inflammatory subpopulations)	[51***]
Re-annotation of [51***]	Knee cartilage	OA	Human	Fresh Frozen; OCT blocks	ST analysis identified distinct cell populations in inflamed OA cartilage	[56]
In-situ capture; Visium	Knee Infrapatellar Fat Pad	OA	Human	Fresh frozen; OCT blocks	Reported 5 subclusters of fibroblasts within KOA fat pad	[57]
GeoMx-DSP	Knee Synovium	OA	Human	Fresh frozen; OCT blocks	Identified association of immune exhaustion and loss of immune regulatory macrophages with worse pain	[58***]
In-situ capture; Visium	Hip synovium	OA	Human	FFPE	Putative role of sublining FLS and fibrotic chondrocytes in molecular mechanisms by which synovial cells promote hip OA pathogenesis from FAI	[59]
In-situ capture; Visium	Bone/Femoral Head	OA	Human	FFPE	Identified spatial gradient of distinct gene expression and signalling pathways stemming from trabecular bone	[60]
In-situ capture; Visium	Hind limbs	OA	Mouse	Fresh frozen; OCT blocks	Identified three chondrocyte subclusters in E18.5 mouse embryonic knee cartilage	[61]
In-situ capture; Visium	Knee joint Synovial fluid	OA	Mouse	FFPE	Demonstrated fat-secreted factors are required for KOA development	[62]
In-situ capture; Visium	Knee joint	OA	Mouse	FFPE	ST of 5-week mice post DMM surgery, Top GO terms were associated with DNA organization, particularly histone-related functions, suggesting potential changes in chromatin structure and transcriptional regulation	[63]
In-situ spatial barcoding (Stahl method)	Knee or Hip Synovium	RA	Human	Fresh frozen; OCT blocks	ST of RA and SpA synovium revealed an abundance of central memory T cells in RA synovium and effector memory T cells in SpA synovium	[64]

Table 2 (Continued)

ST type	Tissue	MSK disease	Species	Sample preparation	Key findings	References
In-situ capture; Visium	Synovium	RA	Human	Fresh frozen; OCT blocks	Spatial analysis revealed a combination of TNF, IFN- γ , and IL-1 β exposures drive 4 distinct FLS subtypes in RA synovium	[65]
In-situ capture; Visium	Knee Synovium	RA	Human	Fresh frozen; OCT blocks	ST analysis revealed high expression of the IFN- α response pathway lining FLS within relapsed RA patients	[66]
In-situ spatial barcoding (Stahl method)	Knee or Hip Synovium	RA	Human	Fresh frozen; OCT blocks	Synovial tissue from two patient groups, seropositive and seronegative RA, underwent ST. Identified regions where infiltrating leukocytes organize into TLO cell-dense areas. Leukocyte migration pathways are enriched within TLOs	[67]
In-situ capture; Visium	Synovium	RA	Human	Fresh frozen; OCT blocks	ST analysis revealed novel subset of activated sublining ITGA5+, which potentially modulates pro-inflammatory response in RA synovium	[68]
GeoMX-DSP	Synovium	RA	Human	FFPE	Investigated the efficacy of two commonly used biological therapies for RA: RTX and TCZ. ST analysis revealed that the expression of FAP, a fibroblast marker, was increased in the synovial sublining of nonresponders	[52]
In-situ capture; Visium	Synovium	RA	Human	Fresh frozen; OCT blocks	Identified S-TPH within TLS in synovial tissue where they interact with B-cells promoting antibody generation	[69]
In-situ capture; Visium	Synovium	RA	Human	FFPE; Formalin	Use of Deep Topic Modelling to identify disease-relevant cellular communities	[70]
Imaged-based spatial capture	CosMx	RA	Human	FFPE	Identified inflammatory DC3s in the hyperplastic lining of RA promoting synovitis	[71]
In-situ capture; Visium	Knee or Wrist Synovium	RA	Human	Fresh frozen; OCT blocks	ST analysis revealed autoreactive plasma cell differentiation in early RA synovium	[72]
In-situ capture; Visium	PLN	RA	Mouse	Fresh frozen; OCT blocks	Identified PLN regions with increased Ig production in TNF-Tg mice with advanced RA	[73]
In-situ capture; Visium	Synovium	PsA and RA	Human	Fresh frozen; OCT blocks	ST analysis revealed CD200+ fibroblasts form mesenchymal network regulating inflammation and tissue repair	[74]
In-situ capture; Visium	Skin	PsA	Human	Fresh frozen; OCT blocks	ST analysis revealed repositioning of immune cells into upper skin layers within Pso lesions	[53]

Table 2 (Continued)

ST type	Tissue	MSK disease	Species	Sample preparation	Key findings	References
In-situ capture; Visium	Skin	PsA	Human	Fresh frozen; OCT blocks	Identified HIF1 α is activated in PsA epidermis	[75**]

ACL, anterior cruciate ligament; DC, dendritic cell; DMM, destabilization of the medial meniscus; FAI, femoroacetabular impingement; FAP, fibroblast activation protein; FFPE, formalin-fixed paraffin-embedded; FLS, fibroblast-like synoviocytes; Geo-seq, geographical position sequencing; GO, Gene Ontology; HIF1 α , hypoxia-inducible factor 1 α ; IFN γ , interferon-gamma; Ig, immunoglobulin; IL, interleukin; KOA, knee osteoarthritis; LCM, laser capture microdissection; MMP, matrix metalloproteinase; MSK, musculoskeletal; OA, osteoarthritis; OCT, optimal cutting temperature; PLN, popliteal lymph node; PsA, psoriatic arthritis; PsO, psoriasis; RA, rheumatoid arthritis; RTX, rituximab; scRNA-seq, single-cell RNA sequencing; SpA, spondylarthritis; ST, spatial transcriptomics; S-TPH, stem-like peripheral helper cell; TCZ, tocilizumab; TLO, tertiary lymphoid organs; TLS, tertiary lymphoid structures; TNF, tumour necrosis factor; TNF-Tg, tumour necrosis factor transgenic mouse model.

and function [86]. In fact, spatial multiomics was named one of the seven technologies to watch by Nature in 2022 [87]. One such example is DBiT-seq, which allows simultaneous profiling of the transcriptome and proteome from the same tissue section [88]. This technology is still in development, with spatial resolution limited to 10 μ m capture areas. Likewise, spatial-CITE-seq and STARmapPLUS also allow for mapping of

transcriptomes and proteomes, albeit with lower resolution and coverage than current spatial transcriptomics techniques [89,90]. Of note, spatial proteomics can provide a more practical option for studying bone and cartilage, which as stated above, require processing that often results in RNA degradation [91]. However, decalcification does not generally affect the antigenicity of proteins and thus research using

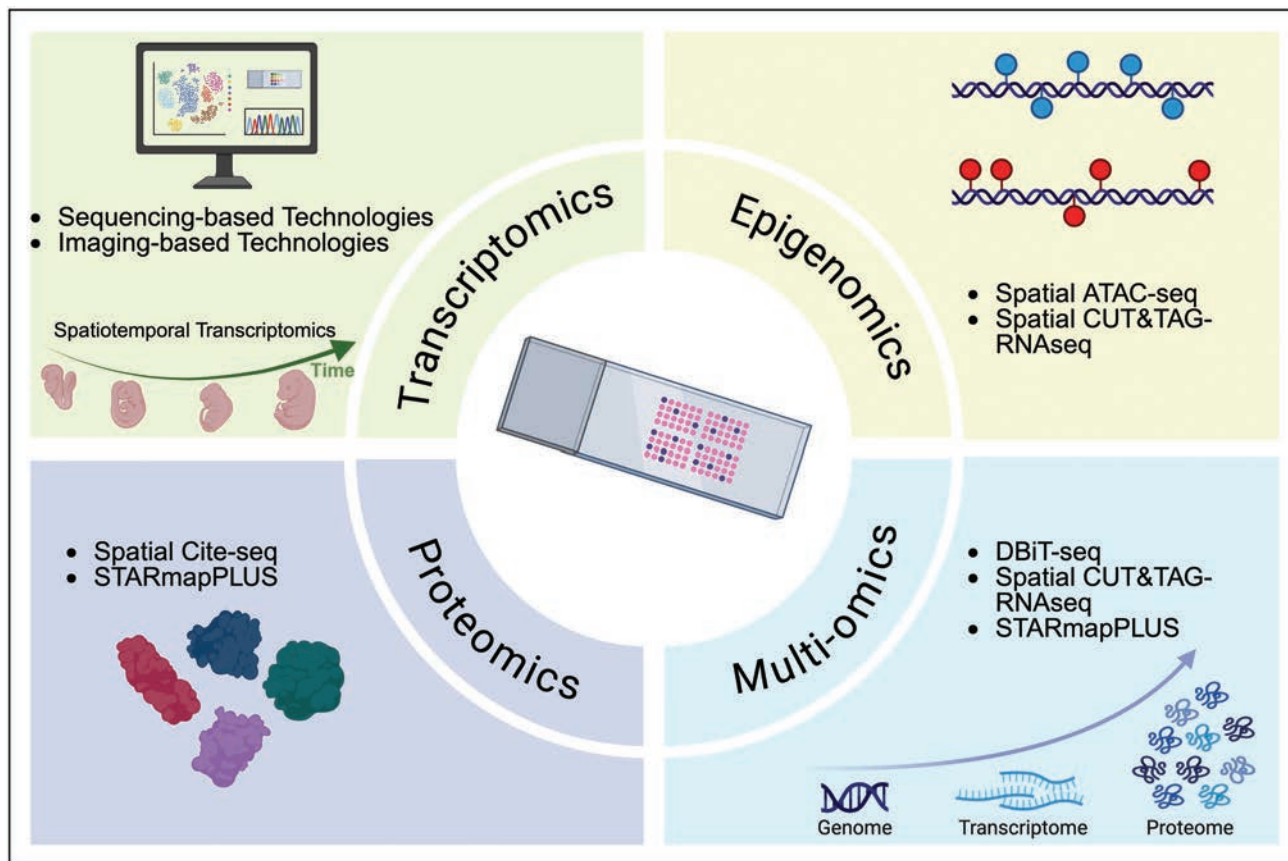


FIGURE 1. Applications of spatial -omics in musculoskeletal diseases. The emergence of Spatial -Omics technologies and methods have enabled the study of transcriptomes, proteomes, epigenomes, and multiomes, among others (such as the metabolome), whilst preserving tissue context at a spatial level. Current methods to perform Spatial Transcriptomics are described in detail in Table 1. Created in BioRender (<https://BioRender.com/wgabpzd>).

antibody-based spatial proteomics may be more feasible [92]. Comprehensive profiling of transcriptomes combined with epigenomic measures, such as chromatin accessibility using Spatial ATAC-RNAseq, or histone modifications using Spatial CUT&Tag-RNAseq, will enable further insights into the complexity of gene regulatory networks [93,94]. Linking transcription with upstream epigenetic regulatory mechanisms may reveal cell-type specific interactions driving further insights into disease heterogeneity and pathology. One such study used scRNA-seq and spatial proteomics to comprehensively profile human bone marrow niche unveiling novel cellular interactions driving haematopoiesis [95]. While integration of multiple modalities presents practical bioinformatic challenges, novel tools, such as SpatialData, have been developed to analyse spatial multiomics data [96].

- (2) Currently, spatial transcriptomics technologies can only capture transient states of tissues. The transcriptomic snapshot belies the molecularly dynamic nature of cells. Spatiotemporal transcriptomic studies have been conducted using independent samples from different time points, which presents a challenge in heterogeneous tissues, or more commonly through mathematically inferring temporal information using computational approaches [16]. The models generated by these tools should be interpreted as statistical assumptions rather than an authentic transitional path of cells. Live-seq is a novel technique providing a temporal dimension to scRNA-seq, allowing a continuous molecular analysis of live cells [97]. Further developments to add spatial context will be necessary to capture spatiotemporal transcriptomics.
- (3) Tissues and their microenvironment exist in three-dimensional structures [98,99]. However, current spatial transcriptomics methods acquire transcriptomic data in two-dimensional planes, masking the complexity of the 3D dynamic cellular assembly and organization regulating cell and tissue function. In fact, most spatial transcriptomics technologies can only profile thin sections, typically 5–20 µm thick. Joint cartilage is composed of a dense extracellular matrix (ECM) with varying chondrocyte density and collagen fibre arrangement among its four layers [100]. Deep-STARmap and Deep-Ribomap are two novel techniques enabling volumetric multicell layer in-situ quantification of the transcriptome and proteome, respectively, in 200 µm thick tissue sections [101]. Capturing the 3D transcriptomic profile across multiple cell layers

or through the zonal organization of cartilage may reveal further insights into spatial chondrocyte function and regulation.

CONCLUSION

Understanding the underlying mechanisms driving MSK disease pathogenesis and progression has become increasingly crucial for the development of therapeutic strategies, which are essential for mitigating the individual and societal burdens posed by this group of diseases. There is a pressing need for additional research leveraging spatial transcriptomics technologies to improve the understanding of MSK disease mechanisms, advance target identification, and develop novel treatments. This article has highlighted novel spatial transcriptomics technologies and how they can be used to elucidate spatially localized cell types and mechanisms driving MSK disease pathology. While spatial transcriptomics holds great promise to provide a deeper understanding of MSK biology, improvements to spatial resolution and efficiency of RNA capture will be crucial for future development of clinical diagnostic or therapeutic approaches.

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Conflicts of interest

M.K. is an officer and board member for the Osteoarthritis Research Society International and serves on the scientific advisory board for Chiron Inc. and GlaxoSmithKline. Other authors declare no competing interests.

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