Editorial introductions

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, and Professor of Epidemiology at the UAB School of Public Health.

Dr Saag is a native of Chicago, following studies in engineering at the University of Michigan, 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, and has 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 on the Finance Committee of the American College of Rheumatology (ACR) and the Gout and Uric Acid Society Board of Directors. He also serves as President on the Board of Trustees of the National Osteoporosis Foundation.

Ann K. Rosenthal

Dr Rosenthal is the Will and Cava Ross Professor of Medicine and Chief of the Rheumatology Division at the Medical College of Wisconsin, USA.

Dr Rosenthal received her MD from the Johns Hopkins University School of Medicine, USA, and completed a residency in Internal Medicine at Strong Memorial Hospital and the University of Rochester, USA. She received her rheumatology training at the Medical College of Wisconsin where she had the privilege of working with Dr Lawrence M. Ryan, a major figure in the field of calcium-crystal arthritis. This fostered her interest in crystal arthritis and since then her work has largely centered on calcium pyrophosphate deposition (CPPD) and pathologic calcification in cartilage. Her work includes bench research as well as clinical trials, and has been funded by the Veteran's Administration Research Service and the National Institutes of Health since 1991. Her additional research interests include osteoarthritis, gout, and musculoskeletal complications of diabetes. She is the author of over 80 original publications, numerous chapters and invited reviews, and has spoken at many national and international meetings.

Dr Rosenthal maintains an active clinical practice, and has been elected to Best Doctors yearly since 1998. She is an elected fellow of the American College of Physicians. She is the recipient of numerous teaching awards. She is currently the Vice Chair for Faculty Development in the Department of Medicine and the medical director of the Zablocki VA Translational Research Center, a key component of the Clinical Translational Science Institute.

Iain McInnes

Iain McInnes is an international authority on the pathogenesis and treatment of inflammatory arthritis. His early studies identified the expression/functional importance of several novel cytokines in rheumatoid arthritis (RA) synovitis. Subsequent investigations identified numerous novel regulators of synovial cytokine production that essentially drive the chronicity of the condition. Parallel studies explore mechanisms underpinning vascular co-morbidity in autoimmune disease. McInnes has edited and published extensively in journals of high impact. He is active in the national academic community serving on numerous grant funding panels. He is Director of the Scottish Clinical Pharmacology and Pathology Training Programme (MRC) and Deputy Director of the Scottish Translational Medicine Initiative. He is the Director of the Arthritis Research UK Rheumatoid Arthritis Pathogenesis Centre of Excellence, and moreover, has created the GLAZgo Discovery Centre in a unique discovery platform to innovate new drug development. He has participated extensively in the workings of the European League Against Rheumatism (EULAR) – formerly as Chair of the Scientific Committee of EULAR, as Chairman of the European Forum, and now as Treasurer of EULAR. He has received numerous invited lectureships and professorships. He was elected FRSE in 2008, and FMedSci in 2012.

Epidemiology of axial spondyloarthritis: an update

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Purpose of review
To provide an update of the prevalence and incidence of axial spondyloarthritis in the general population and in patients with spondyloarthritis-related conditions, environmental risk factors for ankylosing spondylitis, progression from nonradiographic axial spondyloarthritis to ankylosing spondylitis, mortality, and risks for cardiovascular events in patients with ankylosing spondylitis.

Recent findings
Increasingly, administrative healthcare data have been used to study disease frequency and outcomes. The prevalence of ankylosing spondylitis ranged from 9 to 30 per 10 000 persons, which are lower than previous estimates. Data on whether childhood infections influence the risk of ankylosing spondylitis were equivocal, while having been breast-fed may be protective. Progression of patients with nonradiographic axial spondyloarthritis to ankylosing spondylitis is slow, with estimates of 5.1% in 5 years and 19% in 10 years. Risk of mortality is slightly increased in ankylosing spondylitis. Risks for cardiovascular events in ankylosing spondylitis were either not different from, or only slightly higher than in controls. No studies have examined these outcomes in the broader group of patients with axial spondyloarthritis.

Summary
Expanded use of administrative and registry data has facilitated studies of the epidemiology of ankylosing spondylitis, but lack of specific diagnostic codes limits use of these resources for studying axial spondyloarthritis in general.

Keywords
ankylosing spondylitis, axial spondyloarthritis, cardiovascular disease, mortality, prevalence

INTRODUCTION

Axial spondyloarthritis (SpA) is an umbrella term encompassing a number of inflammatory spine conditions, including ankylosing spondylitis, nonradiographic axial SpA (nr-axSpA), SpA associated with inflammatory bowel disease (IBD), and undifferentiated SpA. Since the publication of the Assessment of SpondyloArthritis International Society (ASAS) classification criteria in 2009, several studies have investigated the prevalence and incidence of axial SpA in the general population and in patients with SpA-related conditions. We review studies of the progression of patients with nr-axSpA to ankylosing spondylitis. Environmental factors, particular early life events, have been investigated for potential influence on the risk of later development of ankylosing spondylitis. We review recent studies of mortality in ankylosing spondylitis, and examine evidence of the risk of cardiovascular events in these patients.

PREVALENCE AND INCIDENCE

Prevalence

Recent studies reported the prevalence of ankylosing spondylitis to range from 9 to 30 per 10 000 in the general population, depending on geographic area, study population or data source, case definition, and ascertainment methods (Table 1) [1–7]. Prevalences were higher in selected risk groups. For example, in a Canadian study, the prevalence of ankylosing spondylitis was three times higher in First Nations people, a group with a high prevalence of HLA-B27, than in non-First Nations people [2]. In a Scottish study, the prevalence was three times higher among patients identified from primary care providers than under the care of rheumatologists [3].

Two studies of the prevalence of axial SpA expectedly reported higher prevalences than those

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Curr Opin Rheumatol 2018, 30:137–143
DOI:10.1097/BOR.0000000000000475

KEY POINTS

- Recent epidemiology studies indicate a lower prevalence and incidence of axial spondyloarthritis.
- Patients with ankylosing spondylitis have a slightly increased risk for mortality and a slightly increased risk for cardiovascular events, including vascular death.
- Current data suggested that using diagnostic codes for ankylosing spondylitis in administrative health data has high positive predictive value to identify these patients.

for ankylosing spondylitis alone. In a US study, Curtis *et al.* [6] estimated the prevalence of SpA at 22.6 per 10 000. Among 18 757 employees of the French national utility company, 72 patients self-reported SpA based on a medical questionnaire, and 32 patients were classified with SpA after interview by a rheumatologist, pelvis radiographs, and HLA-B27 testing [7]. Seventy-five percent fulfilled ASAS axial SpA criteria, 25% fulfilled ASAS peripheral SpA criteria, and two-thirds had ankylosing spondylitis. The estimated SpA prevalence was 43 per 10 000.

In a systematic review and meta-analysis, Stolwijk *et al.* [8▪▪] reported the global prevalence of axial SpA ranged from 20 per 10 000 in south-east Asia to 161 per 10 000 in Northern Arctic communities; the prevalence of ankylosing spondylitis varied from 2 per 10 000 in Sub-Saharan Africa to 35 per 10 000 in Northern Arctic communities. Heterogeneity in estimates was related to differences in the proportion of women, mean age of the sample, geographic area, year of data collection, case finding, and case ascertainment.

Incidence

The reported prevalence from these recent studies was substantially lower than what was previously known. Studies from the same geographic location with similar methodology would help inform whether the frequency of axial SpA has truly decreased over time. The incidence of ankylosing spondylitis in Olmsted County, Minnesota from 1935 to 1989 was estimated at 7.3 per 100 000. In

Table 1. Prevalence of axial spondyloarthritis and ankylosing spondylitis in general populations

Reference	Years of observation	Geographic area/ source data	Case definition	Ascertainment method	Number of cases/ total number of patients	Prevalence, per 10 000 (95% CI)
Exarchou *et al.* [1]	2009	Sweden/ National Patient Registry	Clinical diagnosis of ankylosing spondylitis	Individuals with at least one registered ankylosing spondylitis diagnosis by ICD-9 codes by any clinical department (base definition) or by rheumatology/ internal medicine (strict definition)	By base definition: 11 030/5 982 237; by strict definition: 8538/5 982 237	By base definition: 18; by strict definition: 14
Barnabe *et al.* [2]	Mid-point of 2008–2009	Alberta, Canada/ comprehensive provincial health databases	Clinical diagnosis of ankylosing spondylitis	Individuals with two or more ICD-9 or ICD-10 codes by any physician within 2 years; or one hospitalization discharge diagnosis; stratified by First Nation versus non-First Nation ethnicity	7685/NR	First Nations: 60 (50–60) non-First Nations: 20 (20–20)
Dean *et al.* [3]	2011	Scotland/ Primary Care Clinical Informatics Unit Research electronic primary care database	Clinical diagnosis of ankylosing spondylitis	Individuals with Read Codes for ankylosing spondylitis (excluding juvenile ankylosing spondylitis)	1964/1469688	Primary care: 13.4 (12.8–14.0)
	2010–2013	Scotland Registry for Ankylosing Spondylitis	Clinical diagnosis of ankylosing spondylitis	Ankylosing spondylitis patients based on diagnosis by rheumatologists	1700/NR	Rheumatology: 4.7 (4.5–4.9)
Zeng *et al.* [4]	2012	Shantou, China/ two randomly selected population	Clinical diagnosis of ankylosing spondylitis	Community-Oriented Program for the Control of Rheumatic Diseases methodology	12/4056	30 (14–48)
Julián-Santiago *et al.* [5]	2012	Oaxaca, Mexico/ two indigenous populations	Clinical diagnosis of ankylosing spondylitis	Community-Oriented Program for the Control of Rheumatic Diseases methodology	1/1061	9 (0–50)
Curtis *et al.* [6]	1996–2009	California/ Enrollees in Kaiser Permanente health plan	Clinical diagnosis of axial SpA and ankylosing spondylitis	Individuals with one or more inpatient or outpatient ICD-9 codes for ankylosing spondylitis or another inflammatory spondyloarthropathy	5568/NR	Ankylosing spondylitis: 10.7 SpA: 22.6
Costantino *et al.* [7]	2010	France/ population-based cohort	ASAS classification for axial and peripheral SpA	Two-step method	32/6556	43 (26–70)

CI, confidence interval; ICD, International Classification of Diseases; NR, not reported; SpA, spondyloarthritis.

the same population, the incidence of ankylosing spondylitis was 3.1 per 100 000 (95% CI 2.5–3.8) in 1980–2009 [9]. The authors attributed the decrease to increases in the local ethnic minority population. Whether these demographic changes fully explain the decline in ankylosing spondylitis incidence is unclear.

Study methods

Prevalence estimates may be affected by the ascertainment methods used in a study. Some studies used a two-step method, with an initial screening questionnaire followed by physician evaluation of screen-positive individuals. This method enhances accuracy, but can be limited in the number of participants included. Alternatively, population-based medical record linkage systems ensure near-complete case ascertainment, but require substantial time and resources to establish. Increasingly, studies have used administrative data to identify cases with axial SpA or ankylosing spondylitis, which require validation of the diagnosis codes and search algorithms used to identify affected persons. Curtis *et al.* [6] investigated the prevalence of axial SpA and ankylosing spondylitis in Kaiser Permanente health plan members, and described the performance of this method. Among 5568 individuals with at least one ICD-9 diagnosis code for ankylosing spondylitis, 2295 individuals only had a single code by a primary care provider. Ankylosing spondylitis was confirmed in only 2% of this group. Among four different search strategies, having two ICD-9 diagnoses of 720.X by rheumatologists had the highest positive predictive value at 81%, but sensitivity was only 67%.

Similarly, Dubreuil *et al.* [10] tested the validity of ankylosing spondylitis diagnosis codes in United Kingdom's The Health Improvement Network using the general practitioner's diagnosis as the gold standard. They reported a positive predictive value of 88.6% for the presence of two ankylosing spondylitis diagnostic codes separated by at least 7 days, and a positive predictive value of 85.7% for the presence of one ankylosing spondylitis diagnosis code in combination with a disease-modifying drug or biologic prescription.

Bioinformatics tools, such as natural language processing applied to electronic medical records, are being explored as a new tool to identify cases. Walsh *et al.* [11] reported the positive predictive values of these models for several SpA-related concepts, including sacroiliitis, spondy* and HLA-B27+, which ranged from 91.1 to 97.2%. Further studies are needed in this area.

PREVALENCE IN PATIENTS WITH RELATED CONDITIONS

Several studies examined the prevalence of ankylosing spondylitis in patients with related conditions, which may inform ways to improve referral and early diagnosis. Turina *et al.* [12] examined 51 first-degree relatives of patients with HLA-B27-positive ankylosing spondylitis, and 33% fulfilled criteria for SpA. More specifically, 57% had back pain, 6% had low-grade sacroiliitis, and 20% had sacroiliac bone marrow edema on imaging. The authors concluded that a substantial proportion of seemingly healthy relatives of ankylosing spondylitis patients had features of SpA.

Deodhar *et al.* [13] reported the proportion of patients with axial SpA among 751 patients with chronic back pain and either HLA-B27 positivity, inflammatory back pain, or sacroiliitis on imaging in the United States. Of these, 348 fulfilled ASAS axial SpA criteria (238 with nr-axSpA and 108 with ankylosing spondylitis). The authors suggested among patients with chronic back pain with onset younger than 45 years, having one of these three SpA features was an effective way to identify those with possible axial SpA.

Thom *et al.* [14] examined the prevalence of inflammatory back pain and SpA in patients with psoriasis using data from 2009 to 2010 National Health and Nutrition Examination Survey (NHANES), and found higher frequencies of axial pain (31 versus 19%) and inflammatory back pain (9.0 versus 4.9%) in persons with psoriasis than in those without psoriasis. The prevalence of SpA by Amor or European Spondyloarthropathy study group criteria was also significantly higher in the psoriasis group (14.3% versus 1.5%).

Chan *et al.* [15] reported the prevalence of sacroiliitis on computed tomography scans in patients with Crohn's disease, ulcerative colitis and controls as 15, 16.9 and 5.6%. Among 49 patients with IBD who had sacroiliitis on scans, only 5 had been seen by a rheumatologist. In a meta-analysis of 71 studies on the prevalence of axial SpA in patients with IBD, the pooled prevalence of sacroiliitis was 10%, although its prevalence in the subset of population-based studies was only 3% [16▪]. The pooled prevalence of ankylosing spondylitis was 3% overall, and 2% in population-based studies.

PROGRESSION OF NONRADIOGRAPHIC AXIAL SPONDYLOARTHRITIS

Since the development of axial SpA classification criteria, the relationship between nr-axSpA or undifferentiated SpA and ankylosing spondylitis has been of interest, particularly whether most patients with

nr-axSpA progress to ankylosing spondylitis, and what are risk factors for progression.

We investigated these questions in a population-based study in Olmsted County, Minnesota [17▪]. Among 83 patients who fulfilled ASAS criteria for axial SpA but did not have radiographic sacroiliitis, 19% progressed to ankylosing spondylitis after a mean follow-up of 10.6 years. The probability that the condition remained as nonradiographic at 5, 10, 15 years was 93.6, 82.7, and 73.6%. Patients who were classified through the imaging arm had a significantly more frequent and more rapid progression than those classified through the clinical arm (28 versus 17%, $P = 0.02$).

Costantino *et al.* [18] reported a similar rate of progression in patients with axial SpA and having at least one SpA-affected relative. In 145 patients without radiographic sacroiliitis at inclusion, 27.3% developed radiographic sacroiliitis after 3–15 years, a result similar to our study. The Kaplan–Meier estimate of proportion of patients who progressed to radiographic sacroiliitis was 68.5% at 15 years of follow-up; however, in the analysis, patients who lost to follow-up were excluded from the number of patients at risk. Progression was associated with low-grade radiographic sacroiliitis at baseline, buttock pain, and absence of peripheral arthritis.

Dougados *et al.* [19] examined radiographic progression over 2 years in the Devenir des Spondyloarthropathies Indiffererenciees Recentes (DESIR) cohort, a prospective cohort of patients with early inflammatory back pain and high suspicion for axial SpA. Sixteen of 326 patients (4.9%) with nr-ax SpA progressed to ankylosing spondylitis. This was quite different from the GESPIC cohort [20], where 12% progressed to ankylosing spondylitis in 2 years. Current smoking, HLA-B27 positivity, and sacroiliac inflammation on imaging were the predictors for progression. In a follow-up study of the DESIR cohort, net progression from nr-axSpA to ankylosing spondylitis over 5 years was 5.1% [21]. Inflammation on baseline sacroiliac joint MRI predicted the presence of radiographic sacroiliitis at 5 years, both in HLA-B27-positive patients (OR 5.39; 95% CI 3.25–8.94) and in HLA-B27-negative patients (OR 2.16; 95% CI 1.04–4.51).

Xia *et al.* [22] conducted a systematic review and meta-analysis of 16 studies to assess the pooled rate of progression from undifferentiated SpA to ankylosing spondylitis. After 10 years, 40% of patients were projected to have progressed to ankylosing spondylitis.

Together, these findings suggest that only a small proportion of patients classified as nr-axSpA progress to ankylosing spondylitis, at least in the short-term.

ENVIRONMENTAL RISK FACTORS FOR THE DEVELOPMENT OF ANKYLOSING SPONDYLITIS

Ankylosing spondylitis is a highly heritable disease, and few studies have examined environmental risk factors. Three recent studies reported interesting observations suggesting that microbial exposures in childhood may play a role in the later development of ankylosing spondylitis.

Montoya *et al.* [23] investigated whether having been breast-fed was associated with the development of ankylosing spondylitis. Of 203 patients with ankylosing spondylitis, 57% were breast-fed, compared with 72% of 293 unaffected siblings, indicating that breast-feeding was protective (OR 0.53; 95% CI 0.36–0.77). The authors speculated that breast-feeding may have a protective effect on ankylosing spondylitis development in genetically susceptible patients by influencing the gut microbiota.

Lindström *et al.* [24] investigated whether childhood infections were associated with later development of ankylosing spondylitis in a case–control study in Sweden. Of the 2453 ankylosing spondylitis cases and 10 257 age-matched, sex-matched, and county-matched controls, 17.4% of cases and 16.3% of controls had an infection-related hospitalization before age 17 years. Ankylosing spondylitis was associated with slightly more respiratory tract infections (11.2 cases versus 9.2% controls) but few cases of appendicitis (1.5 versus 2.5%). The authors suggested early childhood infections might be associated with the subsequent development of ankylosing spondylitis. In a related analysis of potential maternal and puerperal risk factors, birth by Caesarean section was not associated with the risk of ankylosing spondylitis, but having at least one older sibling, a surrogate for exposure to infections, was associated with a slight increased risk of ankylosing spondylitis [25].

MORTALITY AND CARDIOVASCULAR OUTCOMES

Mortality in ankylosing spondylitis

Recent information on mortality in ankylosing spondylitis is limited. Using the population-based Swedish National Patient Registry, Exarchou *et al.* [26] compared the mortality of persons with ankylosing spondylitis versus the general population. Over 7 years, they observed 496 deaths in 8600 patients with ankylosing spondylitis, compared with 1533 deaths in 40 460 matched controls, for a hazard ratio of 1.60 (95% CI 1.44–1.77). Less education, comorbidities, and history of hip replacement surgery were predictors of death.

In a population-based cohort study, Oza *et al.* [27▪▪] examined the potential survival benefit of statin use in patients with ankylosing spondylitis. In a cohort of ankylosing spondylitis patients in a United Kingom general practice database, they compared mortality between matched cohorts of 1108 statin initiators and 1108 noninitiators using 1-year cohort accrual blocks. Over 5 years, the mortality rate was 16.5 per 1000 person-years among initiators and 23.8 per 1000 person-years among noninitiators (hazard ratio 0.63; 95% CI 0.46–0.85). The authors concluded that statin initiation was associated with a substantially lower risk of mortality in patients with ankylosing spondylitis.

Cardiovascular outcomes in ankylosing spondylitis

Studies on cardiovascular events in patients with ankylosing spondylitis have used different outcomes (Table 2) [28–31]. Overall, results point to a small increase in cardiovascular event risk compared with general population.

In a population-based cohort study using administrative health data from Ontario, Canada, Haroon *et al.* [28] reported an adjusted hazard ratio for cardiovascular and cerebrovascular death in ankylosing spondylitis of 1.36 (95% CI 1.13–1.65), compared with matched nonankylosing spondylitis controls. Risk factors for vascular death included age, male sex, lower income, dementia, chronic kidney disease, peripheral vascular disease. Interestingly, among elderly patients with ankylosing spondylitis, use of nonselective nonsteroidal anti-inflammatory drugs and statins were protective for cardiovascular death.

In a population-based inception cohort of 86 patients with ankylosing spondylitis, Wright *et al.* [9] found a cumulative incidence of cardiovascular disease (including ischemic heart disease, myocardial infarction, angina, cardiovascular death, heart failure, peripheral arterial disease) of 15.8%, three times higher than the expected events predicted by the Framingham Risk Score. However, this study is limited by the small number of events.

Table 2. Prevalence of cardiovascular and cerebrovascular events in patients with ankylosing spondylitis

Author	Study year	Study population	Outcomes	Patients/events (*n*/*n*)	Follow up (patient-years, unless noted)	Hazard ratio (95% CI)
Haroon *et al.* [28]	1995–2011	Ontario, Canada: ankylosing spondylitis: two diagnostic codes of ankylosing spondylitis over 2 years with one by rheumatologist C: age, sex, location of residence matched individuals	Vascular mortality	Ankylosing spondylitis: 21 473/170 C: 86 606/594	Ankylosing spondylitis: 166 920 C: 686 461	1.36 (1.13, 1.65)
Eriksson *et al.* [29]	2006–2011	Swedish National Patient Registry: ankylosing spondylitis: at least one diagnostic code for ankylosing spondylitis by internal medicine or rheumatology C: general population matched on birth year, sex, and residence	First acute coronary syndrome	Ankylosing spondylitis: 4898/69 C: 22 315/216	Ankylosing spondylitis: 20 251 C:91 601	1.3 (1.0, 1.7)
			First stroke	Ankylosing spondylitis: 5248/65 C: 24 225/185	Ankylosing spondylitis: 21 653 C:100 441	1.5 (1.1, 2.0)
Hung *et al.* [30]	2000–2005	Taiwan National Health Insurance Research Database: ankylosing spondylitis: one inpatient or two outpatient diagnoses of ankylosing spondylitis based diagnostic codes C: insured individuals matched on age and sex	Overall CVD: Hypertensive heart disease; coronary heart disease; heart failure; cerebrovascular disease, other.	Ankylosing spondylitis: 537/176 C: 2685/780	Ankylosing spondylitis: 3.71 years C: 4.21 years	1.20 (1.02, 1.42)
Essers *et al.* [31]	1987–2012	British Clinical Practice Research Databank: ankylosing spondylitis: inception cohort of patients with at least one recording of ankylosing spondylitis C: birth year, sex, time and practice location matched non-ankylosing spondylitis patients	First ischemic heart disease event	Ankylosing spondylitis: 3809/102 C: 26 197/600	Overall: 6.6 years	1.20 (0.97, 1.48)
			First acute myocardial infarction	Ankylosing spondylitis: 3809/38 C: 26 197/291		0.91 (0.65, 1.28)

C, comparator; CI, confidence interval; CVD, cardiovascular disease.

Using Swedish population-based registries, Eriksson *et al.* [29] investigated the incidence of cardiovascular events in ankylosing spondylitis. Over 20 251 person-years of follow-up, the age and sex-adjusted relative risk for acute coronary syndromes was 1.3 (95% CI 1.0–1.7) compared with general population, and the relative risk for stroke was 1.5 (95% CI 1.2–1.8). Stroke risks were similarly elevated in ankylosing spondylitis and in patients with rheumatoid arthritis, whereas risks for acute coronary syndromes were only one-half as high in ankylosing spondylitis compared with rheumatoid arthritis.

Using claims data of Taiwan's National Health Insurance Research Database, Hung *et al.* [30] examined the incidence of cardiovascular disease (including hypertensive heart disease, coronary heart disease, congestive heart failure, cerebrovascular disease, and 'other') in an incident cohort of 437 patients with ankylosing spondylitis aged 40 years or older, compared with 2685 non-ankylosing spondylitis patients. The hazard ratio for cardiovascular disease was 1.20 (95% CI 1.02–1.42). However, whenever isolating each condition, only the hazard ratio of 'other' cardiovascular disease was statistically significant.

In contrast, using British Clinical Practice Research Datalink, Essers *et al.* [31] identified 3809 incident ankylosing spondylitis patients from 1987 to 2012, who were each matched to seven nonankylosing spondylitis patients by age, sex, and practice. Risks were not significantly higher in ankylosing spondylitis, with an adjusted hazard ratio for ischemic heart disease of 1.20 (95% CI 0.97, 1.48) and for acute myocardial infarction of 0.91 (95% CI 0.65–1.28).

CONCLUSION

New information on the epidemiology of axial SpA includes a lower prevalence of axial SpA than previously reported, as well as a slightly increased risk for cardiovascular events and mortality. There has been an increase in studies using administrative and registry data to investigate these questions, for which sensitive and reliable methods are needed. On the basis of current data suggesting high predictive values of administrative healthcare codes for ankylosing spondylitis, use of these resources should be expanded. However, the lack of specific diagnostic codes means more work is needed before these methods can be used to study axial SpA in general.

Acknowledgements

None.

Financial support and sponsorship

This work was supported by the Intramural Research Program, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health.

Conflicts of interest

There are no conflicts of interest.

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Epidemiology of systemic lupus erythematosus: an update

George Stojan and Michelle Petri

Purpose of review
Systemic lupus erythematosus (SLE) is the prototypical systemic autoimmune disease with a significant disease burden across the world among different ethnic, racial, and age groups. The pathophysiological understanding of SLE is constantly evolving and with it, the need for a better definition of the disease itself, for understanding the risk among the different affected populations, and for identifying the factors responsible for the damage accrual through the years.

Recent findings
More accurate estimates of incidence and prevalence of SLE among different ethnicities and minority groups not only in the USA, but also in Europe, Middle East, and Asia have provided new insights into the disease burden around the world. Despite advances in treatment, mortality among SLE patients remains high with significant ethnic and geographic variations.

Summary
Sex, race, and ethnicity significantly affect SLE incidence, prevalence, and mortality.

Keywords
incidence, epidemiology, mortality, prevalence, systemic lupus erythematosus

LUPUS IN THE USA

In 2014, data from the Michigan [1] and Georgia [2] Lupus Registries were published and provided a valuable insight into the incidence and prevalence of systemic lupus erythematosus (SLE) in the United States in a population predominantly composed of Caucasians and African Americans (Table 1). A similar Centers for Disease Control and Prevention (CDC)-funded population-based registry [3], determined the prevalence and incidence of SLE among American Indian and Alaska Native people within the Indian Health Service clinical population. These studies overcame the shortcomings of previous epidemiologic data in the USA by using identical case definitions [meeting $\geq$4 American College of Rheumatology (ACR) criteria or a renal biopsy of lupus nephritis/end-stage renal disease or a rheumatologist's diagnosis], and a broad range of case-finding sources. The number of Hispanic and Asian patients in these three registries was small, so the CDC supported the creation of two similar lupus registries in California and New York. The recently published data from the California Lupus Surveillance Project (CLSP) [4] and the Manhattan Lupus Surveillance Program (MLSP) [5▪] included populations with greater numbers of Asian and Hispanic patients. Both studies reported a higher prevalence and incidence rate of SLE in women compared with men, and in African Americans compared with Caucasians, similar to the data reported from Michigan and Georgia. The diverse population allowed estimation of incidence and prevalence among Hispanics and Asians, who had a higher incidence and prevalence of SLE compared with Caucasians, but lower than African Americans (Table 1). The diverse populations included in these two registries allowed the first reliable estimation of incidence and prevalence among the Hispanic and Asian population in the United States.

Ungprasert *et al.* [6] used both the SLICC and the American College of Rheumatology SLE criteria to investigate the incidence of SLE in Olmsted County, Minnesota, from 1993 to 2005. They demonstrated a

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Curr Opin Rheumatol 2018, 30:144–150
DOI:10.1097/BOR.0000000000000480

KEY POINTS

- More accurate estimates of incidence and prevalence of SLE among different ethnicities and minority groups in the USA have shown a higher incidence and prevalence of SLE among Hispanics and Asians.
- Despite advances in treatment, standardized mortality rates in SLE remain three times higher than in the general population with significant ethnic differences.
- Cardiovascular risk in SLE varies based on ethnicity with the highest risk seen among African Americans.

higher incidence of SLE when using SLICC criteria (58 cases) compared with ACR criteria (44 cases), mostly because of cases of isolated lupus nephritis, serologic abnormalities, and nonscarring alopecia.

Furst *et al.* [7] evaluated the incidence and prevalence of SLE in a large national managed-care claims database in the United States using historical data. The incidence and prevalence of SLE was similar to previous estimates (Table 1).

LUPUS WORLDWIDE

Other than the recently published data from the Michigan Lupus Epidemiology and Surveillance Registry [8] which described a 2.1-fold higher incidence of SLE among Arab-Americans compared with non-Arab Caucasians and African Americans [8], little was known about the epidemiology of SLE among the Arab population worldwide or in the Middle East. Al Dhanhani *et al.* [9] studied the incidence and prevalence of SLE in the United Arab Emirates. The age-standardized incidence over the 4-year period was 8.6/100 000 per year (Table 2). The incidence rates described were similar to the ones reported in the Michigan Lupus Epidemiology and Surveillance Registry for the Arab population (7.6/100 000 person-years).

In Europe, Schneider and co-workers [10] used age-specific and sex-specific claims data to estimate the incidence of SLE in the German population (Table 2). The estimated incidence rates of SLE were at the lower end of other estimates from comparable European countries, with the incidence rate for German women being less than half of the French rate [11].

Otsa *et al.* [12] estimated the incidence and point prevalence of SLE in Estonia by extracting SLE ICD-10 codes for individuals older than 20 years of age from the Estonian Health Insurance Fund database (Table 2). The reported SLE incidence in Estonia was lower than in countries with similar prevalence, presumably because of the use of a lower age limit of 20 years as a study inclusion criterion.

In southern Sweden, Ingvarsson *et al.* [13] (Table 2) reported a decrease in the incidence rate of SLE over a period of 26 years, particularly in middle-aged women, whereas disease phenotype remained unchanged. The prevalence of SLE increased slowly over the same period.

In Denmark, Hermansen *et al.* [14] (Table 2) in an analysis of the Danish National registry reported an incidence rate for SLE of 2.35per 100 000. Sex-specific incidence rates of SLE and of lupus nephritis peaked later in life among men than among women.

The first estimates of SLE incidence and prevalence on the island of Crete were reported [15] (Table 2). Although the incidence of SLE and lupus nephritis remained stable over the study period (1999–2013), prevalence increased.

A retrospective cohort study in the United Kingdom [16] (Table 2) using the Clinical Practice Research Datalink showed a decline in the annual SLE incidence of 1.8% whereas in contrast the prevalence increased from 64.9 per 100 000 in 1999 to 97.04 per 100 000 in 2012. There was regional variation in both incidence and prevalence. People of Afro-Caribbean ethnicity had the highest incidence and prevalence.

In a systematic review of worldwide incidence and prevalence of SLE [17▪], the highest estimates of incidence and prevalence of SLE were in North America (23.2/100 000 and 241/100 000 person-years, respectively). Lower incidences of SLE were reported in Africa and Ukraine (0.3/100 000 person-years), and the lowest prevalence was in Northern Australia (0 cases in a sample of 847 people). Women were more frequently affected than men for every age and ethnic group. People of African ethnicity had the highest incidence and prevalence of SLE, whereas those of Caucasian ethnicity had the lowest incidence and prevalence. There appeared to be an increasing trend of SLE prevalence with time.

MORTALITY IN SYSTEMIC LUPUS ERYTHEMATOSUS

A population-based study [18] using the National Vital Statistics System reported data on SLE deaths from 1968 through 2013. After an initial decrease between 1968 and 1975, SLE mortality increased annually for 24 years, followed by a sustained decrease for 14 years starting in 1999. On the other hand, all-cause mortality decreased throughout the study period. Residence in the West conferred the highest SLE mortality risk in all racial/ethnic groups except Caucasians, who had the highest risk in the

Table 1. Lupus incidence and prevalence in the USA- a 2017 update

Authors	Region	Study type	Number of SLE cases	Ethnicity	Age	Sex	Study period	Incidence	Incidence by ethnicity	Prevalence	Prevalence by ethnicity
Somers *et al.* [1]	Southeastern Michigan	Population survey	2139	African American ($n=1219$) Caucasian (820) Hispanic (39)	All	8.5% men	2002–2004	5.5 (5.0–6.1)	African American 7.9 (6.9–9.1) Caucasian 3.7 (3.1–4.3)	72.8 (70.8–74.8)	African American 111.6 (107.7–115.6) Caucasian 47.5 (45.5–49.7)
Lim *et al.* [2]	Georgia	Population survey	1446	African American ($n=1094$) Caucasian ($n=328$)	All	13.5% men	2002–2004	6.9 (6.2,7.7)	African American 10.7 (9.5,12.1) Caucasian 3.3 (2.7,4.2)	92.1 (87.4,97)	African American 147.5 (139.2-156.4) Caucasian 43.1 (38.5,48.1)
Dall'Era *et al.* [4]	San Francisco county	Population survey	1257	Caucasian ($n=294$) Asian/Pacific Islander ($n=290$) African American ($n=160$) Hispanic ($n=118$) American Indian/ Alaskan native ($n=4$)	All	10.5% men	2007–2009	5.2 (4.3–6.2)	African American 16.0 (11.1–23.3) Caucasian 3.3 (2.4–4.4) Asian/Pacific Islander 4.6 (3.3–6.3) Hispanic 5.6 (3.6–8.7)	96.8 (90.2–103.9)	African American 261.0 (222.3–306.5) Caucasian 64.9 (57.8–72.8) Asian/Pacific Islander 102.5 (91.3–115.1) Hispanic 110.5 (93.0–131.3)
Izmirly *et al.* [5▪]	New York county	Population survey	1078	Caucasian ($n=307$) African American ($n=282$) Hispanic ($n=344$) Asian ($n=111$)	All	9.3% men	2007–2009	6.0 (4.6–7.4)	African American 10.1 (9.1–11.0) Caucasian 5.6 (4.2–7.1) Asian 5.4 (3.3–7.5) Hispanic 4.1 (3.8–4.5)	75.9 (70.6–81.2)	African American 133.1 (130.6–135.7) Caucasian 51.4 (45.0–57.7) Asian 75.5 (66.0–85.0) Hispanic 84.6 (83.8–85.3)
Ferucci *et al.* [3]	Indian Health Service	Population survey	285	American Indian/ Alaska Native only	All	11.9% men	2007–2009	7.4 (5.1–10.4)	N/A	178 (157–200)	N/A
Ungprasert *et al.* [6]	Olmstead County, MN	Hospital and clinical records	58 (SLICC) 44 (ACR)	African American 7% Caucasian 86%	Over 18	16% men (SLICC) 7% men (ACR)	1993–2005	4.9 (SLICC) 3.7 (ACR97)	N/A	N/A	N/A
Furst *et al.* [7]	USA	Claims data	15396	N/A	Over 18	16% men	2003–2008	7.22	N/A	102.94	N/A

Table 2. Lupus incidence and prevalence worldwide: a 2017 update

Authors	Region	Study type	Number of SLE cases	Ethnicity	Age	Sex	Study period	Incidence	Incidence by ethnicity	Prevalence	Prevalence by ethnicity
Al Dhanhani *et al.* [9]	Al Ain region, United Arab Emirates	Hospital records, laboratory results, histopathology	15	Arab	All	20% men	2009–2012	8.6 (4.2–15.9)	N/A	103 (84.5–124.4)	N/A
Brinks *et al.* [10]	Germany	Population survey	845	N/A	All	19.5% men	2002	Women: 3.6 (2.9–4.3) Men: 2.2 (1.0–3.4)	N/A	N/A	N/A
Otsa *et al.* [12]	Estonia	Population survey	677	N/A	Adults over 20 years of age	10.5% men	2006–2010	1.4–1.7	N/A	37–40	N/A
Ingvarsson *et al.* [13]	Southern Sweden	Diagnosis registries, hospital records, laboratory databases	174	N/A	All	14.9% men	1981–2006	3.9 (2.1–5.5)	N/A	55–65	N/A
Hermanssen *et al.* [14]	Denmark	Population survey	1644	N/A	Adults over 18 years of age	14.3% men	1995–2011	2.35 (2.24–2.49)	N/A	45.2 (43.3–47.4)	N/A
Gergianaki *et al.* [15]	Crete	Chart review	750	N/A	Older than 15 years of age	7% men	1990–2011	8.6 (8.0 to 9.0)	N/A	123.4 (113.9–132.9)	N/A
Rees *et al.* [16]	United Kingdom	Retrospective cohort	7732	Caucasian 1700 African/ Carribean 128 Indian 45	All	14% men	1999–2012	4.91 (4.73–5.09)	Caucasian 6.73 (6.35–7.14) African/Carribean 31.46 (22.48–44.03) Indian 9.90 (6.32–15.53)	97.04 (94.19–99.94)	Caucasian 134.53 (128.21–141.08) African/Carribean 517.51 (398.54–660.84) Indian 193.09 (140.84–258.37)

SLE, systemic lupus erythematosus.

South. Residence in the Northeast conferred the lowest mortality risk regardless of sex or ethnicity.

Costenbader *et al.* [19] analyzed Medicaid claims data and reported higher SLE mortality rates per 1000 patient-years among Native American (27.52), Caucasian (20.17), and African American (24.13) patients. Mortality rates were lower among Hispanic (7.12) or Asian (5.18) patients.

In a general population based study in the United Kingdom, SLE patients were shown to have nearly double the premature mortality risk of their peers [20].

Lee *et al.* [21▪] performed a meta-analysis of studies examining all-cause and cause-specific standard mortality rates (SMR) in SLE. All-cause SMR were increased 2.6-fold in SLE patients. The risk of mortality was significantly increased for mortality because of renal disease (SMR 4.689), cardiovascular disease (SMR 2.253), and infection (SMR 4.980), but not because of cancer (SMR 1.163).

IMPACT OF FAMILY HISTORY

A study from Denmark [22] identified hospitalized patients with SLE over a period of 36 years and coupled them with their relatives through the Civil Registration System followed by identification of twins using the Danish twin registry. Hazard ratios of SLE were high among first-degree (hazard ratio 10.3) and second-degree or third-degree relatives of SLE patients (hazard ratio 3.60). Risk of other autoimmune diseases was significantly increased both among SLE-affected first-degree (hazard ratio 2.08) and second-degree or third-degree relatives (hazard ratio 1.38).

In a separate publication [23], same authors reported a lower SLE twin concordance in Denmark than previously reported. Among seven monozygotic, eight same-sex dizygotic and five opposite-sex dizygotic twin pairs, one monozygotic and one dizygotic same-sex pair were concordant for SLE. This corresponded to proband and pairwise concordance rates of 25 and 14.3% for monozygotic twins, and proband and pairwise concordance rates of 7.7% for dizygotic twins.

IMPACT OF AGE AND SEX

The RELESSER cohort data on sex differences among SLE patients [24] showed men to be diagnosed at a more advanced age than women. Men also had more cardiovascular comorbidities and were hospitalized more frequently. Men were more likely to lose weight, have lupus nephritis, lymphadenopathy, splenomegaly, and pulmonary fibrosis. Female patients were more likely to have inflammatory rash, alopecia, Raynaud's phenomenon, and arthritis.

A prospective single-center cohort in South Korea followed 133 children and 979 adults with SLE over a period of 14 years [25]. Children with SLE had a higher number of cumulative ACR criteria and a higher adjusted mean SLE Disease Activity Index, but there was no difference in SLICC/ACR damage index. Immunosuppressants were used more frequently by children with SLE. The standardized mortality rate in pediatric SLE was 18.8, compared with 2.9 in adult SLE, a highly statistically significant difference.

MALIGNANCY RISK IN SYSTEMIC LUPUS ERYTHEMATOSUS

Several studies examined the malignancy risk among SLE patients. A retrospective nested case–control study [26], which included 14 842 patients in Taiwan analyzed the risk of malignancy among SLE patients on azathioprine, cyclophosphamide, methotrexate, hydroxychloroquine, and glucocorticoids. A total of 330 patients developed a malignancy. The top five types of cancers were breast (16.9%), hematological (11.7%), colorectal (11.0%), lung (10.6%), and hepatobiliary (10.4%) cancers. The adjusted analyses showed an association of a higher cumulative cyclophosphamide dose (Odds ratio (OR) 1.09) and lower hydroxychloroquine dose (OR 0.93) with cancer risk in comparison with the controls.

A retrospective case–control study [27] included 40 011 patients with an ICD-9 coded diagnosis of primary autoimmune disease, 311 of which had a concomitant coded diagnosis of myelodysplastic syndrome or acute myeloid leukemia. Among the 86 patients who met inclusion criteria, 12 had SLE. Patients on azathioprine had an odds ratio of 7.05 for development of a myeloproliferative syndrome ($P < 0.001$). Methotrexate (OR 0.60), mercaptopurine (OR 0.62), and mycophenolate mofetil (OR 0.66) had favorable ORs that were not statistically significant. No association was found for anti-tumor necrosis factor agents.

Wadström *et al.* [28] examined the risk of cervical neoplasia in women with SLE in Sweden. There was an increased risk of cervical neoplasia in women with SLE compared with the general population (hazard ratio 2.12). The subcohort treated with immunosuppressants was at highest risk of cervical neoplasia, compared with those treated with antimalarials.

CARDIOVASCULAR DISEASE IN SYSTEMIC LUPUS ERYTHEMATOSUS

Hermassen *et al.* [29] in a nationwide, population-based cohort study demonstrated a significantly

higher risk of myocardial infarction (MI) and cardiovascular mortality in SLE patients with lupus nephritis compared with SLE patients without lupus nephritis ((hazard ratio 18.3 versus 2.2 for MI and hazard ratio 7.8 versus 1.6 for cardiovascular mortality). The higher risk of stroke in SLE was not significantly affected by the presence of lupus nephritis.

Using data from the Swedish National Patient Register, Arkema *et al.* [30] studied the occurrence of ischemic and hemorrhagic stroke in patients with SLE. The relative risk of ischemic stroke in SLE was more than doubled compared with the general population (hazard ratio 2.2), and importantly, the highest relative risks were observed within the first year after SLE diagnosis (hazard ratio 3.7).

To study ethnic differences in the cardiovascular risk among patients with SLE, Barbhaiya *et al.* [31] analyzed Medicaid data from 2000 to 2010 and identified 65 788 SLE patients: 93.1% were women and 42% were African American, 38% were Caucasia, 16% were Hispanic, 3% were Asian, and 1% were American Indian/Alaska Native. The risk of cardiovascular events was increased among African Americans (hazard ratio 1.14) compared with Caucasians, whereas Hispanics and Asians had a lower risk of MI (HR 0.61 and HR 0.57, respectively). Blacks and Hispanics had a higher risk of stroke (HR 1.31 and HR 1.22, respectively).

CONCLUSION

Over the past year, we have gained more insight into the worldwide incidence and prevalence of SLE. Data from the California Lupus Surveillance Project and the Manhattan Lupus Surveillance Program allowed estimation of incidence and prevalence among Hispanics and Asians who had a higher incidence and prevalence of SLE compared with Caucasians, but lower than African Americans. In Germany, the SLE incidence rate for German women was less than half of the French rate. A decline in the annual SLE incidence of 1.8% was observed in the United Kingdom, whereas in contrast the prevalence increased by 50% over a period of 15 years ending with 2012.

Despite advances in treatment, standardized mortality rates in SLE remain three times higher than in the general population. The risk of mortality is significantly increased for mortality due to renal disease, cardiovascular disease, and infection.

SLE is a risk factor for cervical neoplasia, in particular, for premalignant cervical lesions. The risk is highest among patients on immunosuppressants. Treatment-wise, azathioprine was shown to increase the risk of acute myeloid leukemia or myelodysplastic syndrome seven-fold in an autoimmune population, but the study included only a small number of SLE patients.

Lupus nephritis was shown to be an important cardiovascular risk factor with a hazard ratio nine times higher compared with SLE patients without lupus nephritis. SLE doubles the risk of stroke with the highest relative risk for stroke observed within the first year after diagnosis.

Acknowledgements

None.

Financial support and sponsorship

The Hopkins Lupus Cohort was funded by NIH AR 43727 and AR 69572.

Conflicts of interest

There are no conflicts of interest.

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Exercise in the management of knee and hip osteoarthritis

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Purpose of review
This review focuses on studies published during July 2001 to August 2017 of exercise as an intervention in knee and hip osteoarthritis, including its influence on an array of patient outcomes.

Recent findings
Studies continue to illustrate the efficacy of exercise in treating and managing osteoarthritis, with current literature more focused on the knee compared with the hip joint. Both traditional (e.g. strength, aerobic, flexibility) and more nontraditional (e.g. yoga, Tai Chi, aquatic) training modes improve patient outcomes related to joint symptoms, mobility, quality of life, psychological health, musculoskeletal properties, body composition, sleep, and fatigue. Exercise that is adequately dosed (e.g. frequency, intensity) and progressive in nature demonstrated the greatest improvements in patient outcomes. Supervised, partially supervised, and nonsupervised interventions can be successful in the treatment of osteoarthritis, but patient preference regarding level of supervision and mode of exercise may be key predictors in exercise adherence and degree of outcome improvement. A topic of increasing interest in osteoarthritis is the supplementary role of behavior training in exercise interventions.

Summary
Osteoarthritis is a complex, multifactorial disease that can be successfully managed and treated through exercise, with minimal risk for negative consequences. However, to have greatest impact, appropriate exercise prescription is needed. Efforts to achieve correct exercise doses and mitigate patient nonadherence are needed to lessen the lifelong burden of osteoarthritis.

Keywords
osteoarthritis, physical activity, physical therapy, training

INTRODUCTION

Osteoarthritis is a degenerative disease of the articular cartilage and surrounding structures that frequently affects lower extremity joints, particularly in the hip and knee [1]. The prevalence of knee osteoarthritis is nearly 28% in individuals over the age of 45, corresponding to 27% in individuals over 45 for hip osteoarthritis [1–3]. Individuals with osteoarthritis often experience pain, stiffness, or decreased physical function [4]. Additional negative consequences include psychological distress, socioeconomic burden, disability, and potential for major surgical intervention [5,6].

Effective treatment options for osteoarthritis are limited. Pharmacologic strategies, such as nonsteroidal anti-inflammatory drugs, are used for pain management, whereas nonpharmacologic options can address a range of osteoarthritis outcomes, including pain, physical function, and psychological health. Nonpharmacologic options for the management of knee and hip osteoarthritis include weight reduction and management, foot orthoses, bracing, cognitive behavior therapy, acupuncture, pain control modalities (e.g. transcutaneous electrical stimulation), and exercise [7]. Exercise is strongly recommended by the Osteoarthritis Research Society International and the American College of Rheumatology for the nonsurgical management of osteoarthritis [8,9]. The purpose of this review was to provide an updated analysis of recently published reports of exercise as an intervention in knee and

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Curr Opin Rheumatol 2018, 30:151–159
DOI:10.1097/BOR.0000000000000478

KEY POINTS

- Exercise is a safe, nonpharmacologic intervention for knee and hip osteoarthritis that improves patient outcomes related to symptoms, mobility, quality of life, and psychological health.
- Emerging evidence suggests patient preference regarding exercise supervision and supplementation of behavior training techniques in exercise interventions for osteoarthritis may enhance patient outcomes.
- Future research studies should carefully consider pragmatic designs, severity of OA, and longer term outcomes to improve real-world utilization of exercise for treatment of osteoarthritis.

hip osteoarthritis, including its influence on outcomes of pain, physical impairments, physical function, quality of life, psychological variables, musculoskeletal properties, body composition, sleep, and fatigue. Literature searches in PubMed and CINAHL were conducted by a university librarian under the direction of one author (E.W.) to retrieve relevant English-language articles published within the last year (July 2016 to August 2017). Articles were included if they were randomized control trials (RCT), observational studies, pragmatic trials, and systematic reviews/meta-analyses that studied exercise as an intervention of at least 6 weeks duration in a population of adults over 18 years old with knee or hip osteoarthritis, excluding total or partial joint replacement. Exercise could include walking, strengthening, Tai Chi, biking, aquatic therapy, dynamic balance exercises, yoga, or other forms of supervised or unsupervised exercise. Exercise included in a supervised rehabilitation setting was excluded if combined with manual therapy or modalities for pain control. Of the 102 articles identified and reviewed by both authors, 34 met inclusion/exclusion criteria (summaries provided in Table 1) [10,11▪▪,12▪,13,14▪▪,15–22,23▪,24▪,25–32,33▪–35▪,36–43].

PAIN

Overwhelming evidence supports the use of exercise to decrease joint-related pain because of osteoarthritis, including muscle strengthening, aerobic/cardiovascular exercise, dynamic balance training, Tai Chi, yoga, and aquatic exercise [10,11▪▪,12▪,13,14▪▪,15,17,19–23▪,25,28,30,34▪,36–40,42,43]. A common thread across both knee and hip osteoarthritis is that exercise must be appropriately dosed (i.e. frequency, intensity) and progressed to improve pain and other outcomes. A systematic review and meta-analysis by Bartholdy *et al.* [11▪▪] of 45 studies estimated that a 30% increase in knee extensor strength would be required to improve pain outcomes. However, only exercises that met the American College of Sports Medicine definition of muscle strengthening (>40% 1-repetition maximum, 2–4 sets of 8–12 repetitions, 2–3 sessions/week) resulted in greater knee extensor strength in participants with knee osteoarthritis. A similar review in participants with hip osteoarthritis by Moseng *et al.* [34▪] found that strength, flexibility, and cardiovascular exercises with high compliance to the American College of Sports Medicine dosing guidelines improved pain and physical function more than exercise that did not meet these guidelines. Evidence also suggests that exercise does not worsen pain in those with osteoarthritis. In a study of participants with exacerbations of knee osteoarthritis (knee pain $\geq$5/10), strengthening and coordination exercises completed three times per week for 12 weeks resulted in decreased pain levels after 63% of sessions (-2.6 $\pm$ 2.3), no change in 27% of sessions, and increased pain in only 10% of sessions (1.3 $\pm$ 0.5) [12▪].

To determine best practice for clinical implementation of exercise, one pragmatic study evaluated support strategies for osteoarthritic individuals receiving exercise therapy. Bennell *et al.* [15] aimed to determine if the addition of 6–12 telephone coaching sessions to their exercise intervention (Table 1) would benefit individuals with symptomatic knee osteoarthritis ($\geq$4/10). No statistically significant differences between those who did and did not receive the additional phone calls existed in numeric pain rating scores (0–10) or function on the Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) at 6, 12 or 18 months, with both groups demonstrating clinically meaningful improvements. Many other studies have demonstrated pain-reducing effects of partially supervised or nonsupervised exercise in individuals with knee or hip osteoarthritis [10,15,25,39,40]. Osteoarthritis treatment strategies emphasizing patient self-management skills may provide cost-effective alternatives to long periods of highly supervised episodes of care.

Many recent studies have investigated the influence of Tai Chi and yoga in knee osteoarthritis, all demonstrating a beneficial impact on pain symptoms [19,20,28,43]. In a study comparing Tai Chi to manual and/or exercise physical therapy, no between-group differences existed, as both groups demonstrated significant improvements in WOMAC pain and function scores at 12 weeks that were maintained at 24 and 52 weeks [43]. Cheung *et al.* [20] conducted a pilot study comparing partially supervised Hatha yoga to combined strengthening and aerobic training

Table 1. Summary of studies included in review

Study authors	Study design:	Location of osteoarthritis	Number of subjects/studies	Intervention studied:	Relevant outcomes
Anwer *et al.* [10]	Systematic review & meta-analysis	Knee	19 studies	Home exercise programs (any exericse type) compared with inpatient or outpatient physical therapy or no intervention	WOMAC, VAS (pain), McGill Pain Questionnaire, Japanese Knee Osteoarthritis Measure
Bartholdy *et al.* [11▪▪]	Systematic review & meta-analysis	Knee	45 studies	Strength training per ACSM guidelines versus strength training not per ACSM guidelines or any other type of exercise	Muscle strength, WOMAC, NRS (pain), VAS (pain), KOOS, AIMS2, OASI, Lequesne Index Score, SF-36
Bartholdy *et al.* [12▪]	Observational	Knee	$n=129$	Nonweightbearing core strengthening and coordination, hip coordination, and hip abductor strengthening	NRS (pain), KOOS
Beckwée *et al.* [13]	RCT	Knee	$n=35$	Strength training (33% supervised by physical therapy, 67% unsupervised) versus walking training (33% supervised by physical therapy, 67% unsupervised)	Bone marrow lesions (MRI)
Bennell *et al.* [14▪▪]	Multisite RCT	Knee	$n=568$	Exercise versus pain coping skills training versus pain coping skills training and exericse; exercise included 10 supervised visits (physical therapy) with prescribed home exercise program for lower extremity strengthening. Pain coping skills training consisted of 10 physical therapy-delivered modules.	VAS, WOMAC, AQoL, Physical Activity Scale for the Elderly, Arthritis Self-Efficacy Scale, Pain Catastrohpizing Scale, Depression, Anxiety, Stress Scales in 21 items, Quadriceps strength, 30-s sit-to-stand test, 20-meter fast-paced walking velocity
Bennell *et al.* [15]	Pragmatic RCT	Knee	$n=406$	Home exercise program of 4–6 lower extremity strengthening exercises and provision of pedometer with 5 supervised visits (physical therapy) for education and exercise prescription with or without additional 6–12 telephone coaching sessions (physical therapy)	NRS (pain), WOMAC
Bieler *et al.* [16]	RCT'	Hip	$n=126$	Lower extremity strength training versus Nordic walking (both groups: 66% in group setting supervised by physical therapy, 33% unsupervised) versus Controls (home-based stretching, range of motion, and strength exercises recommended by the Danish Arthritis Association)	30-s chair stand test, timed stair climbing test, 8-foot up and go test, 15-s marching on the spot test, 6-min walk test
Brenneman *et al.* [17]	Observational	Knee	$n=40$	Supervised lower extremity strength training, functional movement training, static stretching	KOOS, muscle strength
Casilda-Lopez *et al.* [18]	RCT	Knee	$n=34$	Aquatic dance-based exercise versus Traditional aquatic exercise (both groups: supervised by physical therapy)	WOMAC, treadmill 6-min walk test with heart rate monitoring, VAS (fatigue)
Chang *et al.* [19]	Systematic review & meta-analysis	Knee	11 studies	Tai Chi Chuan versus controls (not practicing Tai Chi Chuan)	WOMAC, muscle strength, bone mineral density (DEXA), body weight, BMI, 6-min walk test, stair climb test, sit-to-stand test, timed-up-and-go test, SF-36
Cheung *et al.* [20]	RCT	Knee	$n=83$	Hatha yoga (supervised (yoga teacher) and unsupervised) versus aerobic/ strength training [supervised (certified arthritis exercise instructor) and unsupervised] versus education attention control group	WOMAC, VAS (pain), Short Physical Performance Battery, walking speed, Hospital Anxiety and Depression Scale, Fall Efficacy Scale-International, SF-36
Cordeiro Aguiar *et al.* [21]	Observational	Knee	$n=27$	Supervised (physical therapy) strength training and flexibility training	SF-36, WOMAC, VAS (pain), walking speed
de Rooij *et al.* [22]	RCT	Knee	$n=126$	Supervised (physical therapy) lower extremity strength training, aerobic training, and training of ADL's versus control group (current medical care for osteoarthritis)	WOMAC, 6-min walk test, NRS (pain, fatigue), SF-36, get-up-and-go test, time walking up-down stairs test, LAPAQ, muscle strength
Edwards *et al.* [23▪]	Systematic review & meta-analysis	Knee	15 studies	Running	Onset or progression of osteoarthritis, knee joint surgery for osteoarthritis, knee pain
Focht *et al.* [24▪]	RCT	Knee	$n=80$	Group-based exercise therapy (walking, lower extremity strength training) versus group-based exercise therapy and group-mediated cognitive behavior training	Self-Regulatory Self-Efficacy, Mobility-Related Self-Efficacy, 400-meter walk test

Table 1 (*Continued*)

Study authors	Study design:	Location of osteoarthritis	Number of subjects/studies	Intervention studied:	Relevant outcomes
Fukumoto *et al.* [25]	RCT	Hip	$n=46$	Unsupervised high-velocity versus low-velocity strength training prescribed by physical therapy	Muscle strength, stair ascending test, Harris Hip Score, VAS (pain)
Ghandali *et al.* [26]	Observational	Knee	$n=20$	Supervised Tai Chi (Yang style)	Center of pressure measured on force plate
Gomes *et al.* [27]	Observational	Knee	$n=16$	Supervised walk training	Graded treadmill test, SF-36
Kan *et al.* [28]	systematic review	Knee	6 studies	Yoga	WOMAC, KOOS, SF-36, VAS (pain), 50-foot walk time, 6-min walk test, 30-s chair stand test
Kean *et al.* [29]	RCT	Knee	$n=97$	Unsupervised quadriceps strength training with seven physical therapy visits for education and exercise progression versus controls (no intervention)	Muscle strength
Li *et al.* [30]	Systematic review and meta-analysis	Knee	17 studies	Strength training versus controls (no intervention or psycho-education intervention)	WOMAC, VAS (pain), OASI, KPS
Loew *et al.* [31]	RCT	Knee	$n=69$	Supervised (physical therapy) versus unsupervised walking program	Waist circumference, BMI, 6-min walk test, timedup and go test, WOMAC
Lu *et al.* [32]	RCT	Knee	$n=46$	Tai Ji Quan versus controls (wellness education classes)	SF-36, Berg Balance Scale, timed up and go test
Miller *et al.* [33▪]	Observational	Knee	$n=17$	Lower extremity moderate-intensity strength training	Muscle strength, body composition
Moseng *et al.* [34▪]	Systematic review and meta-analysis	Hip	12 studies	Land-based exercise with high versus low compliance with ACSM dosage guidelines	WOMAC, NRS (pain), VAS (pain), HOOS, SF-36, IRGL, GARS
Multanen *et al.* [35▪]	RCT	Knee	$n=80$	Supervised high-impact aerobic (jumping) and step-aerobic exercise versus controls (no intervention with option of social group meetings)	Femoral neck structural strength (DEXA), T2 cartilage mapping and dGEMRIC), Physical activity (accelerometers), RAQND-36, WOMAC
Munukka *et al.* [36]	Secondary analysis of RCT	Knee	$n=84$	Aquatic resistance training versus controls (no intervention)	T2 relaxation times; dGEMERIC; V02 max via walking test; muscle strength; KOOS
Munukka *et al.* [37]	RCT	Knee	$n=87$	Aquatic resistance training versus controls (no intervention)	T2 relaxation times, dGEMERIC, V02 max via walking test, muscle strength, KOOS
Sampath *et al.* [38]	Systematic review and meta-analysis	Hip	7 studies	Exericse therapy (type varies) versus manual therapy versus combined exercise and manual therapy	WOMAC, VAS (pain), NRS (pain), GARS
Svege *et al.* [39]	RCT	Hip	$n=109$	Group education versus group education + exercise (strength training, functional exercises, stretching)	ROM, muscle strength, Astrand bicycle ergometer test, 6-min walk test
Takacs *et al.* [40]	RCT	Knee	$n=40$	Partially supervised (kinesiologist) balance training, lower extremity strength training, and core stability exercises versus controls (no intervention)	Community Balance and Mobility Score, WOMAC, NRS (pain), Brief Fear of Movement Scale, muscle strength
Tanaka *et al.* [41]	Systematic review and meta-analysis	Knee	28 studies	Exercise therapy (any form) versus controls (no intervention or psychoeducational intervention)	Gait speed, 6-min walk test, time spent walking
Waller *et al.* [42]	RCT	Knee	$n=87$	Group aquatic resistance training versus controls (no intervention)	Body composition, walking speed, KOOS, leisure time physical activity (measured by daily diary)
Wang *et al.* [43]	RCT	Knee	$n=204$	Tai Chi versus physical therapy (with manual therapy and/or exercise) with home exercise program	WOMAC, Beck Depression Inventory-II score, SF-36, Arthritis Self-Efficacy Scale, 6-min walk test, 20-meter walk test

ACSM, American College of Sports Medicine; ADL's, activities of daily living; AIMS2, Arthritis Impact Measurement Scales 2; AQoL, Assessment of Quality of Life; DEXA, dual energy X-ray absorptiometry; dGEMERIC, delayed gadolinium-enhanced MRI; GARS, Groningen Activity Restriction Scale; HOOS, Hip disability and Osteoarthritis Outcome Score; IRGL, impact of rheumatic diseases on general health and lifestyle; KOOS, Knee Injury and Osteoarthritis Outcome Score; KPS, Knee Pain Scale; LAPAQ, Longitudinal Aging Study Amsterdam Physical Activity Questionnaire; NRS, Numeric Rating Scale; OASI, Osteoarthritis Screening Index; RCT, randomized controlled trial; SF-36, Medical Outcomes Study Short-Form Health Survey; VAS, Visual Analog Scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

targeting the entire body in 83 individuals with knee osteoarthritis. The yoga group demonstrated greater improvements in pain on the WOMAC and 0–10 Visual Analog Scale immediately after the 8-week intervention period. However, notably the strengthening and aerobic training group's intervention did not target specific impairments present in knee osteoarthritis (e.g. weak knee extensor muscles), which may have limited pain improvements in this group.

High-impact exercise can be difficult to prescribe in osteoarthritis because of fear that pain symptoms will be exacerbated. However, a systematic review and meta-analyses of 15 studies by Edwards *et al.* concluded that pain was no worse in individuals who were runners than nonrunners [23▪]. Further, their findings suggested that running reduces the risk of needing surgery to repair osteoarthritis disease. Therefore, in individuals with a history of running for exercise, running should not be excluded as a potential form of physical activity following an osteoarthritis diagnosis.

Although fewer studies have compared exercise in hip osteoarthritis versus knee osteoarthritis, exercise provides similar pain-reducing benefits [25,34▪,38,39]. Sampath *et al.* [38] conducted a systematic review and meta-analysis comparing manual therapy, exercise therapy, and a combination of both in individuals with hip osteoarthritis. High-quality evidence suggests exercise may improve a variety of outcomes in both pain and physical function immediately posttreatment (pain: standardized mean difference (SMD) 0.27; 95% CI 0.5–0.04; physical function: SMD 0.29; 95% CI 0.47–0.11) and at follow-up (pain: SMD 0.24, 95% CI 0.41–0.06; physical function: SMD 0.33; 95% CI 0.5–0.15).

PHYSICAL IMPAIRMENTS

Impairments such as muscle weakness, reduced cardiorespiratory capacity, and poor balance are common in individuals with osteoarthritis. Individuals can significantly improve muscle strength through supervised, land-based resistance exercise at proper doses and intensities according to a patient's strength capacity [11▪▪,29,33▪]. Strength does not consistently improve whenever strength-training interventions are not targeted (e.g. quadriceps muscle for knee osteoarthritis) and progressive (i.e. maintaining $\geq$40% 1-repetition maximum) [17,25,37,39,40]. Tai Chi has demonstrated the ability to decrease the magnitude and velocity of center of pressure (CoP; i.e. greater postural stability) during standing (area of CoP (cm^2): $P < 0.01$, pre: 7.02 ± 0.68; post: 4.29 ± 0.33; mean velocity of CoP: $P < 0.001$, pre: 8.48 ± 0.86; post:4.36 ± 0.16; $N = 20$) [26], but Tai Ji Quan and dynamic balance interventions have not been efficacious in improving balance during functional tasks ($N = 40$ and 46, respectively) [32,40]. VO_2 max increased 21% following 12 weeks of a progressive walking program in 16 elderly women with knee osteoarthritis [27], whereas VO_2 max increased 9.8% following 16 weeks of aquatic resistance exercises in an RCT of 87 postmenopausal women with knee osteoarthritis [37].

PHYSICAL FUNCTION

Recent literature consistently reports an increase in physical function following exercise interventions in individuals with knee and hip osteoarthritis~[10,11▪▪,12▪,14▪▪,15–22,24▪,25,28,30–32,34▪,35▪,36–43]. Traditional modes of exercise including strength, flexibility, and aerobic training are effective in improving subjective physical function [e.g. WOMAC, Knee Injury and Osteoarthritis Outcome Score (KOOS)] and objective function (e.g. 6-min walk test, 30-s chair stand test) for individuals with osteoarthritis [10,11▪▪,12▪,14▪▪,15–17,21,22,24▪,25,30,31,34▪,35▪,38–41]. The effects of less commonly prescribed modes of exercise on function have also been recently explored. Heinonen and colleagues studied the efficacy of a 4-month aquatic training program with high-intensity resistance compared with regular physical activity levels in postmenopausal women with knee osteoarthritis [36,37,42]. Although walking speed increased in the aquatic treatment group at 12 months ($P = 0.002$; 0.052 m/s, 95% CI 0.018–0.086 m/s), KOOS scores did not differ between groups. Chang *et al.* concluded in a meta-analysis that Tai Chi Chuan has small to moderate effects on physical function in individuals with knee osteoarthritis [physical function scale of the WOMAC (total SMD = −0.16; 95% CI = −0.44 to −0.11); 6-min walk test (SMD = −0.16; 95% CI = −1.23 to 0.90); and stair climb test (SMD = −0.76; 95% CI = −1.34 to 0.15)] [19]. A systematic review of six studies of knee osteoarthritis reported inconclusive evidence that yoga interventions (typically 40–90 min per session for 8 weeks duration) improve physical function and mobility [28]. In 126 participants with hip osteoarthritis, Bieler *et al.* [16] compared 4 months of Nordic walking (i.e. fast walking with specially designed walking poles) to a progressive strength-training group for lower extremities and a home-based exercise group. Contrary to the authors' hypotheses, the Nordic walking group demonstrated the greatest improvements in physical function at 12 months (change score (95% CI): 30-s chair stand test: 2.5 repetitions (1.2–3.7), timed stair-climbing test: −1.9 s (−3.3 – (−) 0.5),

8-foot up-and-go test: −1.2 s (−1.7 – (−) 0.6), 6-min walk test: 76 meters (40–113)).

QUALITY OF LIFE

Health-related quality of life, which represents the patient-perceived benefit of an intervention, can incorporate the patient's emotional, physical, social, and subjective feelings of well being. In individuals with knee osteoarthritis, land-based exercise interventions are more efficacious in improving quality of life than aquatic interventions [14▪▪,17,27,28,32,37,42]. Land-based interventions may mimic day-to-day applications of physical function more closely than aquatic exercise, resulting in more participants perceiving improvement. One study by Gomes *et al.* [27] reported a 47% improvement in SF-36 scores following a progressive, 12-week walking program in 16 participants with knee osteoarthritis. Bennell *et al.* [14▪▪] indicates that the addition of behavior training may improve health-related quality of life even more than exercise alone. Participants with knee osteoarthritis ($N = 406$) who completed 10 sessions of lower extremity strengthening with pain coping skills training reported greater improvements in Assessment of Quality of Life scores ($P < 0.001$; -0.1 ± 0.0) at 1 year than those completing strengthening only (0.0 ± 0.0). Several studies also demonstrated improvements in health-related quality of life measures after periods of yoga and Tai Ji Quan compared with controls completing no exercise interventions [28,32], with benefits similar in magnitude to aerobic and strength training [20].

MUSCULOSKELETAL PROPERTIES AND BODY COMPOSITION

Several recent studies confirm that exercise is safe in osteoarthritis, and may even be beneficial to the damaged joint and surrounding tissues [27,33▪,35▪,36,37]. In a study by Multanen *et al.* [35▪], 80 participants with knee osteoarthritis were randomized to either 12 months of high-impact aerobic and step-aerobic exercise or a control group with no intervention. The exercise group demonstrated greater femoral neck bending strength measured by dual energy X-ray absorptiometry (DEXA) after intervention compared with the control group ($P < 0.01$, between-group difference of 4.4%) without any greater compromise to the articular cartilage as measured by quantitative magnetic resonance imaging. However, a study by Miller *et al.* demonstrated that understanding the underlying mechanisms for physical improvements following exercise is not straightforward. Unlike high-intensity resistance training that increases muscle size and function and thus muscle capacity, they found that 14 weeks of moderate-intensity resistance training caused minimal changes to skeletal muscle structure in the vastus lateralis in 17 older, inactive adults with knee osteoarthritis [33▪].

Loew *et al.* demonstrated the importance of patient satisfaction during exercise in improving weight-related outcomes [31]. Participants with knee osteoarthritis who received their preference of either a 6-month supervised or unsupervised progressive walking program had decreased body weight 3 months after the intervention. Similarly, those who adhered to their walking sessions demonstrated significant decreases in waist circumference compared with non-adherent participants. In contrast, exercise programs consisting of moderate-intensity strengthening and aquatic exercise with no incorporation of patient preference did not result in meaningful improvements in body weight or fat mass [33▪,42].

PSYCHOLOGICAL FACTORS

Approximately 20% of adults with osteoarthritis have depression, leading to increased healthcare expenditures and burden [44]. Nationally, an estimated 18% of all depression cases are attributable to arthritis [45]. Regular exercise is associated with fewer symptoms of depression and anxiety by way of complex physiological and psychological mechanisms [46], and several recent studies exploring exercise in osteoarthritis have demonstrated improvements in depression, self-efficacy, stress, pain catastrophizing, anxiety, and fear of movement [14▪▪,19,20,24▪,40,43]. In an RCT of 406 participants with knee osteoarthritis, Bennell *et al.* [14▪▪] found that the addition of pain coping skills training was superior to 10 sessions of exercise alone in reducing scores on the Depression, Anxiety, Stress Scales in 21 items at 32–52 week follow-up (between-group difference (95% CI): depression: $P < 0.05$, 2.8 (0.1–5.6); anxiety: $P < 0.05$, 2.1 (0.0–4.1); stress: $P < 0.05$, 3.7 (0.7–6.7). The combination also improved pain coping strategies and self-efficacy regarding the consequences of osteoarthritis at 6–12 months after the 12-week intervention. Focht *et al.* [24▪] compared 36 sessions of group-based walking and lower extremity strength training delivered over 3 months to an intervention that spread the same 36 exercise sessions out over 12 months while also integrating group-based cognitive behavioral counseling designed to improve activity-related self-regulatory skills in an RCT of 80 sedentary adults with knee osteoarthritis. The addition of behavioral training was superior to exercise alone in improving self-efficacy to organize, plan, and schedule regular physical activity and in boosting satisfaction with physical activity – improvements that correlated with increased physical activity and mobility.

SLEEP AND FATIGUE

Lu *et al.* [32] reported that Tai Ji Quan was more effective than wellness education in improving sleep latency, sleep duration, and total sleep time in participants with knee osteoarthritis. Eight weeks of aquatic dance-based exercise resulted in decreased preexercise fatigue of 2.25 measured on a 0–10 numeric rating scale [18]. A RCT of 126 participants with knee osteoarthritis by de Rooij *et al.* [22] also reported greater improvements in fatigue measured on a 0–10 scale following 20 individualized physical therapy sessions of strength, aerobic, and daily activity training at 20-week follow-up compared with those not receiving physical therapy [$P < 0.01$; between-group difference: 0.91 (95% CI 0.71–1.66)] but not at 10-week [$P > 0.05$; between-group difference: 0.91 (95% CI 0.71–1.66)] or 32-week follow-up ($P > 0.05$, between group difference: 0.59 (95% CI: −0.23–1.41)].

FUTURE RESEARCH DIRECTIONS

Several areas need further research regarding exercise for individuals with osteoarthritis. Studies of exercise for patients with hip osteoarthritis are limited, and some exercise approaches used for knee osteoarthritis could be examined for the hip. Studies of exercise for osteoarthritis typically exclude individuals with comorbid conditions, resulting in findings with limited generalizability. Future pragmatic trials of exercise programs should include individuals with comorbid conditions common in osteoarthritis, such as cardiovascular disease or diabetes. Most studies to date have focused on individuals with mild-to-moderate osteoarthritis, and our updated review did not reveal new findings about the role of exercise by severity of osteoarthritis. A few reports (published outside of the time period of this review) suggest short-term improvements in pain and function with exercise interventions for adults with severe osteoarthritis [47–50]; although one study reported no change in pain after a 12-week walking program [51]. Water-based exercise programs may be an alternative to land-based approaches for individuals with severe osteoarthritis because of the reduction of joint loading in water. However, evidence supporting the long-term effects of land-based versus water-based exercise for severe osteoarthritis is lacking. High-quality trials with larger samples and longer term outcomes are needed to inform exercise approaches for severe osteoarthritis. Finally, guidance is needed on proper dosage and progression of exercise modes, accounting for symptoms, baseline physical function, comorbid conditions, and individual preferences.

CONCLUSION

Recent research has continued to highlight the beneficial impact of exercise in knee and hip osteoarthritis. Traditional modes of exercise such as strength, aerobic, and flexibility training improve patient outcomes, and emerging types, such as yoga, Tai Chi, and aquatic exercise, also show benefit in recent investigations. Exercise can promote improvements in a variety of outcomes, including pain, physical impairments, physical function, quality of life, psychological variables, musculoskeletal properties, body composition, sleep, and fatigue. The degree of improvement likely depends on proper dosage and progression of exercise and may be enhanced through additional behavioral training techniques. As current research continues to support exercise as an efficacious treatment for osteoarthritis, future efforts are needed to establish proper dosage and progression of exercise, accounting for comorbid conditions and individual preferences, so that both patients and clinicians can effectively implement these findings in real-world situations.

Acknowledgements

We would like to thank Christian Minter, M.S., at the University of Nebraska Medical Center's McGoogan Library of Medicine for her assistance in completing the literature search for this review article.

Financial support and sponsorship

This work was supported in part by a New Investigator Fellowship Training Initiative (NIFTI) award from the Foundation for Physical Therapy for E.W. in which Y.G. serves as a mentor.

Conflicts of interest

Y.G. is currently receiving grant funding from the National Institutes of Health (R01 AR071440, R21 HD088852, R01 AR067743, P60 AR062760), Centers for Disease Control and Prevention (RFA-DP16–1606, RFA-DP-16–003), and Department of Defense (W81XWH-14-DMRDP-CRMRP-NMSIRA).

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Epidemiology of osteoarthritis: literature update

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Purpose of review
The purpose of this review is to highlight recent studies of osteoarthritis epidemiology, including research on prevalence, disease impact, and potential risk factors.

Recent findings
Osteoarthritis is highly prevalent in the United States and around the globe. It is a leading cause of disability and can negatively impact people's physical and mental well being. Healthcare resources and costs associated with managing the disease can be substantial. There is increasing evidence that there are different osteoarthritis phenotypes that reflect different mechanisms of the disease. Various person-level risk factors are recognized, including sociodemographic characteristics (e.g. female sex, African-American race), genetic predispositions, obesity, diet-related factors, and high bone density/mass. Joint-level risk factors include specific bone/joint shapes, thigh flexor muscle weakness, joint malalignment, participation in certain occupational/sports activities, and joint injury. Recent studies have enhanced our understanding of preradiographic lesions associated with osteoarthritis.

Summary
Application of these new findings may allow us to develop innovative strategies and novel therapies with the purpose of preventing new disease onset and minimizing disease progression.

Keywords
epidemiology, impact, osteoarthritis, phenotypes, risk factors

INTRODUCTION

A number of reviews on the epidemiology of osteoarthritis have been conducted in the past decade [1–5]. This review highlights new research findings since the middle of 2016. Similar to the other reviews [1–3,5], we will begin by presenting recent data on disease prevalence. We will then discuss recent findings on the impact of osteoarthritis and the distinct phenotypes of the disease. Finally, we will describe new information concerning systemic-level and local-level risk factors associated with osteoarthritis development and/or progression.

PREVALENCE

The estimated prevalence and incidence of osteoarthritis vary depending on the definition of osteoarthritis, the specific joint(s) being evaluated, and the population being studied [1–3]. Using data from the National Health Interview Survey, it was recently estimated that 14 million people in the United States have symptomatic knee osteoarthritis (KOA), including more than 3 million racial/ethnic minorities [6]. Notably, more than half those with KOA are less than 65 years of age. Recent cohort and community-based studies have also measured the prevalence of osteoarthritis of different joints in various communities in South America [7,8], Asia [9–11], and the Middle East [12].

IMPACT OF OSTEOARTHRITIS

Osteoarthritis is a well known cause of disability around the globe [13]. In a large cohort study of Mexican Americans, the number of activities of daily living impairments was 1.12–1.35 times greater among those with osteoarthritis, compared with those without it [14]. In a nationwide survey conducted in Korea, the estimated years lived with disability was exceptionally high among elderly men (836 per 100 000) and women (3039 per 100 000) with osteoarthritis [15]. In a population-based study in Sweden, the greater risk for sick leave

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Curr Opin Rheumatol 2018, 30:160–167
DOI:10.1097/BOR.0000000000000479

KEY POINTS

- Osteoarthritis (osteoarthritis) continues to impact the lives of a substantial proportion of adults globally.
- More recent evidence suggests that there are several osteoarthritis clinical phenotypes that represent different disease mechanisms.
- Person-level risk factors associated with osteoarthritis include genetic and environmental influences.
- Joint-level risk factors associated with osteoarthritis include structural abnormalities in bone shape, muscle mass, and joint alignment.
- New magnetic resonance imaging studies have begun to allow prediction of radiographic/symptomatic osteoarthritis development and progression.

or disability among those working in women-dominated or men-dominated job sectors was attributed to KOA [16].

In addition to affecting people's physical health, osteoarthritis may also negatively impact people's mental health. Data from the Osteoarthritis Initiative (OAI) study demonstrated that those with lower limb osteoarthritis had greater odds of developing depressive symptoms than those without the disease [17]. Osteoarthritis was also associated with greater odds of suicidal ideation [18]. Another study found a strong relationship between osteoarthritis and perceived memory loss that was partially mediated by sleep and mood impairments [19].

There is also increasing evidence that osteoarthritis is a risk factor for cardiovascular disease development. A meta-analysis found that the risk of myocardial infarction was significantly increased in osteoarthritis and other types of arthritis [20▪]. Other studies similarly linked coronary heart disease with osteoarthritis [21,22]. In parallel, the Chingford Cohort study found an increased risk of cardiovascular disease-specific and all-cause mortality among women with symptomatic KOA compared with women without signs/symptoms of osteoarthritis [23]. Interestingly, there was no relationship found between hand osteoarthritis and mortality risk. A Swedish study reported no increased mortality in patients with knee and hip osteoarthritis compared with the general population [24].

In addition, osteoarthritis consumes a substantial amount of healthcare resources and costs. Studies have demonstrated that osteoarthritis was associated with higher risk of hospitalization and emergency department charges among those who present in the emergency room for other reasons [25,26]. The average direct cost of osteoarthritis in Canada increased from $577 to $811 per patient/year between 2003 and 2010, primarily because of joint replacement surgery costs [27]. In the United States, the estimated total annual average direct per patient cost varied from $1442 to $21335 (adjusted to 2015 US$ equivalent) [28]. Observed variations in cost were partly attributed to differences in healthcare resource categories measured between claims data and survey data-based studies.

PHENOTYPES

A phenotype can be defined as a combination of disease attributes that describes differences between patients as they relate to distinct outcomes of interest [29]. KOA is a heterogeneous disease with varying phenotypes. There is growing consensus that these variations are because of the existence of different phenotypes that may represent different mechanisms of the disease [4,30,31]. With different phenotypes, clinicians may tailor their disease management [30]. A recent systematic review identified six variables, which represent six clinical phenotypes [31]: chronic pain (with prominent central mechanism), inflammation, metabolic syndrome, bone and cartilage metabolism, mechanical overload, and minimal joint disease. The six phenotypes may represent different disease causes with the exception of the minimal joint disease phenotype that classifies patients based on disease progression.

Another systematic review reported on which characteristics are most relevant in distinguishing KOA phenotypes [32▪▪]. Clinical phenotypes are the KOA phenotypes most frequently investigated, followed by laboratory and imaging phenotypes (Table 1). Authors of the review concluded that pain sensitization, psychological distress, radiographic severity, BMI, muscle strength, inflammation, and comorbidities (especially metabolic syndrome) were most associated with clinically distinct phenotypes. They also reported that sex, metabolic abnormalities, pattern of cartilage damage, and inflammation were most relevant in distinguishing structural phenotypes.

RISK FACTORS: SYSTEMIC

The World Health Organization defines risk factor as any attribute, characteristic or exposure of an individual that increases the likelihood of developing a disease [33]. Current evidence on person-level risk factors associated with osteoarthritis disease development and/or progression is discussed in the following section.

Table 1. Osteoarthritis phenotypes and their distinguishing characteristics

Category	Distinguishing characteristics
Clinical	Pain sensitization profile
	Psychological profile
	Comorbid symptoms profile
	Clinical characteristics
	Knee joint alignment
	Metabolic
	Gait parameters
	Mechanistic factors
Imaging	Knee chondrocalcinosis
	MRI-detected denuded bone areas
	Imaging features and clinical symptoms
	Knee joint compartment (patellofemoral, tibiofemoral)
Laboratory	Biochemical marker patterns
	Inflammatory profile
	Cytokine/chemokine profile (synovial fluid)
	Serum biochemical markers of bone metabolism
	Serum biochemical markers of cartilage metabolism
	Profile of gene expression in peripheral blood leukocytes

Derived from Deveza *et al.* [32▪▪].

Sociodemographic

Older age is a well known risk factor for osteoarthritis [1–3]. Compared with men, women are more likely to develop hand, foot, and KOA but are less likely to develop cervical spine osteoarthritis [1]. A new study of incident diagnoses of osteoarthritis among United States service members comparably found that the rates of shoulder and cervical spine osteoarthritis were higher among men than women [34]. Another found that lower levels of endogenous sex hormones were associated with increased knee effusion-synovitis only in women and not in men with symptomatic osteoarthritis [35].

Compared with other races, African-Americans are also more likely to develop symptomatic knee and hip osteoarthritis [2,5]. There are known racial/ethnic differences in radiographic osteoarthritis features [5]. In a longitudinal study, it was recently discovered that African-American men had higher risk of medial knee joint space width (JSW) loss over time than African-American women and whites [36]. Controlling for other known risk factors for KOA attenuated these differences, however.

Genetic

Approximately 30–65% of the risk of osteoarthritis is genetically determined [1,3]. A recent review by Warner *et al.* [37▪▪] highlighted the main findings from genetic association studies on osteoarthritis to date. They reported that genome-wide associated scan (GWAS) studies have so far identified 21 independent susceptibility loci for osteoarthritis. Since this review's publication, the single nucleotide polymorphism (SNP) rs4238326 in the *ALDH1A2* gene was linked with KOA risk in a Chinese sample study [38]. This is relevant, as genetic variants within the *ALDH1A2* gene was only previously linked with hand osteoarthritis in European populations [37▪▪]. Data from the Chingford study also found that the SNP rs11688000 in the neurokinin 1 receptor gene (*TACR1*) was associated with decreased risk of symptomatic osteoarthritis [39].

An issue with conducting genetic association studies for osteoarthritis is the heterogeneity of phenotypes used. Using endophenotypes, which can be more reliably quantified (e.g. minimum JSW), can help reduce this problem [37▪▪,40▪]. Four distinct loci were recently associated with minimum JSW in a hip osteoarthritis study [41].

Obesity and metabolic syndrome

Obesity has long been identified as a risk factor for KOA [1–4]. An updated meta-analysis also showed that increased BMI moderately contributed to increased susceptibility to radiographic and/or clinical hand osteoarthritis [42]. Although the association between obesity and hip osteoarthritis had been weak based on previous studies [1,2], a cross-sectional study from Japan [43] and a prospective cohort study from Spain [44▪] recently found an independent association between weight gain and hip osteoarthritis diagnosis. Conversely, weight loss has been consistently associated with improved arthritis symptoms in a dose–response manner and slower knee cartilage degeneration in two different study populations [45,46].

Very few previous studies have investigated the relationship between hyperlipidemia and osteoarthritis [2]. A recent case–control study from the United Kingdom demonstrated that hyperlipidemia was an independent risk factor for new onset hand osteoarthritis [47]. In the Chingford study, higher levels of high-density lipoprotein cholesterol was protective against the incidence of radiographic hand osteoarthritis [48]. In parallel, use of antilipemic agents (primarily ezetimibe, and excluding statins and fibric acid) was associated with fewer structural and better knee pain changes among OAI participants [49]. Statin use was not associated with reduced risk of consultation or surgery for hip or KOA in a pooled analysis of four cohort studies done in Sweden, however [50].

Examination of the OAI data found an association between higher systolic blood pressure and increased incidence of radiographic KOA [51]. A recent report does not support an association between diabetes mellitus and hand/knee osteoarthritis [52–54]. There was also no significant association found between metabolic syndrome and radiographic hand osteoarthritis using Framingham data [55].

Vitamins/diet

As vitamin D plays a major role in cartilage and bone metabolism, it has been hypothesized that low levels of it may increase osteoarthritis risk. Previous studies have been conflicting [1–3]. In the Vitamin D Effect on Osteoarthritis study [56,57,58▪▪], patients with vitamin D insufficiency and KOA were randomized to receive either vitamin D3 or placebo. Vitamin D3 supplementation neither slowed progression of joint space narrowing nor did it reduce Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) subscale scores [56]. After 2 years, though, effusion synovitis (measured by MRI) remained stable in the vitamin D group but increased in the placebo group [57]. Those with consistently sufficient 25-hydroxyvitamin D levels also had less loss of tibial cartilage volume, less increase in effusion synovitis, and less decrease in physical functioning compared with those with consistently insufficient levels [58▪▪].

Research on the role of specific diets in osteoarthritis has also been active. Using OAI data, high dietary fiber intake was linked to lower risk of developing moderate–severe knee pain over time [59]. Findings from two prospective cohort studies also showed that higher total fiber intake was related to lower risk of symptomatic KOA, but its relation to radiographic KOA was unclear [60]. Another study found that higher soy milk intake was negatively associated with prevalence of radiographic knee osteophytes [61]. Finally, higher adherence to a Mediterranean diet was associated with lower prevalence of clinical and radiographic KOA [62].

Bone density and mass

Previous reviews reported that high bone mineral density (BMD) was a risk factor for incidence [3] and prevalence [2] of lower extremity osteoarthritis. Supplementing these findings, high resolution peripheral quantitative computed tomography tests showed that men with hip joint osteophytes had higher radial trabecular volumetric BMD, whereas men with hip sclerosis had higher cortical volumetric BMD at the tibia [63]. New evidence suggests that high systemic BMD predates early structural KOA features; higher spine and total hip BMD were recently linked to progression of tibiofemoral cartilage defects as measured by MRI in adults without clinical symptoms [64]. High bone mass was also recently associated with radiographic hand osteoarthritis findings [65] but not with osteoarthritis in the temporomandibular joint (TMJ) [66].

RISK FACTORS: JOINT-LEVEL

Current evidence on joint-level risk factors associated with osteoarthritis disease development and/or progression is discussed in the following section.

Bone/joint shape

Bone shape may contribute to the risk of osteoarthritis as had been previously described primarily in the hip joint [2,3]. Contributing to the body of evidence, a recent population-based osteoarthritis cohort study in France used five measures to describe hip morphology [67▪]. Among all measures, acetabular index was most strongly associated with the severity and progression of hip osteoarthritis. In addition, the Rotterdam Study found that those with cam deformity or acetabular dysplasia had double the risk of developing hip osteoarthritis compared with those without deformity [68].

Recent studies are also exploring the contribution of bone/joint shape in osteoarthritis development in other joints. In the OAI, changes in bone area and shape of the knee over 24 months among those with mild-to-moderate osteoarthritis were associated with radiographic and pain progression over 48 months [69]. In the Tasmanian Older Adult Cohort study, uncommon proximal tibiofibular joint shapes were positively linked to cartilage defects, bone marrow lesions, and osteophytes in the lateral knee compartment [70]. In the Johnston County OA Project, certain ankle morphologies were linked to injury history that could lead to greater predisposition for ankle osteoarthritis [71▪].

Muscle strength

The association between muscle strength and osteoarthritis may vary depending on the muscles and joints being studied [1–3]. In an examination of anterior cruciate ligament (ACL) injured knees, high thigh muscle cross-sectional area (CSA) and high muscle/fat ratio had a protective effect against KOA prevalence [72]. On the other hand, among OAI patients without radiographic KOA and with minimal extension strength variability, higher total extensor CSA, and vastus medialis CSA were found

to increase patellofemoral cartilage loss over time [73]. There was also a strong positive association between extensor–flexor CSA ratio and patellofemoral cartilage deterioration. Similarly, higher knee extensor strength in adolescent men was associated with greater risk of KOA by middle age in a longitudinal study of Swedish registries [74]. However, in a cross-sectional study of hip muscle strength and joints of patients with hip osteoarthritis, greater isometric strength of hip and thigh muscle groups was associated with better self-reported physical function [75].

Joint loads and alignment

Knee malalignment is a strong predictor of KOA disease progression [1–3]. The association between malalignment and the incidence of KOA is less clear, however [1,2]. More recent studies confirm these assertions [76,77]. In an OAI study, varus thrust (i.e. first appearance/worsening of varus alignment during stance) was associated with KOA progression, but not KOA incidence [77]. In the Multicenter Osteoarthritis Study (MOST), varus thrust increased the odds of worsening medial bone marrow lesions (BMLs) and medial cartilage loss as well as the odds of incident medial BMLs of the knee among those with KOA and those with increased risk of KOA, respectively [78].

Occupation and sports

Particular repetitive activities inherent in certain occupations (e.g. firefighting, construction work) have long been and continue to be associated with greater risk of osteoarthritis [1,3,79]. Reports of the associations between sports activities and osteoarthritis have been conflicting [1,3,80–83] (Table 2). It is also unclear if positive associations are because of sports participation itself or to consequences of injury that occurred with sports participation.

Injury/surgery

ACL injury, meniscal tear, and direct articular cartilage damage following injury have all been linked to subsequent Kosteoarthritis development [1–3,5]. In a retrospective cohort study, those with ACL tears and lateral meniscal tears had higher risk of developing arthritis and undergoing total knee replacement (TKR) surgery than those without ACL tears over 10 years [84]. Using a computer simulation model of KOA natural history and management, it was estimated that those with ACL injury and meniscal tear were 2.5 times more likely to develop osteoarthritis and 4 times more likely to undergo TKR surgery than those without injury [85▪▪].

Surgical reconstruction may not necessarily protect those who had sustained these injuries from developing KOA [2]. In the computer simulation model, the estimated cumulative lifetime risk of developing KOA minimally differed between those with ACL tears who were surgically treated versus those who were not [85▪▪]. In another study, having a history of partial meniscectomy was associated with greater risk of incident KOA within a year [86].

Preradiographic lesions

Although previous evidence was sparse [2], new studies have begun focusing on the predictive value of preradiographic lesions that may be detected only by MRI.

Synovitis

Effusion and Hoffa synovitis [hyperintensity in the infrapatellar fat pad (IPFP)] were previously associated with the development of incident radiographic KOA [87]. Recently, the Tasmanian cohort study found that baseline IPFP signal score predicted increases in KOA symptoms, tibiofemoral cartilage defects and BMLs, and loss of lateral tibial cartilage volume [88,89]. In the MOST study, Hoffa synovitis

Table 2. Recent review studies evaluating the potential association between sports and osteoarthritis

Study	Activity	Effects
Alentorn-Geli *et al.* [81]	Running (recreational)	Decreased risk of knee and hip osteoarthritis
Driban *et al.* [82]	Soccer Long-distance running Weight lifting Wrestling	Increased knee osteoarthritis prevalence
Vigdorchik *et al.* [83]	Soccer Handball Track and field Hockey	Increased radiographically confirmed hip osteoarthritis
	Long-distance running	No increased risk of radiographically confirmed hip osteoarthritis

was associated with structural damage in the patellofemoral and tibiofemoral joints [90]. Moreover, superolateral Hoffa's fat pad hyperintensity was found to be a local marker of patellofemoral joint structural damage. Change in total synovitis score (from 11 sites) was not found to be related to change in knee pain in a small study of KOA patients, however [91].

In studies of patients with hand osteoarthritis, synovitis was associated with joint tenderness and self-reported hand pain [92,93]. In the Hand Osteoarthritis in Secondary Care (OSTAS) cohort, synovitis was also associated with hand osteoarthritis radiographic progression [94▪▪]. MRI synovitis did not correlate with clinical findings and biological markers of inflammation in a third hand osteoarthritis study, though [95].

Bone marrow, cartilage, and meniscal abnormalities

Several new OAI studies have elucidated the relationship of MRI-detected abnormalities with KOA risk. In one study, BMLs, cartilage damage, and menisci extrusion were assessed at baseline and 3 years after [96]. Worsening of these MRI lesions was associated with incident radiographic KOA. In a similar study with 7 years of follow-up data, these MRI lesions improved prediction of mild and moderate radiographic KOA development whenever added to prediction models that only included sociodemographic and patient-reported clinical variables [97▪▪]. In a case–control study, worsening of these lesions was more often detected among those who had radiographic and pain progression because of KOA compared with the control group [98]. Finally, BMLs and meniscal extrusion were recently associated with eventual TKR surgery receipt [99].

Other studies have evaluated the association of these preradiographic lesions with the risk of other osteoarthritis types. In the OSTAS study, BMLs did not associate with hand pain in the absence of synovitis [93]. In a different cohort of erosive hand osteoarthritis patients, BMLs at the proximal and distal joints correlated with examined joint tenderness [92]. BMLs were also linked to radiographic hand osteoarthritis progression after 2 years in another study [94▪▪]. The Tasmanian cohort study also found that hip cartilage defects were associated with greater pain and radiographic hip osteoarthritis diagnosis [100].

CONCLUSION

Osteoarthritis continues to be a leading cause of morbidity and healthcare cost in the United States and around the globe. There may be different osteoarthritis clinical phenotypes that reflect heterogeneous disease mechanisms. A variety of person-level and joint-level risk factors have been linked to disease development and progression. Although many of these risk factors are difficult to change, some may be more amenable to medical and behavioral interventions (e.g. obesity, muscle strength). Recent MRI studies have improved our understanding of MRI-detected damage, which precedes radiographic evidence of osteoarthritis.

Acknowledgements

None.

Financial support and sponsorship

E.R.V. and C.K.K. receive funding from the NIH/National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), award numbers: K23AR067226 (E.R.V.) and R01AR066601 (C.K.K.).

Conflicts of interest

C.K.K. has received grants from Abbvie and EMD Serono and consulted for Astellas, EMD Serono, Thusane, Express Scripts and Novartis. E.R.V. has consulted for Astra Zeneca.

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Basic calcium phosphate crystal-associated musculoskeletal syndromes: an update

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Purpose of review
Basic calcium phosphate (BCP) crystals are associated with two important musculoskeletal syndromes. Deposition of BCP crystals in tendons, bursae, and other soft tissues around joints causes calcific periarthritis, whereas intra-articular BCP crystals contribute to osteoarthritis and cause the highly destructive arthritis known as Milwaukee Shoulder Syndrome. The epidemiology and natural history of these syndromes are poorly understood, and because the pathogenesis remains unclear, few targeted therapies are available. I will review new developments in this field.

Recent findings
I will discuss a case collection of calcific periarthritis of the hip, and evidence-based management strategies for shoulder calcific periarthritis that might be applied to calcific periarthritis at other locations. I will summarize several recent articles addressing mechanisms of crystal formation and identifying pathways through which BCP crystals produce tissue damage and explore some newly identified risk factors for pathologic mineralization.

Summary
We are making slow, but steady progress in understanding the clinical presentation of calcific periarthritis in sites other than the shoulder. A growing appreciation of the mechanisms through which BCP crystals mediate tissue damage should lead to the development of novel management strategies for these common musculoskeletal syndromes.

Keywords
basic calcium phosphate crystals, calcific periarthritis, osteoarthritis

INTRODUCTION

The term 'basic calcium phosphate' (BCP) refers to a trio of calcium phosphate crystals consisting of carbonate substituted hydroxyapatite, octacalcium phosphate, and tricalcium phosphate. BCP crystals are similar to the calcium phosphate mineral that is a normal component of bones and teeth. However, in pathologic situations, BCP crystals can produce vigorous inflammatory responses, disrupt normal tissue biomechanics, and directly interact with nearby cells to induce production of destructive cytokines and prostaglandins. In the musculoskeletal system, BCP crystals are most commonly associated with two clinical syndromes. These include calcific periarthritis, in which BCP crystals deposit in tendons, bursae, and other soft tissues around the joint, and BCP-associated arthritis, which produces clinical manifestations ranging from typical osteoarthritis to the aggressively destructive arthropathy known as Milwaukee Shoulder Syndrome (MSS). In this review, I will discuss some new clinical findings in calcific periarthritis at the hip and evidence-based management strategies for calcific tendinitis. I will summarize several recent advancements in understanding mechanisms through which crystals produce tissue damage, and explore some newly identified risk factors for and mechanisms of BCP crystal formation.

CALCIFIC PERIARTHRITIS

Calcific periarthritis occurs at many sites, but is most easily recognized and best studied in the shoulder. The natural history and clinical presentations of

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Curr Opin Rheumatol 2018, 30:168–172
DOI:10.1097/BOR.0000000000000477

KEY POINTS

- Calcific periarthritis around the hip can cause a heterogeneous group of symptoms.
- Genetic and metabolic abnormalities including hypophosphatasia should be considered in patients with recurrent episodes of calcific periarthritis.
- BCP-induced inflammation may involve the spleen tyrosine kinase pathway and contribute to joint destruction though stimulation of osteoclastogenesis.
- Pyrophosphate and its analogs may be useful as therapeutic agents for pathologic calcification in some settings.

calcific periarthritis at sites other than the shoulder are still not well understood. Park *et al.* [1] recently described a large series of patients with calcific periarthritis around the hip joint. Thirty patients were identified. As is true of most series of calcific periarthritis, the majority were female (73%) and while the average age was 51 years, a wide age range (28–78) was noted. The most commonly involved tendon was the gluteus medius tendon, with the reflected head of the rectus femoris, the second most common site. Other locations included the direct head of the rectus femoris, the iliopsoas, the piriformis, and three out of 30 of the calcifications were located in the joint capsule. The latter finding supports the continued use of the more accurate term 'calcific periarthritis' over the commonly used term 'calcific tendinitis'. Most patients were treated conservatively with NSAIDs and tramadol and had relatively rapid resolution of their symptoms. The mean duration of symptoms in this cohort was 4.4 months (range 0.1–18 months). As demonstrated in prior shoulder studies [2], there was a poor correlation between the size or density of the calcific deposit and the clinical course and pain severity scores. Several patients failed conservative therapy and required more aggressive interventions such as barbotage. Barbotage involves ultrasound-guided injection of corticosteroids and lidocaine with the goal of physically breaking up the crystal deposit. Those who failed this intervention were managed with arthroscopic surgery. In these patients, the insidious onset of pain and radiographically larger calcifications seemed to predict the need for more aggressive treatments. This series contributes to our knowledge of the clinical presentation and natural history of calcific periarthritis at 'nonshoulder' sites. Similar work in other areas may highlight similarities and differences between calcific periarthritis at the peripheral joints of the hands and feet, for example, compared with large joints such as the hip and shoulder.

In patients with recurrent or multiple sites of calcific periarthritis, metabolic abnormalities should be considered. Elevated levels of circulating calcium or phosphate, such as that associated with calcifylaxis in end-stage renal disease, may cause pathologic calcification at multiple sites. However, there are other more subtle clinical syndromes in which calcific periarthritis occurs. Mild forms of hypophosphatasia, for example, can present with calcific periarthritis. Hypophosphatasia is caused by deficiencies in alkaline phosphatase activity [3]. Guanabens *et al.* [4] recently described three middle-aged sisters in whom calcific periarthritis was the presenting clinical manifestation of this disease. These women had recurrent episodes of pain around the hips, shoulders, elbows, wrists, and Achilles tendons. They had low alkaline phosphatase activity levels, hyperphosphatemia, and increased concentrations of pyridoxal 5′ phosphate. Genome sequencing revealed a unique 18 base pair duplication in the *TNSALP* gene. Hypophosphatasia should be considered in patients with recurrent or familial calcific periarthritis and findings of tooth loss, or bone abnormalities such as rickets or osteomalacia. Historically, calcium pyrophosphate (PPi) deposition has been associated with hypophosphatasia, but this interesting case description suggests that BCP crystal-related syndromes may be the presenting manifestation of this disease.

Calcific periarthritis was described recently in a family with a deficiency in ENT1 (equilibrative nucleoside transporter-1, SLC29A1) and the Augustine-null blood type [5]. The Augustine null mutation was described in 1960s as a cause of severe hemolytic transfusion reactions and mild hemolytic disease of the newborn. This ENT1 mutation presented with acute inflammatory attacks consistent with calcific periarthritis around large and small joints in three affected sisters in their early 20s. ENT-1 transports adenosine across the cell membrane and regulates levels of this highly bioactive nucleoside [6]. A loss of function in ENT-1 in mice causes ectopic spinal calcification [7]. A role for ENT-1 in pathologic calcification is plausible because adenosine metabolism is closely tied to regulation of ATP and PPi levels. ATP and PPi are critical regulators of mineral formation and abnormal adenosine levels likely directly affect levels of ATP and PPi. Further work will be necessary to confirm the chemical composition of these calcifications, but this interesting report further implicates the ENT family of enzymes in BCP mineral deposition.

Treatments for calcific periarthritis generally are not evidenced-based and few comparative

effectiveness trials exist. First-line therapies include NSAIDs and intralesional corticosteroids. Large calcific densities associated with chronic symptoms are often managed with a variety of interventions designed to break up the mineral deposits. These interventions vary from barbotage to shockwave therapy. Iontophoresis with agents that dissolve mineral, such as acetic acid, has recently been shown to have little efficacy in calcific periarthritis [8]. A recent systematic review compared the effectiveness of high-energy extracorporeal shockwave (ESTW) therapy to barbotage and arthroscopic surgery [9▪]. The authors identified 22 studies that satisfied their inclusion criteria, which included studies which followed patients for at least 6 months, eliminated other causes of shoulder pain such as full-thickness rotator cuff tears, and examined two relevant outcome measures based on shoulder function and size of the calcific deposit. The studies satisfying these criteria included over 1200 shoulders. Of the 22 studies, 11 were conducted as prospective randomized controlled trials. On the contrary, variations in the techniques, particularly those involving ESTW significantly affected the authors' ability to combine studies or to do head-to-head comparisons. We are left with a conclusion that all three modalities are well tolerated and effective, but little else. Carefully planned prospective studies of various management strategies will be required to determine the effectiveness of these expensive interventions.

BASIC CALCIUM PHOSPHATE-ASSOCIATED ARTHRITIS

BCP crystals are common components of osteoarthritis joints and in MSS, they cause a severe destructive arthritis. Recently, Hawellek *et al.* [10▪] studied the prevalence of BCP crystal deposition in cartilage of the shoulder joint. These investigators used the highly sensitive method of digital contact radiography (DCR) to study 180 humeral head from 90 donors in this cross-sectional study of cartilage calcification in the shoulder in the general population. They excluded samples from patients with shoulder disease other than osteoarthritis, such as those with prior shoulder surgery, tumors, infection or known rheumatic disease. They correlated the presence of mineralization as seen with DCR with age and histologic grade of osteoarthritis. von Kossa and Alizarin Red S staining were used to identify the composition of the deposits. Mean donor age was 62.7 years (range 20–93). Significantly, 98.9% of the samples had DCR evidence of cartilage calcification. Significant histologic evidence of osteoarthritis was noted in 18.9% of the samples, which alone is an interesting finding, as we often think of shoulder osteoarthritis as a relatively rare condition. Using the technique of data analysis known as 'structural equation modeling', cartilage calcification correlated with the histologic grade and presence of osteoarthritis, but not with age. This interesting work supports older work by Scotchford and Ali [11] suggesting that calcium phosphate crystals may be common and possibly normal components of articular cartilage in large joints. Scotchford and Ali [11] found that these deposits were composed of magnesium whitlockite which may be less inflammatory than BCP crystals. Stains such as Alizarin Red S and von Kossa cannot distinguish between BCP and calcium PPi crystals. Hawellek *et al.* did not carefully identify the chemical composition of these crystals, and this is a major issue with this work.

Understanding mechanisms through which BCP crystals signal to incite inflammation or initiate catabolic responses in articular cells remains an active area of study. Initially the NLRP3 (NRL family, pyrin domain containing 3) inflammasome was implicated in the signaling mechanism based on in-vitro studies [12]. There remains some controversy in this area based on in-vivo studies which do not support a role for this pathway [13]. Recent elegant work implicated the membrane proximal kinase, spleen tyrosine kinase (Syk), and phosphatidylinositol 3 kinase (PI3K) in BCP crystal-induced inflammation. These second messengers mediate the interactions of monosodium urate (MSU) crystals with neutrophils and dendritic cells via a process known as membrane affinity-triggered signaling. This process involves the formation of lipid rafts in the membrane. Similar processes mediate macrophage phagocytosis after Fc receptor engagement [14▪▪]. This group demonstrated that BCP crystals activate Syk and PI3K in primary human macrophages and dendritic cells and that this drives IL-1 production and involves lipid raft formation. Significantly, the induction by synthetic BCP crystals of a variety of catabolic mediators and cytokines was augmented when macrophages were exposed to both osteoarthritis synovial fluid and BCP crystals showing that there are cofactors in synovial fluid which augment the crystals' inflammatory effects. This important work delineates mechanisms through which BCP crystals contribute to osteoarthritis and may result in novel drug development.

This year, Cunningham *et al.* [15▪▪] showed that BCP crystals promote osteoclast formation by inhibiting antiosteoclastogenic factors. BCP crystals can cause extensive bone destruction as seen in MSS, and there is increasing support for a role for subchondral bone abnormalities in osteoarthritis [16]. BCP crystals have been shown to induce

prostaglandin E2, a potent inducer of osteoclast formation. The authors show that BCP and MSU crystals inhibit IL-6 and IFN-γ signaling in early and late osteoclast precursors thus promoting osteoclastogenesis. They conclude that BCP crystals contribute to osteoarthritis by opposing antiosteclastogenesis factors, resulting in increased subchondral bone dysfunction and joint destruction.

Factors involved in modulating the inflammatory potential of BCP crystals in pathologic settings remain poorly understood. Vitamin K dependent Gla-rich proteins (GRPs) have been shown to play a potential role in this process in the setting of osteoarthritis [17▪▪]. GRP is an understudied member of the family of vitamin K-dependent proteins. It was recently shown be upregulated in chondrocytes and synoviocytes during extracellular matrix calcification as well as after IL-1β exposure. Furthermore, when BCP crystals were coated with GRP, their inflammatory potential was decreased [17▪▪]. The recent work by Viegas *et al.* [18▪▪] further addresses the inflammation-calcification connection and GRP's role in these processes. Protein levels of GRP were increased after exposure of THP1 (a human monocytic cell line) cells or primary macrophages to BCP crystals. Coating of BCP crystals with GRP decreased their inflammatory potential, and overexpression of GRP decreased the inflammatory response to a variety of stimuli in THP1 cells and primary macrophages. This interesting work suggests that GRP and other members of this class of proteins may have both anti-inflammatory and anticalcification actions and thus may be interesting potential therapies for diseases such as osteoarthritis where both processes are involved.

There are few effective treatment strategies for BCP crystal-associated arthritis and dietary risk factors are not well defined. Joubert *et al.* [19] recently proposed that phytate (myo-inositol hexaphosphate) might contribute to pathologic vascular calcification in renal disease patients. Phytate is a polyphosphate found in nuts, whole grains, and seeds and is a natural inhibitor of calcification in a class with matrix Gla protein, PPi, and fetuin. Patients with renal disease are often on low phytate diets and levels are further reduced by dialysis. Phytate supplementation has been shown to decelerate vascular calcification in aging rats. Low levels may correlate with valvular calcification in elderly humans [20]. Sufficient levels would be difficult to achieve with diet alone, but intravenous forms of phytate are in early drug development stages. This interesting work postulates a potential role for dietary factors in pathologic BCP crystal formation and further studies may reveal a therapeutic potential for phytate in BCP crystal-associated musculoskeletal syndromes.

PPi is a key regulator of BCP crystal formation. The potential use of PPi as a therapeutic agent was recently highlighted [21▪▪]. For these studies, Pomozi *et al.* used a mouse model of pathologic calcification based on mutations in ATP binding cassette subfamily C member 6 (ABCC6). ABCC6 is an ATP-dependent organic anion transporter. It is critically involved in ATP efflux in some cell types and may be responsible for generating up to 60% of circulating PPi levels in plasma. Loss of function mutations in ABCC6 have been associated with diseases associated with vascular calcification such as pseudoxanthoma elasticum, generalized arterial calcification of infancy, and β thalassemia. Mice with loss of function mutations in ABCC6 have an inducible phenotype known as dystrophic cardiac calcification. The authors of this interesting study set out to determine if intravenous PPi administration could counteract the pathologic calcification that characterizes ABCC6 deficient states. The bisphosphonate drugs, etidronate, and alendronate are PPi analogs and were used as comparisons. Although intravenously administered, PPi had a half-life of only 42 min, administration of a single dose after the initial injury that initiates calcification halted subsequent calcification. Similar results were seen with etidronate, but not with alendronate [21▪▪]. This fascinating work suggests that even transiently elevated levels of circulating PPi may reverse BCP crystal deposition in some settings. This work also supports a re-examination of bisphosphonates as potential therapies for some diseases involving pathologic calcification.

CONCLUSION

BCP crystal-associated musculoskeletal syndromes are common and can be challenging to treat. We are making some slow progress in understanding the clinical presentation and management of calcific periarthritis, and the role of BCP crystals in osteoarthritis. The characterization of novel modulators and mechanisms of BCP crystal formation and resultant tissue damage should ultimately lead to more effective treatment strategies for these syndromes.

Acknowledgements

None.

Financial support and sponsorship

The VA national research service (Merit Review CX001143).

Conflicts of interest

There are no conflicts of interest.

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Crystalline arthropathy and bone health

Ian Chang and David Gazeley

Purpose of review
The purpose of this review is to provide insight on the proposed association between crystal arthritis and bone health. Crystal arthritis is the most common type of inflammatory arthritis, and fractures contribute to significant morbidity and mortality, therefore, the relationship between the two is of clinical importance.

Recent findings
There have been variable findings regarding hyperuricemia, low bone density and risk of fracture. A recent systematic review and meta-analysis of available literature showed a correlation between increased serum uric acid and lower risk of fracture. Less is known about calcium pyrophosphate deposition disease and bone health, although two large studies have suggested an association with osteopenia.

Summary
A systematic review and meta-analysis of available data suggest a correlation between increased serum uric acid and lower risk of fracture. Findings support an association between bone health and crystal arthritis which warrants further study and may have implications for how we treat gout.

Keywords
calcium pyrophosphate deposition disease, crystal arthritis, gout, hyperuricemia, osteoporosis

INTRODUCTION

Crystal arthritis consists of gout and calcium pyrophosphate deposition disease (CPDD) and together they are the most common cause of inflammatory arthritis in adults. Most commonly, patients present with a sudden onset of intensely inflammatory monoarticular disease. However, more indolent and polyarticular presentations of both diseases are possible. Both conditions involve abnormal deposition of crystals in joints and surrounding tissues. Broadly, one can speculate many potential reasons why bone quality and fracture risk could be affected by crystal arthritis. Among possible mechanisms include systemic inflammation damages bone, uric acid is an antixodiant with potential protective benefits to bone, patients with poorly controlled arthritis are less active and unlikely to perform weight-bearing activities and genetic factors associated with both gout and CPDD influence bone density. A literature attempting to understand these disease associations and there potentially important treatment implications is evolving.

GOUT

Hyperuricemia is a risk factor for developing gout and other conditions such as metabolic syndrome, diabetes and cardiovascular disease [1▪▪]. In most cases, pathogenesis of hyperuricemia involves an underexcretion of uric acid. In humans, approximately two-thirds of the serum uric acid is excreted in urine and the rest is degraded by intestinal bacteria. Given a close association between hyperuricemia and the pathogenesis of gout, pharmacologically lowering serum uric acid levels with a treat-to-target approach remains a primary goal in gout management. However, uric acid is a strong endogenous antioxidant, with a presumed important role in the normal health physiology, which raises concern about potential dangers of urate-lowering therapies.

The antioxidant role of serum uric acid has been demonstrated in in-vitro experiments, animal models and epidemiological studies with estimates suggesting that it accounts for nearly 50% of plasma antioxidant activity [2]. For example, uric acid can scavenge oxygen radicals and protect erythrocyte membranes from lipid oxidation [3▪▪]. Bone metabolism is affected by oxidative stress and is influenced by antioxidants including uric acid. However, the literature regarding serum uric acid levels impacts on BMD and,

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Curr Opin Rheumatol 2018, 30:173–176

DOI:10.1097/BOR.0000000000000469

KEY POINTS

- Hyperuricemia may be associated with higher BMD and lower fracture risk although additional studies, particularly of women, are necessary.
- There are several proposed mechanisms to explain the association including the antioxidant activity of uric acid, uric acids effect on osteoclastogenesis, PTH activity and vitamin D metabolism.
- Any potential deleterious effects regarding bone health related to urate-lowering therapy are unknown.
- There is epidemiologic evidence that CPDD is associated with lower BMD.

more importantly, fracture risk is not entirely consistent although some patterns may be emerging.

There are multiple reports demonstrating a direct relationship between serum uric acid concentrations, BMD and fracture risk. Early evidence linking serum uric acid levels with low BMD and fracture came from a 2011 Australian study of more than 1700 community dwelling men older than 70 years. The authors concluded that higher serum uric acid was associated with higher BMD as well as a lower prevalence of vertebral and nonvertebral fractures [4]. Later case-cohort data from the Osteoporotic Fractures in Men (MrOS) study showed that higher serum uric acid levels were associated with higher hip BMD and reduced risk of nonspine fractures. Looking specifically at hip fracture, a lower risk of hip fracture was only demonstrated in men with the highest serum uric acid levels. Interestingly, after excluding 144 men with gout and/or allopurinol medication use, there was no significant association between nonspine fractures or hip fractures and uric acid levels [5]. A large longitudinal study of Korean men was also able to demonstrate that men without an incident fracture had higher serum uric acid levels [6]. Some data on women are available. A large cross-sectional study examining more than 7500 healthy postmenopausal Korean women was able to demonstrate, after adjusting for cofounding variables, a positive correlation between serum uric acid level and BMD at all sites and that study participants with vertebral fractures were found to have lower serum uric acid levels [7]. Furthermore, while causality could not be proven, a meta-analysis of 19 observational studies involving more than 55 000 individuals was able to demonstrate a strong association between high serum uric acid level and high BMD [1▪▪]. Most recently, Yin *et al.* [3▪▪] published a systematic review and meta-analysis regarding hyperuricemia and risk of fracture. They analyzed five prospective studies containing a total of 29 110 participants. Three of the five studies suggested that uric acid is a protective factor against fractures and concluded that increased serum uric acid concentrations are associated with lower risk of fracture. However, the generalization of the meta-analysis studies to women should be questioned given a general lack of women-specific data.

Available literature does not uniformly support a clear association between hyperuricemia (and indirectly gout history) and higher BMD particularly in studies solely with women participants. For example, in a prospective cohort study using data from the Nurse' Health Study, a history of gout was associated with an increased risk of hip fracture in women. A reasonable criticism of the study is that the validity of gout diagnosis in these participants was uncertain [8▪]. Using claims data, Tzeng *et al.* [9] reported a significant higher risk of vertebral fracture, upper limb fracture, leg/knee fracture and ankle/foot fracture in individuals with gout and particularly in female individuals. However, there was no significant association with hip, wrist, proximal humerus or thigh fractures. Of importance, the results did not consider cofounding variables such as BMI, smoking habits, alcohol consumption, BMD and serum uric acid levels.

Overall, there is a suggestion that uric acid protects bone integrity and may prevent fractures. Any proposed mechanism linking benefits of higher uric acid levels to high BMD and fracture risk reduction can only be described as speculative. Moreover, it is not clear whether uric acid functioning as antioxidant is the primary physiology or if other mechanisms are involved. Some proposed ideas are based on in-vitro studies which show that uric acid decreases osteoclastogenesis and reduces the production of reactive oxygen species by osteoclast precursors [7]. In addition, there is a potential mechanism linking uric acid and incased parathyroid hormone (PTH) levels likely via reduced renal clearance of urate [10]. In a rat model, hyperuricemia suppresses 1-α-hydroxylase resulting in lower 1,25 (OH)2 vitamin D levels and elevated PTH levels [11]. Alternatively, there is some evidence that hyperuricemia and gout-related inflammation could negatively influence bone density. Uric acid crystals promote bone erosion at the tophus–bone interface with evidence that human osteoblasts cultured with monosodium urate crystals inhibit osteoblast viability and differentiation [12]. In addition, Interleukin-1β, an inflammatory cytokine important in gouty inflammation, has been shown to be a stimulator of in-vitro and in-vivo bone resorption by upregulating receptor activator of nuclear factor-kB ligand and stimulating osteoclastogenesis [13].

A clear clinical concern is whether treatment of gout and, in particular, urate-lowering therapies could have a deleterious effect on bone. The negative impact of exogenous glucocorticoid therapy on bone health is well documented. Interestingly, though of unclear clinical significance, are older studies in the orthopedic literature which suggest that patients with familial Mediterranean fever treated with long-term colchicine had less heterotopic ossification following hip arthroplasty and that rats given high doses of colchicine for a short period had reduced bone healing [14]. On the basis of above epidemiological data regarding potential bone protective effects of hyperuricemia, clinicians might wonder whether urate-lowering therapy with commonly used xanthine oxidase inhibitors might damage bone architecture. However, there is limited in-vitro evidence which shows that allopurinol and oxypuriniol increase bone formation by promoting osteoblast differentiation, though further in-vivo and epidemiological studies are necessary [15▪].

CALCIUM PYROPHOSPHATE DEPOSITION DISEASE

There is less published literature examining the association between CPDD and bone health. A case–control study using the Genetics of Osteoarthritis and Lifestyle database suggested that the presence of chondrocalcinosis may be associated with low cortical BMD as determined by a metacarpal index and calcaneal Dual-energy x-ray absorptiometry [16]. More recent analysis of a large national database of predominantly male US veterans also demonstrated a positive association between CPDD and osteoporosis as determined by diagnosis code [multivariate Odds Ratio 1.26 (1.16–1.36)] [17▪▪]. These identified associations are particularly fascinating because osteoarthritis, which is often associated with CPDD, has variably been associated with normal or high BMD [18]. Pyrophosphate (PPi) is a known inhibitor of basic calcium phosphate mineralization. The concentration of PPi is elevated in joint fluid from patients with chondrocalcinosis [19]. Although it is not clear whether this local phenomenon of PPi inhibiting mineralization can be applied to a systemic bone disease, it does offer a conceivable mechanism linking CPDD and low bone density. A clear association between primary hyperparathyroidism and CPDD has been established offering a potential endocrinologic explanation associating CPDD and low BMD.

CONCLUSION

There are convincing data in the literature to suggest an association between hyperuricemia and BMD as well as risk of fracture. The mechanism is not exactly known, but there are several potential theories including antioxidant effects of uric acid and a relationship between uric acid and PTH and subsequently bone metabolism. Epidemiological evidence also suggests an association between CPDD disease and metabolic bone disease. Further research in the proposed antioxidant properties of uric acid, uric acid precursors and PPi would be of benefit. Additional study of the relationship between crystal arthritis and fracture risk is necessary before any changes to long-term treatment strategies of gout would be advised.

Acknowledgements

The authors would like to thank Dr Ann Rosenthal, Chief of the Division of Rheumatology at the Medical College of Wisconsin, for helpful review while drafting article.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

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New urate-lowing therapies

Abhishek Abhishek

Purpose of review
To discuss recent studies of lesinurad and arhalofenate.

Recent findings
Lesinurad acts by blocking urate reabsorption channels URAT-1 and OAT-4. It has urate-lowering effect when used alone and in combination with xanthine oxidase inhibitors (XOIs). Its uricosuric activity depends on glomerular filtration, and its' efficacy is impaired at eGFR less than 30 ml/min. Lesinurad monotherapy (400 mg/day) associates with serum creatinine elevations. However, this risk is substantially attenuated with coprescription of a XOI and when prescribed at a dose of 200 mg/day. Given its' modest urate-lowering effect, and the risk of serum creatinine elevation when used alone, it is licenced for use in combination with XOI for people unable to achieve target serum uric acid with XOI alone. Lesinurad does not have the drug interactions associated with probenecid, however, it is metabolized by CYP2C9, and should be used with caution if CYP2C9 inhibitors are coprescribed. Arhalofenate also acts by blocking URAT-1; however, it also blocks the NALP-3 inflammasome providing gout-specific anti-inflammatory effect. Arhalofenate has a weaker urate-lowering effect than lesinurad and further phase III evaluation is planned.

Summary
Lesinurad provides an additional option for people with gout unable to achieve target serum uric acid with XOI alone.

Keywords
arhalofenate, gout, lesinurad, uricosuric drugs

INTRODUCTION

Gout is the commonest inflammatory arthritis and affects 2.5–3.9% adults in the United Kingdom and the United States of America [1,2]. It occurs as a consequence of hyperuricaemia and is the only form of arthritis that has the potential of being cured with urate-lowering treatment (ULT) in the long term. Although most people with gout have reduced urinary urate excretion, historically, the greater efficacy and safety of xanthine oxidase inhibitors (XOIs) allopurinol and febuxostat compared with the uricosuric drugs such as probenecid, sulfinpyrazone, and benzbromarone have resulted in the XOIs being the first choice pharmacologic ULT [3–6]. The purpose of this review is to discuss lesinurad, a recently licenced uricosuric ULT, and arhalofenate, an emerging uricosuric anti-inflammatory ULT [7▪,8,9▪,10–12,13▪,14]. Of these, lesinurad has been approved by the US Food and Drug Administration (FDA) in December 2015 and by the European Medicines Agency in February 2016 for the management of hyperuricaemia in gout. It is indicated in combination with another XOI in people who have not achieved the target serum uric acid (SUA) level with an XOI alone.

LESINURAD

Lesinurad lowers SUA by inhibiting renal urate reabsorption. It blocks the urate reabsorption channels URAT-1 and OAT-4, but not GLUT-9 [9▪]. URAT-1 is also the site of action of probenecid and benzbromarone [15,16]. In addition, unlike for probenecid, OAT-1 and OAT-3 channels are not blocked by lesinurad, thus reducing the potential for drug interactions [9▪]. Similarly, lesinurad is not known to activate OAT-1 and ABCG-2, two protein channels that participate in the secretion of urate in the renal proximal convoluted tubule [9▪]. Thus, lesinurad exerts its effect on reducing SUA by inhibiting the reabsorption of filtered urate [9▪].

Lesinurad increases the fractional excretion of urinary urate within 6 h of a single dose (from 5.8%

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Curr Opin Rheumatol 2018, 30:177–182

DOI:10.1097/BOR.0000000000000476

KEY POINTS

- XOIs remain first line for treatment of hyperuricaemia in gout.
- Lesinurad is only licenced as an add-on therapy with a XOI.
- Elevations in serum creatinine when treated with lesinurad mostly resolve on their own.

at baseline to 21.8% at 6 h), and, the urinary excretion normalized by 24 h of a single dose [9▪]. Similarly, the serum urate reduces by 6 h of treatment with a single dose, and slowly returns towards the baseline level thereafter [9▪]. Lesinurad is 98.4% bound to plasma proteins and is concentrated in the renal tract by active renal excretion and urinary concentration [9▪]. It does not affect the plasma pharmacokinetics or urinary excretion of allopurinol and reduces the plasma exposure to oxypurinol by approximately one-third [10]. Approximately half of the oral lesinurad dose is cleared via CYP2C9 metabolism, and caution is required when it is administered with CYP2C9 inhibitors (e.g., fluconazole and amiodarone) [17].

In short-term phase II studies, it increased the fractional excretion of UA by 50.7, 110.8, and 129%, and reduced the SUA by 16, 22, and 30% at 4 weeks when its' dose was increased from 200 to 400 and 600 mg/day, respectively [10]. It appears to be effective in lowering SUA in people on a range of allopurinol doses (200–900 mg/day) and across a wide range of SUA [7▪,10].

Although the plasma concentration of lesinurad increases with progressive reduction in renal function, its' urate-lowering effect reduces suggesting dependence on glomerular filtration [18]. For instance, the urate lowering and uricosuric effect of a single dose of lesinurad was diminished significantly in those with eCrCl less than 30 ml/min, with a milder reduction in those with eCrCl 30–60 ml/min [18].

Phase III Studies

There have been four Phase III studies of lesinurad (CLEAR 1, CLEAR 2, CRYSTAL, and LIGHT) published to date [7▪,8,11,12]. CLEAR 1 and CLEAR 2 are replicate studies and their results will be discussed together [7▪,11].

The participants in these studies were predominantly male, with a high flare rate, long disease duration, and a significant proportion had tophi, even in the studies in which this was not required by design (Table 1) [7▪,8,11,12]. These phase III RCTs were between 6 and 12 months in duration, and the proportion of patients reaching SUA acid less than 6 mg/dl at 6 months (<5 mg/dl in the CRYSTAL study) was the primary endpoint, with flare reduction and tophi resolution important secondary end points [7▪,8,11,12]. Key exclusion criteria included eCrCl less than 30 ml/min in all studies, and additionally a history of nephrolithiasis in the LIGHT study which involved lesinurad monotherapy at a dose of 400 mg/day [7▪,8,11,12].

The CLEAR 1 and CLEAR 2 studies randomized participants in 1 : 1 : 1 ratio to receive lesinurad 200 mg/day, lesinurad 400 mg/day, or matching placebo for 12 months on a background of usual care stable-dose Allopurinol, with 90.4 and 84.2% participants receiving 300-mg allopurinol daily at the baseline visit, respectively [7▪,11]. To be eligible, participants were required to have SUA at least 6.5 mg/dl at the screening visit (−28 days), and at least 6.0 mg/dl 7 days before randomization [7▪,11]. The proportion of study participants achieving SUA less than 6.0 mg/dl by month 6 were 27.9, 23.3; 54.2, 55.4; and 59.2, 66.5% in the groups taking

Table 1. Baseline disease and demographic characteristics of people in phase III studies of lesinurad

	CLEAR 1	CLEAR 2	LIGHT	CRYSTAL
% Male	94.0	96.2	91.1	95.4
Age (years)[a]	51.90 (11.28)	51.20 (10.90)	54.4 (12.3)	54.1 (11.0)
Disease duration (years)[a]	11.84 (9.37)	11.53 (9.26)	11.2 (8.7)	14.7 (10.9)
Serum uric acid (mg/dl)[a]	6.94 (1.27)	6.9 (1.2)	9.3 (1.5)	5.3 (1.6)[b]
% with tophi	14.3%	23.6%	25.2%	100%
Flares in previous 12 months[a]	4.8 (3.6)	6.2. (5.93)	6.2 (7.3)	6.7 (8.2)
Background urate-lowering treatment, daily dose range	Allopurinol (200–600 mg)	Allopurinol (200–900 mg)	Nil	Febuxostat (80 mg)

[a]Mean (SD).
[b]Participants in this study had febuxostat 80 mg/day for 3 weeks prior to study entry and the mean (SD) serum uric acid prior to this was 8.7 (1.6) mg/dl.

allopurinol alone, lesinurad 200 mg and allopurinol, and lesinurad 400 mg and allopurinol in the CLEAR 1 and 2 studies, respectively [7▪,11]. The reduction in SUA was significantly greater in each of the lesinurad arms compared with allopurinol [7▪,11]. There was no advantage for lesinurad compared with stable dose allopurinol in achieving tophus resolution in the CLEAR 1 study, while participants randomized to either doses of lesinurad on a background of stable dose allopurinol when considered together were significantly more likely to achieve tophus resolution than those on stable dose allopurinol in the CLEAR 2 study [7▪,11].

The CRYSTAL study randomized participants with tophaceous gout in 1 : 1 : 1 ratio to lesinurad 200 mg/day, lesinurad 400 mg/day, or matching placebo for 12 months on a background of Febuxostat 80 mg/day for at least 3 weeks prior to randomization [8]. Eligibility criteria included SUA at least 8.0 mg/dl in people not taking ULT, and at least 6.0 mg/dl in those taking ULT at the screening visit [8]. All participants were required to have at least one tophus between 5 and 20 mm in the maximum size, and their usual ULT was discontinued at the screening visit, and participants took febuxostat 80 mg/day for 3 weeks prior to randomization [8].

The proportion of people who achieved SUA less than 5.0 mg/dl (primary outcome) by month 6 was 46.8% in the febuxostat group, 56.6% in the lesinurad 200 mg and febuxostat group ($P = 0.13$), and 76.1% in the lesinurad 400 mg and febuxostat ($P < 0.0001$) [8].

Among the 49.7% who did not achieve SUA less than 5 mg/dl at the baseline visit that is, after treatment with Febuxostat 80 mg/day for 3 weeks, significantly more achieved serum urate less than 5 mg/dl at 6 month on lesinurad 200 mg/day (44.1%) and 400 mg/day (70.6%) than with febuxostat alone (23.5%), P less than 0.05 for both comparisons [8]. This suggests that some people with gout may be more responsive to a uricosuric drug than others.

There was a significantly greater difference in target tophus area at month 12 in people on lesinurad 200 and 400 mg/day compared with people on febuxostat alone; however, the proportion of people who had complete or partial resolution of one target tophus was similar in the three groups [8]. This raises the possibility that change in target tophus area may be more sensitive to change than tophus resolution.

The LIGHT study randomized participants with a previous intolerance to allopurinol or febuxostat in a 1 : 1 ratio to receive either lesinurad 400 mg/day or matching placebo for 6 months with a 24-month open-label extension phase [12]. Participants had SUA at least 6.5 mg/dl at study entry, and 29.9% achieved the primary outcome of SUA less than 6.0 mg/dl at month 6, and similar reduction in SUA was observed in the open label phase.

The gout flare frequency did not improve with lesinurad in any of the phase III studies, given the short study duration [7▪,8,11,12]. Compliance with lesinurad was high, either alone or in combination with allopurinol or febuxostat [7▪,8,11,12].

Side effects

Renal toxicity remains one of the main concerns for lesinurad, especially those treated with this drug alone. Renal toxicity is believed to be caused by increased urinary excretion of uric acid, which can result in uric acid crystallization inside the renal tubules, that results in elevated serum creatinine. Lesinurad does not increase the urinary albumin or protein–creatinine ratio, suggesting that glomerular injury is unlikely to be a significant contributor [6,8,10].

In the LIGHT study ($n = 214$), in which people were randomized to lesinurad 400 mg/day or placebo, 8.4 and 24.3% participants randomized to lesinurad 400 mg/day had at least 1.5, and at least two-fold elevation in their baseline serum creatinine values compared with 0% in the placebo arm, and this returned to 1.2 times or less the baseline values (defined as resolution by the study investigators) in 53.9 and 66.7% instances [12]. Results of another phase II study ($n = 227$) suggests that lesinurad has a dose-dependent increased risk of renal toxicity even when used in combination with allopurinol 200–600 mg/day [10]. However, reassuringly, none of the participants randomized to lesinurad 200 mg/day developed serum creatinine at least 1.5 times their baseline values in this study [10]. Data from other phase III studies suggests that lesinurad at a dose of 200 mg/day in combination with another XOI only uncommonly causes unresolved significant serum creatinine elevations, with most elevations in serum creatinine resolving without study drug discontinuation (Table 2) [7▪,8,11]. The prevalence of serum creatinine elevations was lower in the CLEAR 1, CLEAR 2, and CRYSTAL studies [7▪,8,11], than in the LIGHT study [12] as participants in these studies were treated with a XOI which may have suppressed uric acid production, that results in a lower concentration of urinary urate, and reduces the risk of tubular urate crystallization.

Renal stones were reported as an adverse event in all groups in the four phase III RCTs in small numbers [7▪,8,11,12]. Within the study limitations, there does not appear to be an increased risk of urolithiasis with lesinurad based on the existing trial data.

Table 2. Prevalence of elevation in serum creatinine in phase III studies of lesinurad

Study, arm, (safety population)	≥1.5 × baseline *n* (%)	Unresolved[a] *n* (%)	≥2.0 × baseline *n* (%)	Unresolved[a] *n* (%)
LIGHT				
Placebo ($n=107$)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Lesinurad 400 mg/day ($n=107$)	26 (24.3%)	12 (11.2%)	9 (8.4%)	3 (2.8%)
CLEAR 1				
Allopurinol + placebo ($n=201$)	2 (0.9%)	0 (0%)	0 (0%)	0 (0%)
Allopurinol + lesinurad 200 mg/day ($n=201$)	12 (6.0%)	2 (0.9%)	2 (0.9%)	0 (0.0%)
Allopurinol + lesinurad 400 mg/day ($n=201$)	32 (15.9%)	9 (4.5%)	12 (6.0%)	2 (0.9%)
CLEAR 2				
Allopurinol + placebo ($n=206$)	7 (3.4%)	3 (1.5%)	0 (0%)	0 (0%)
Allopurinol + lesinurad 200 mg/day ($n=204$)	12 (5.9%)	0 (0%)	4 (2.0%)	0 (0%)
Allopurinol + lesinurad 400 mg/day ($n=200$)	30 (15.0%)	7 (3.5%)	16 (8.0%)	5 (2.5%)
CRYSTAL				
Febuxostat + placebo ($n=109$)	3 (2.8%)	0 (0%)	0 (0%)	0 (0%)
Febuxostat + lesinurad 200 mg/day ($n=106$)	5 (4.7%)	1 (0.9%)	3 (2.8%)	1 (0.9%)
Febuxostat + lesinurad 400 mg/day ($n=109$)	11 (10.1%)	1 (0.9%)	6 (5.5%)	1 (0.9%)

[a]Defined as 1.2 × upper limit or less of baseline value.

Data from the LIGHT study do not indicate an increased risk of cardiovascular events with lesinurad, whereas those form the CLEAR 2 study show a numerically lower number of cardiovascular events with lesinurad and with increasing dose [7▪,12]. On the contrary, data from the CLEAR 1 and CRYSTAL study demonstrate a numerical increase in number of cardiovascular events with lesinurad; however, this did not increase with increasing lesinurad doses [8,11]. No formal statistical testing was done, and these studies are not powered to detect long-term safety. Data presented to the FDA and EMEA and summarized in another review suggests that the licenced dose of lesinurad 200 mg/day does not increase the risk of death or cardiovascular events compared with placebo [19].

Role of lesinurad in the management of gout

Up titrated allopurinol, or febuxostat (if the former is contraindicated) remains first-line treatment of hyperuricemia in gout [3–6]. Lesinurad is licenced at a daily dose of 200 mg in combination with a XOI for the treatment of hyperuricemia in those with gout in the USA and Europe, if the former cannot achieve target SUA on its own. Lesinurad is not approved for the treatment of asymptomatic hyperuricaemia, or for use without a XOI. In published studies, it was taken in the morning, with food and a cup of water and the participants were required to maintain at least 2-l fluid intake/day [7▪,8,10–12]. The morning administration and adequate fluid intake are intended to reduce the potential risk of microcrystallization in the renal tubules. The FDA contraindicates its prescription in the presence of severe renal impairment, end-stage renal disease, kidney transplant, dialysis, tumour lysis syndrome, or Lesch–Nyhan syndrome. It is not indicated in those with eCrCl less than 45 ml/min.

ARHALOFENATE

Arhalofenate is an anti-inflammatory uricosuric drug which blocks URAT-1-mediated uric acid reabsorption and inhibits monosodium urate crystal-induced inflammation by inhibiting the NALP-3 inflammasome [20–22]. It may be of relevance to the treatment of gout in the populations who are unable to tolerate long-term colchicine for flare prophylaxis or have contraindications to corticosteroids and NSAIDs, for example, the elderly. On its' own, it only has a modest urate-lowering effect and reduces the serum urate by 12.5–19% and 16–24% at doses of 600 and 800 mg/day, respectively [13▪,14]. Expectedly, combination arhalofenate and Febuxostat reduces serum urate to a greater degree, and all participants on combination of arhalofenate 800 mg/day and Febuxostat 80 mg/day achieved a serum urate less than 6 mg/dl in small study primarily designed to assess pharmacokinetics [14].

The antiflare effect of arhalofenate was demonstrated in a randomized double-blind active

comparator and placebo controlled study in which participants were randomized to either arhalofenate 600 mg/day, arhalofenate 800 mg/day, allopurinol 300 mg/day with colchicine 0.6 mg/day, allopurinol 300 mg/day, or placebo [13▪]. There were significantly fewer flares in those receiving arhalofenate 800 mg/day compared with those receiving allopurinol 300 mg/day or placebo (mean number of gout flares: 0.66 vs. 1.24, and 0.66 vs. 1.13, $P < 0.05$ for both). However, participants randomized to allopurinol 300 mg/day and colchicine 0.6 mg/day had 0.4 flares on an average ($P = 0.09$ compared with arhalofenate 800 mg/day). Overall, arhalofenate appeared to be well tolerated with no serious adverse events, including elevated serum creatinine [13▪,14], which along with its anti-inflammatory effect is a particular attraction compared with lesinurad. However, the arhalofenate development programme is still underway and it is not currently FDA or EMEA approved for the treatment of gout. Moreover, additional data about the safety and efficacy of arhalofenate is needed, especially in those with CKD as the studies to date have been restricted to a younger population and with preserved renal function. Further studies are required before arhalofenate can be recommended for clinical use in people with gout.

CONCLUSION

XOIs remain first line for the management of hyperuricaemia in people with gout. The indications for lesinurad in real-world clinical scenarios may include [1] inability to achieve target SUA levels despite maximum licenced doses of XOI, or [2] inability to tolerate sufficiently high doses of a XOI that allows reduction in SUA to below the treatment target level. Lesinurad should be preferred over other uricosuric drugs such as sulfinpyrazone and probenecid given the potential for side effects and drug interactions with these medicines.

Despite the recent licencing of lesinurad, and the potential of arhalofenate on the horizon, there is still need for a urate-lowering agent that can be used in the presence of significant renal impairment. Thus, drug developers and big pharmaceutic companies should focus on this target group.

Acknowledgements

None.

Financial support and sponsorship

A.A. has received departmental research grants from AstraZeneca, and Oxford Immunotec on studies related to gout. A.A. reports royalties from Uptodate on an unrelated topic and speaker bureau fees from Menarini.

Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
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Uric acid and cognitive decline: a double-edge sword?

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Purpose of review
This narrative review aims to highlight recent findings on the relation between uric acid level and cognitive decline or dementia.

Recent findings
The antioxidant properties of uric acid, which have supported the hypothesis that uric acid may be neuroprotective, have been questioned by preclinical data. Studies investigating the relation between serum uric acid (SUA) level and Alzheimer disease are mostly cross-sectional, and results are often inconclusive. Similarly, data for an association between uric acid level and cognitive performance are inconsistent. There is some evidence that low SUA level might be associated with Parkinson disease, but studies are limited by methodological heterogeneity and risk of bias. Patients with gout may have decreased risk for Alzheimer disease, but the impact of treatment is unclear. Recent data suggest an increased risk of vascular dementia with high SUA level via increased cerebrovascular burden in older patients. The relation between SUA level and neurologic disorders may be U-shaped.

Summary
We lack strong evidence for an association between low SUA level and cognitive decline over time. Conversely, high SUA level might increase the cerebrovascular burden and the risk of vascular dementia; physicians should continue to treat hyperuricemia when appropriate.

Keywords
cerebrovascular disease, cognition, dementia, gout, uric acid

INTRODUCTION

Uric acid is the product of purine catalysis by xanthine oxidase. Serum uric acid (SUA) level is determined by the balance between dietary purine intake and renal excretion of uric acid and by xanthine oxidase activity, which is inhibited by urate-lowering therapies (ULT), such as allopurinol and febuxostat. Chronic hyperuricemia is defined by repeated measurements of SUA level above the threshold of 360 μmol/l (6 mg/dl) and can lead to deposition of monosodium urate crystals and several diseases such as gout, the leading cause of inflammatory arthritis in Western countries [1].

The aim of gout management, as defined by most recent international guidelines, is the long-term lowering of SUA levels below the treatment target of 360 μmol/l and below 300 μmol/l in severe cases [2,3]. However, given the important antioxidant properties of uric acid, maintaining a too-low SUA level in the long term might conversely expose patients with gout to increased oxidative stress and associated disorders. In particular, some concerns have been raised about a putative inverse association between SUA level and neurodegenerative diseases [4,5]. This narrative review highlights recent findings on the relation between uric acid level and cognitive decline or dementia.

OXIDATIVE STRESS: THE LINK BETWEEN URIC ACID AND COGNITION?

The antioxidant properties of uric acid were described a few decades ago. Uric acid acts mainly as a scavenger of reactive oxygen species and peroxinitrite, but it also protects against iron-mediated

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Curr Opin Rheumatol 2018, 30:183–187
DOI:10.1097/BOR.0000000000000472

KEY POINTS

- The heterogeneity of studies strongly limits the interpretation of the association between uric acid and cognitive performance.
- High serum uric acid level might increase the risk of vascular dementia via increased cerebrovascular burden in older people.
- Given the lack of clear evidence supporting the neuroprotective effect of uric acid, clinicians should continue to treat hyperuricemia when appropriate.

ascorbate oxidation [6,7]. In vitro, uric acid has similar antioxidant capacities as ascorbate. However, a much higher serum level of uric acid than ascorbate, the consequence of the loss of uricase during human evolution, suggests that uric acid is a major antioxidant in humans. Also, this situation underlies the hypothesis of the evolutionary advantage of the uricase loss, by providing high antioxidant capacity and a natural protection against age-related diseases [8]. However, this suggestion has been tempered by several studies showing that uric acid might also be pro-oxidant, depending for instance on the presence of transition metals in the microenvironment [9]. Important insights have also been provided by studying the plasma of patients with gout treated with pegloticase, a recombinant uricase that dramatically and rapidly lowers SUA level [10]. In this study, no change in oxidative stress markers were detected up to 7 days after pegloticase infusions, but SUA levels were still very low, which questions the antioxidant capacity of uric acid *in vivo*.

The complex role of uric acid regarding oxidative stress is a critical matter when addressing the relation between uric acid and cognition. Indeed, uric acid level in cerebrospinal fluid is positively correlated with SUA level, especially in the presence of impaired blood–brain barrier [11]. Therefore, SUA level might determine at least in part the antioxidant (or pro-oxidant?) activity in the brain. Oxidative stress is a pivotal feature in the pathogenesis of the most common neurodegenerative disorders such as Alzheimer disease and Parkinson disease, which are also major causes of cognitive impairment [12,13].

Thus, one major hypothesis driving research in the field is that SUA affects the risk of dementia by modifying the level of oxidative stress in the brain. However, the antioxidant properties of uric acid in the brain have been questioned by recent preclinical data suggesting that uric acid may induce a pro-inflammatory and pro-oxidant response in brain cells [14,15]. Consequently, the precise role of uric acid in cognitive decline and neurodegenerative diseases is debated and has been addressed in epidemiological studies, often providing conflicting results.

URIC ACID AND NEURODEGENERATIVE DEMENTIA

Evidence regarding the association between uric acid and the neurodegenerative causes of dementia are conflicting. Two recent meta-analyses, including mostly cross-sectional studies, investigated the association between SUA level and Alzheimer disease. One included 31 studies ($n = 7021$ participants) and showed lower SUA level in cognitive impairment/dementia cases than in dementia-free controls [standardized mean difference (SMD) −0.325; 95% confidence interval (CI), not provided; $P < 0.001$] [16▪▪]. This association tended to be stronger when considering only the 22 studies including patients with Alzheimer disease (SMD −0.417; 95% CI, not provided; $P < 0.001$), or only the seven studies including patients with Parkinson disease-associated dementia (PDD; SMD −0.672; 95% CI, not provided; $P = 0.001$). However, further adjusted logistic regression analysis across five cohort studies found no association between SUA level and cognitive impairment (odds ratio 1.18; 95% CI, 0.96–1.46; $P = 0.12$). In addition, there was no correlation between SUA level and mini mental state examination score ($r = -0.084$; $P = 0.274$), except in studies investigating PDD ($r = -0.155$; $P = 0.003$) [16▪▪].

Another meta-analysis of 11 studies comparing SUA level between Alzheimer disease patients and healthy controls ($n = 2708$ participants) found no statistically significant difference (SMD −0.50; 95% CI, −1.23 to 0.22) [17]. These two meta-analyses were limited by significant heterogeneity across studies and a relatively high risk of bias for most studies included. Therefore, based on these two reviews of cross-sectional data, we have no clear evidence for a protective role of high SUA level on risk of cognitive decline, except maybe in PDD.

One large longitudinal study conducted with the Rotterdam cohort assessed the impact of SUA level on risk of incident dementia [18]. It included 4618 participants age 55 years and older (61% females, mean ± SD age: 69.4 ± 8.6 years) with mean ± SD SUA level of 322.3 ± 80.5 μmol/l. During a mean ± SD follow-up of 9.0 ± 3.5 years (41 651 person-years), 457 incident cases of dementia were diagnosed. In this study, risk of dementia was decreased with high SUA level after adjustment for age, sex, education level, and traditional cardiovascular risk factors

[hazard ratio 0.73; 95% CI, 0.55–0.97] for the highest versus the lowest quartile of SUA ($P_{trend} = 0.030$). In addition, for participants in whom dementia did not develop, high SUA level at baseline was associated with better cognitive performance later in life. By contrast, a cross-sectional study based on the same cohort subsequently found an association between high SUA level and worse cognitive performance and white matter atrophy as detected by brain MRI [19].

Finally, two population-based cohort studies found decreased risk of Alzheimer disease in patients with gout [20,21]. A recent study based on the 5% Medicare data (Medicare covers all Americans aged 65 years and older) found that the initiation of ULT (allopurinol, febuxostat) did not affect the risk of dementia developing over a mean follow-up of 683 days [22]. However, these studies did not specifically investigate the impact of SUA level and results must be interpreted with caution. Of note, beyond ULT, gout medications such as nonsteroidal anti-inflammatory drugs (NSAIDs) may modify the risk of Alzheimer disease by modulating oxidative stress or systemic inflammation [23].

URIC ACID AND VASCULAR DEMENTIA

One more-recent longitudinal French study contradicted these previous findings [24▪]. This population-based study involved 1598 healthy participants aged 65 years and older at baseline (62% females, mean ± SD age: 72.4 ± 4.1 years) with brain MRI data available. Participants taking ULT were excluded from the analysis, and mean ± SD baseline SUA level was 273.7 ± 70.4 μmol/l. During a mean follow-up of 10.1 years (13,357 person-years), dementia developed in 110 participants. The risk of incident dementia was increased for patients with the highest quartile of SUA level (hazard ratio 1.79; 95% CI, 1.17–2.73), $P = 0.007$). Interestingly, the risk was higher for participants with vascular or mixed dementia (i.e., all cases of dementia with a vascular component, $n = 20$ cases; hazard ratio 3.66; 95% CI, 1.29–10.41; $P = 0.015$) than those with Alzheimer disease ($n = 76$ cases; hazard ratio 1.55; 95% CI, 0.92–2.61; $P = 0.10$). Sensitivity analyses supported this association between high SUA level and incident vascular dementia, which disappeared after adjustment for interim strokes, which suggests a mediating effect of stroke on this subtype of dementia. SUA level was not associated with MRI markers of cerebrovascular disease or hippocampal volume (a biomarker for Alzheimer disease) [24▪].

These results suggest an increased risk of incident dementia with high SUA level in older people, probably via increased risk of cerebrovascular disease. This suggestion is consistent with the increased cardiovascular risk observed in patients with hyperuricemia, especially those with gout [25]. Indeed, the association between uric acid and MRI biomarkers of cerebrovascular disease has been suggested by previous epidemiological data [26–28]. Another cross-sectional study found that cerebral ischemia mediates the association between high SUA level and poor cognitive performance [29].

URIC ACID AND COGNITIVE PERFORMANCE

One systematic review found no clear association between uric acid level and cognition, but it analyzed studies including both dementia-free patients and patients with Alzheimer disease, Parkinson disease, or mild cognitive impairment (MCI), so results were difficult to interpret [16▪▪]. In addition to the Rotterdam study mentioned above [18], several studies have focused on the association between SUA level and cognition assessed by different cognitive tests in patients without a diagnosis of dementia or MCI.

A longitudinal study of 2630 healthy participants (mean ± SD age: 47.0 ± 0.3 years) with a mean follow-up of 4.6 ± 0.9 years found high SUA level at baseline associated with faster cognitive decline over time in a visual memory/visuo-construction ability test [30]. Another study based on the Women's Health and Aging Study found a cross-sectional association between high SUA level and poor performance on a test of attention in 423 dementia-free women aged 73.6 ± 2.8 years but no association with cognitive decline over time in longitudinal models [31]. Conversely, another recent study of 1451 dementia-free participants aged 26–99 years separately analyzed males (mean ± SD age: 65.8 ± 14.1 years) and females (62.5 ± 13.7 years) and found, over 3 years of follow-up, high baseline SUA level associated with reduced rate of cognitive decline in men but not women [32]. This sex-specific effect of uric acid on cognitive function has been supported by a cross-sectional study of the ELSA-Brasil cohort [33]. Some other smaller studies, mostly cross-sectional, reported poor cognitive performance in patients with high SUA level [34,35], whereas others supported a beneficial effect [36–38].

The inconsistent findings reported in the literature on the effect of uric acid on cognition might be because of significant heterogeneity in the design of the studies. Indeed, age of participants, baseline SUA levels, rates of comorbidities such as kidney or cardiovascular disease, duration of follow-up, types of statistical adjustment and also the type of cognitive tests used in the studies might greatly differ among

studies. Moreover, even if the studies provide interesting insights into the pathogenic role of uric acid in cognition, the evaluation of clinical relevance of small albeit significant changes in cognitive tests is challenging.

A PARTICULAR CASE: FAMILIAL RENAL HYPOURICEMIA

When addressing the impact of SUA level on brain tissue, it may also be relevant to consider extreme conditions such as familial renal hypouricemia. This genetic disease is characterized by defective renal uric acid reabsorption secondary to a loss of function in the urate transporter URAT1 (type 1) or glucose transporter GLUT9 (type 2) and results in very low SUA level from birth, below 120–180 μmol/l (2–3 mg/dl) [39]. Usual complications of the disease are nephrolithiasis and exercise-induced acute renal failure (EIARF). Several papers have reported the occurrence of posterior reversible encephalopathy syndrome with EIARF, which raised concerns about the neurological consequences of very low SUA level in the long term [40–42]. This rare complication, although not directly related to cognitive outcomes, suggests a U-shaped relationship between SUA level and neurologic disorders (i.e., the risk increases with both low and high SUA level), as has been described for other outcomes such as mortality [43], stroke [44], or loss of kidney function [45,46].

CONCLUSION

Epidemiological data regarding the impact of uric acid on cognitive disorders are conflicting. As discussed in this review, the vast heterogeneity of study design, the definition for dementia or cognitive impairment, and the approach to diagnosis may significantly vary among studies. The relation between uric acid level and neurologic disorders is likely U- or J-shaped, but we have no clear evidence supporting an association of low SUA level and increased risk of neurodegenerative dementia or cognitive impairment. Conversely, some consistent data indicate a possible association of high SUA level and increased risk of vascular dementia via an increased cerebrovascular burden in older people.

In this field, some issues need to be addressed in further research. There is a strong need for more solid longitudinal study to better determine the long-term impact of high or low SUA level on cognition and biomarkers (e.g. brain MRI features of neurodegenerative or cerebrovascular diseases) in both healthy middle-aged and older people. This effect should be also assessed in patients with hyperuricemia and gout, with appropriate evaluation of the weight of cerebrovascular disease in this context. Finally, the impact of changes in SUA over time, especially under ULT, should be investigated appropriately.

Acknowledgements

The authors acknowledge the support of the ART Viggo association.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

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- ■■ of outstanding interest

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Epigenetics of inflammatory arthritis

Deepa Hammaker and Gary S. Firestein

Purpose of review
Aberrant epigenetic changes in DNA methylation, histone marks, and noncoding RNA expression regulate the pathogenesis of many rheumatic diseases. The present article will review the recent advances in the epigenetic profile of inflammatory arthritis and discuss diagnostic biomarkers and potential therapeutic targets.

Recent findings
Methylation signatures of fibroblast-like synoviocytes not only distinguish rheumatoid arthritis (RA) and osteoarthritis (OA), but also early RA from late RA or juvenile idiopathic arthritis. Methylation patterns are also specific to individual joint locations, which might explain the distribution of joint involvement in some rheumatic diseases. Hypomethylation in systemic lupus erythematosus (SLE) T cells is, in part, because of active demethylation and 5-hydroxymethylation. The methylation status of some genes in SLE is associated with disease severity and has potential as a diagnostic marker. An integrative analysis of OA methylome, transcriptome, and proteome in chondrocytes has identified multiple-evidence genes that might be evaluated for therapeutic potential. Class-specific histone deacetylase inhibitors are being evaluated for therapy in inflammatory arthritis.

Summary
Disease pathogenesis is regulated by the interplay of genetics, environment, and epigenetics. Understanding how these mechanisms regulate cell function in health and disease has implications for individualized therapy.

Keywords
ankylosing spondylitis, epigenetics, histone, inflammatory arthritis, methylation, microRNA, osteoarthritis, rheumatoid arthritis, systemic lupus erythematosus

INTRODUCTION

Recent data using genome-wide methods indicate that epigenetics contributes to the pathogenesis of inflammatory synovitis. The studies most relevant to synovial pathology have involved rheumatoid arthritis (RA), primarily because clinical samples are available from arthroplasty and biopsy. Although this is the most relevant tissue, some data using peripheral blood cells also implicate epigenetically marked pathways that could have an impact on the joint. Thus, this review will focus primarily on synovial epigenetics in RA, but will discuss the evolving status of blood mononuclear cell DNA methylation and additional epigenetic signatures in other diseases.

The contribution of genetics to disease susceptibility in RA and systemic lupus erythematosus (SLE) has been clearly defined. Class II major histocompatibility (MHC) risk alleles in RA and SLE are the dominant risk alleles, but over 100 non-MHC risk alleles have also been identified [1]. However, genetic predisposition explains disease onset in a relatively small percentage of patients [2]. Studies on identical twins who are discordant for RA or SLE indicate that environmental or behavioral factors such as smoking, diet, ultraviolet light, and exposure to toxins can synergize with genetic predisposition to accelerate the onset and severity of disease [3]. The link between environment and the genome is largely mediated by epigenetic marks that decorate the DNA, including DNA methylation and histone modification (Fig. 1) [4]. Noncoding RNA can also influence gene regulation and contribute to nongenetic risk [5,6]. Understanding how these mechanisms control gene expression and cell

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Curr Opin Rheumatol 2018, 30:188–196
DOI:10.1097/BOR.0000000000000471

KEY POINTS

- Epigenetic imprinting through DNA methylation, histone marks and noncoding RNA occurs in inflammatory arthritis and could contribute to disease pathogenesis.
- Pathogenic epigenetic modifications can vary depending on location, cell type, and the course of disease.
- Epigenetic modulators are promising therapeutic approaches to inflammatory diseases.

function in physiological and pathogenic conditions has implications for disease prevention and individualized therapy.

RHEUMATOID ARTHRITIS AND DNA METHYLATION

DNA methylation involves adding a methyl group from S-adenosyl methionine (SAM) to a cytosine residue in the context of a CpG dinucleotide. CpG methylation is regulated by several families of proteins that function as 'writers', namely DNA methyltransferases (DNMTs), 'readers', which include the methyl-CpG-binding domain proteins (MBD) and 'erasers' that demethylate CpG, such as ten-eleven translocation (TET) enzymes [7]. In general, a low level or lack of DNA methylation in the promoter CpGs favors the formation of transcription complexes and gene transcription. Conversely, methylation of promoter CpGs favors a closed chromatin conformation and blocks transcription, resulting in gene silencing [8]. CpG islands located within the gene body, enhancers or introns are also regulated by methylation but the effects on gene expression are more complex and not well understood [9].

Fibroblast-like synoviocytes

Compared with osteoarthritis (OA) and/or normal FLS, some studies suggest that RA synoviocytes are globally hypomethylated, which has been linked to increased activity of spermidine/ spermine N1-acetyl transferase, causing excessive consumption of SAM [10,11]. However, genome-wide studies using chip technology did not show differences in global methylation between RA and OA FLS; nevertheless, there is agreement that the FLS are differentially methylated compared with controls [12]. The differentially methylated loci (DML) in RA are associated with genes involved in cell migration, focal adhesion, and extracellular matrix interactions, which is consistent with the invasive nature of RA [13]. This methylation signature in the cells remains constant for many months in culture and suggests that they are 'imprinted' by their sojourn through the rheumatoid synovium [14].

Methylation patterns of FLS from patients with early RA differed from late stage RA, although they formed a distinct RA subgroup that was easily distinguished from OA by hierarchical clustering (Fig. 2) [15]. The differences were localized to genes related to Wnt, integrin, and PDGF signaling and suggest that cell imprinting related to differentiation, adhesion and proliferation changes during the evolution of the disease. Other forms of arthritis, notably juvenile idiopathic arthritis, are also imprinted and form a subset in the RA super-group (Fig. 2) [15]. Thus, the presence of inflammation could contribute to abnormal methylation with more subtle variations that are dependent on the type of arthritis or stage of disease (Fig. 2). The observation is supported by data indicating that DNMTs are regulated by cytokines like IL-1 and TNF in control FLS and can mimic some of the DMLs in RA FLS [16].

Perhaps more interesting, the methylomes in RA and other diseases also vary depending on their joint of origin (Fig. 3) [17▪▪,18▪▪]. The methylation patterns of either RA or OA FLS derived from the hip differed compared with the knee, particularly in genes associated with cell differentiation like homeobox (HOX) and Wnt families. Similar joint-specific patterns are also apparent in mouse FLS and support the notion that epigenetics help determine synovial function that is tailored to the biomechanics of specific joints [18▪▪]. However, when the disease independent genes and pathways are subtracted from RA, a new group of RA-specific pathways emerge that could relate to distinct joint-specific disease mechanisms. Several key pathways were identified, including JAK-STAT and IL-6 signaling, which was also confirmed by documenting joint-specific transcriptomes [17▪▪].

Candidate gene approaches have shed light on potential RA pathogenic genes. For example, hypomethylation of pro-inflammatory proteins such as CXCL12 and IL-6 and the transcription factor TBX5 have been documented and correlate with increased gene expression in RA FLS [19,20]. Increased TBX5 expression increases the production of pro-inflammatory cytokines, IL-8, CCL20, and CXCL2 [21]. To identify novel pathogenic genes using unbiased methodology, integrative analysis using three datasets – RA GWAS risk alleles, DMLs, and differentially expressed genes (*DEGs*) was performed in RA and OA FLS [22]. Of several triple-evidence genes, *ELMO1*

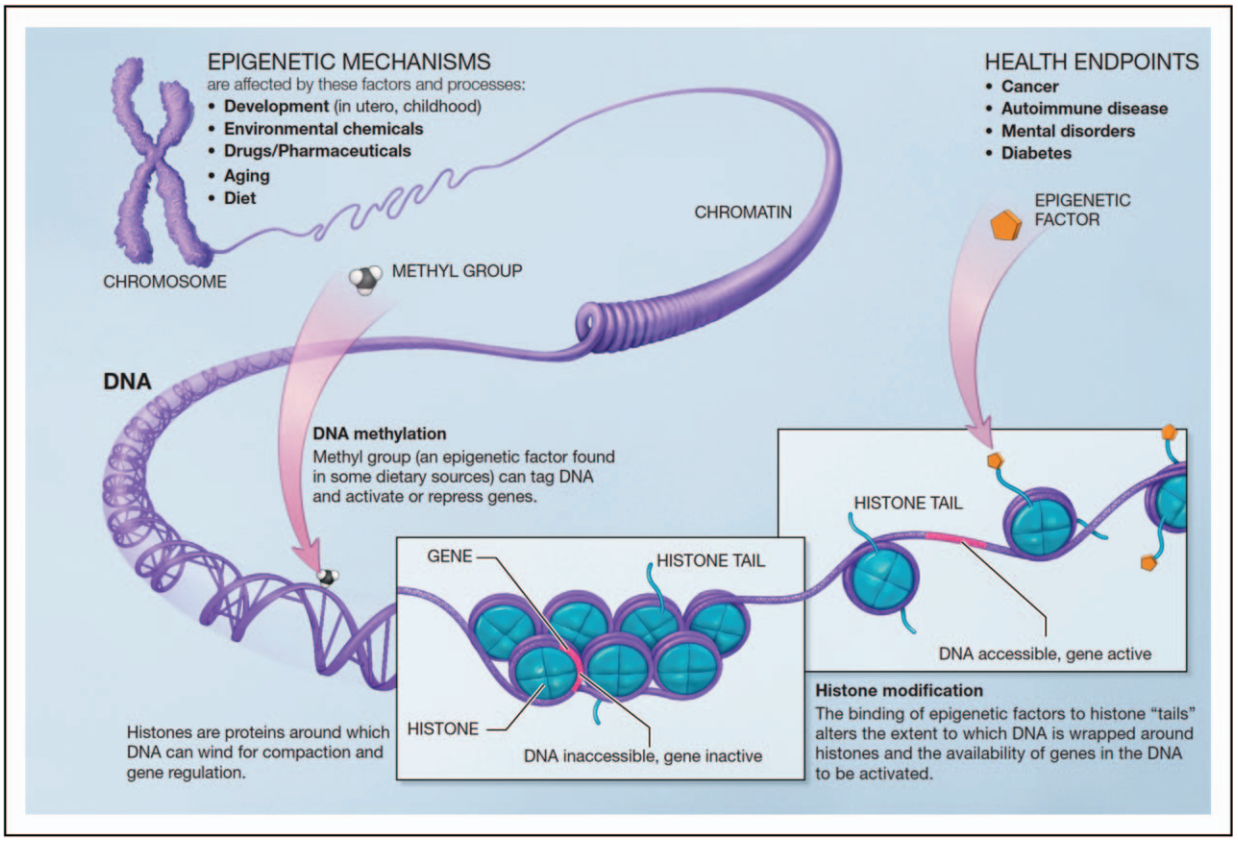

FIGURE 1. Epigenetic mechanisms in inflammatory arthritis. Epigenetics is defined as the study of heritable changes that do not involve changes in the DNA sequence. Epigenetic modifications such as DNA methylation, histone modification, and noncoding RNA translate extracellular or environmental stimuli to switch on and off gene expression and therefore regulate cell function. Aberrant gene expression can compromise cellular function, contributing to disease pathogenesis. Source: Creative Commons (National Institutes of Health) https://commonfund.nih.gov/epigenomics.

was highly expressed in RA FLS and knock-down of *ELMO1* decreased cell migration.

A follow-up integrative analysis expanded the promoter DMLs to include enhancers identified two more unexpected multievidence genes, *LBH* and *PTPN11* [23,24]. *LBH* gene variants are associated with SLE, coeliac disease, and RA [25–28]. *LBH* deficiency blocks S-phase in the cell cycle in RA FLS and increases DNA damage because of impaired DNA repair mechanisms [29]. Furthermore, *LBH* deficiency *in vivo* also leads to cell-cycle abnormalities and increased arthritis severity in the serum transfer mouse model [29]. The methylation status of an enhancer DML in combination with a risk variant regulates the enhancer function and *LBH* expression, demonstrating how genetic risk and epigenetic marks can interact to alter cell function [23]. *PTPN11*, which encodes the protein tyrosine phosphatase SHP2, is highly expressed in RA FLS, where it regulates cell migration [24]. SHP2 inhibition attenuates arthritis in the serum transfer model, indicating that it is a potential therapeutic target. Increased expression of *PTPN11* in RA FLS is controlled, in part, by methylation of a novel intronic enhancer with a glucocorticoid-receptor binding site [24].

Peripheral blood mononuclear cells

Monitoring methylation changes might be a useful tool to predict and assess the course of disease and response to therapeutics. Recent studies have evaluated the methylation status in easily accessible tissues such as blood or synovial fluid to determine if they mirror synovial pathology. One study showed that fibroblasts isolated from RA synovial fluid showed similar methylation changes as tissue-derived synoviocytes and suggests that these cells might be used as a surrogate for tissue-derived FLS [30]. Another study showed that naïve blood T cells in RA are hypermethylated at loci similar to RA FLS [31]. Recently, a link between DNA methylation in T cells and response to DMARD treatment in early RA was explored [32]. A combination

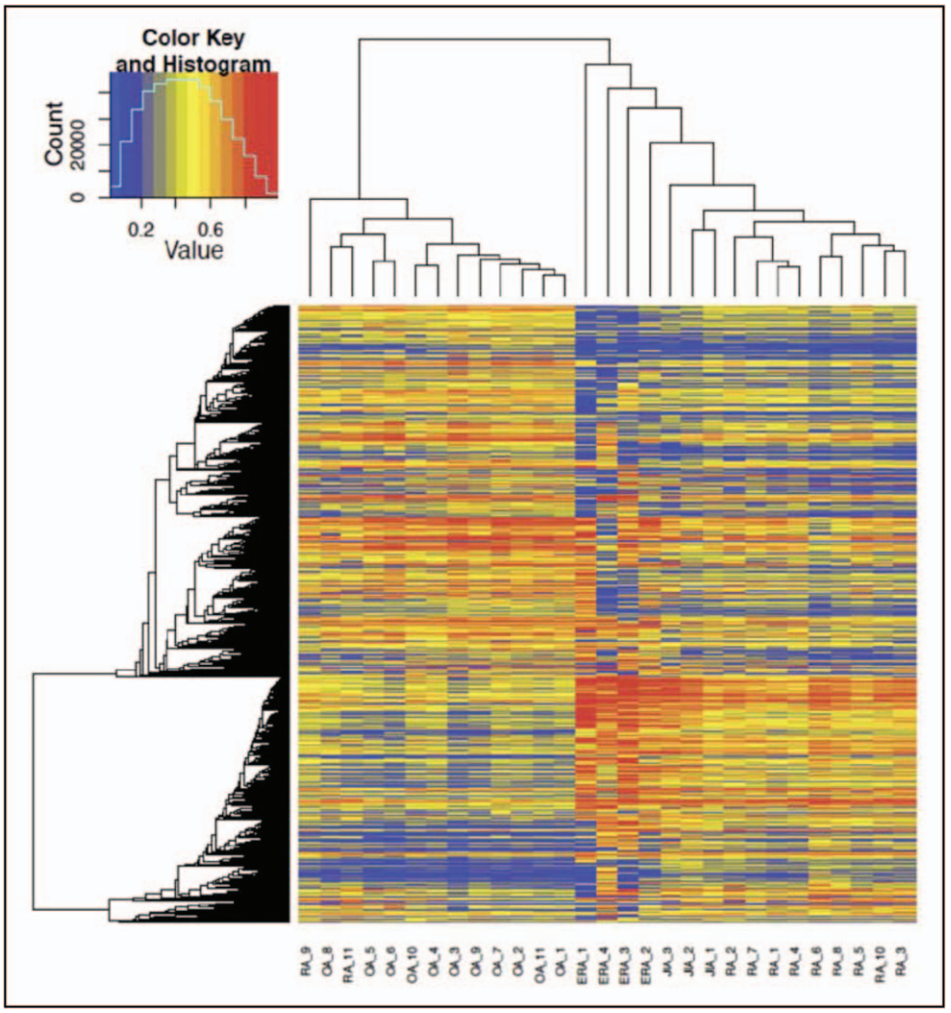

FIGURE 2. Unique methylation signatures in disease. Hierarchical clustering of differentially methylated loci shows segregation of RA and OA signatures. Early rheumatoid arthritis (ERA) clusters with late RA but forms a distinct subgroup, and other forms of inflammatory arthritis such as juvenile idiopathic arthritis (JIA) also cluster with RA, but form a distinct subgroup. Source: [15]. OA, osteoarthritis; RA, rheumatoid arthritis.

of a hypermethylated CpG in *ADAMTSL2* promoter and a hypomethylated CpG in *BTN3A2* distinguished responders from nonresponders. Another study reported that patients with RA who responded to etanercept had four hypomethylated CpGs located within an exon of the *LRPAP1* gene [33]. These interesting but small studies need to be replicated in larger cohorts.

RHEUMATOID ARTHRITIS AND HISTONE MARKS

The nucleosome consists of a short segment of DNA wrapped around an octamer of four histone proteins (H2A, H2B, H3, and H4) (Fig. 1) [34]. The histones can be posttranslationally modified in many ways, including acetylation, methylation, ubiquitination, phosphorylation, and sumoylation [35]. Histone methylation can be permissive or repressive. For example, tri-methylation of H3 at lysine 4 (H3K4me3) signals gene transcription whereas tri-methylation of lysine 27 (H3K27me3) indicates repressed histone conformation. Histone acetyltransferases (HATs) are 'writers' of acetylation on lysines, whereas bromodomain proteins (BRD) function as 'readers' that recognize acetylated lysines. Histone deacetylases (HDACs) are acetylation 'erasers' that favor a closed chromatin and inhibition of transcription. HDACs can be divided into four groups: class I (HDAC1–3, 8), class II (HDAC4–7, 9,10), class III sirtuins (Sirt1–7), and class IV (HDAC11) [36]. Although class I HDACs are ubiquitous, class II HDACs are tissue specific.

Initial studies evaluating the activity of HATs and HDACs in RA synovial tissue gave contradictory results, possibly due to different selection criteria of

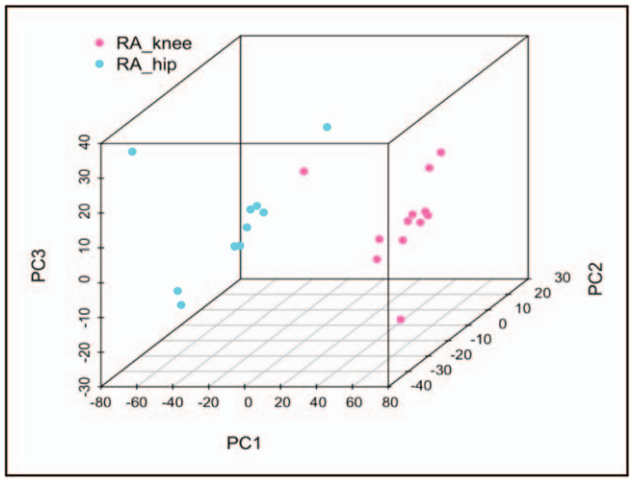

FIGURE 3. Joint location-specific DNA methylation patterns in RA. Principle component analysis shows that hip and knee fibroblast-like synoviocytes have distinct DNA methylation patterns. Source: [17▪▪]. RA, rheumatoid arthritis.

patients [37,38]. Later studies showed that TNF levels in RA synovial tissuess correlated with HDAC1, HDAC2, and HDAC3 expression [39]. In contrast, HDAC5 expression in RA synovial tissue negatively correlated with disease activity and IL-6 expression, suggesting an anti-inflammatory role in RA [40]. No correlations were observed for HDAC8 or the other class II HDACs. FLS from patients with RA and OA express HDACs 1 to 11 but only HDAC1 expression was consistently elevated in RA [39]. Sirtuins 1 to 7 are also expressed in RA FLS but their role in RA is controversial. Some studies showed that SIRT1 expression was increased in RA synovium compared with OA [41]. In RA FLS, TNF-induced SIRT1 expression increased IL-6 and IL-8 expression and reduced apoptosis. Other studies showed that RA FLS expressed lower levels SIRT1 mRNA and protein compared with normal FLS [42]. High expression of SIRT1 inhibited MMP1 and MMP13 expression. However, in some preclinical studies, SIRT1 levels were decreased in the joint tissue of mice with collagen-induced arthritis (CIA) and *SIRT1* deletion in myeloid cells increased disease severity in a serum transfer arthritis model [43,44].

HDAC inhibitors (HDACi) have been extensively studied in cancer and are being explored in RA. Givinostat, a pan-class I/II HDACi, reduced inflammatory cytokines in RA FLS and decreased inflammation in arthritis models and is currently being explored in juvenile idiopathic arthritis [45–48]. A selective HDAC3/6 inhibitor significantly reduced IL-1β-induced interferon response genes, IL-6, IL-8, MMP1, and MMP3 and blocked STAT1 phosphorylation [49]. HDAC3 knockdown recapitulated the inhibitory effect of pan-HDACi, suggesting that it is the most relevant HDAC therapeutic target for RA. A novel HDAC6i, CKD-L, reduced pro-inflammatory cytokines and increased IL-10 expression in RA PBMCs and effectively reduced synovial inflammation in CIA [50]. Finally, I-BET151, a selective inhibitor of the bromodomain and extra-terminal (BET) proteins, reduced joint swelling and inflammation in a serum transfer arthritis model and inhibited osteoclastogenesis and bone loss [51▪]. In RA FLS, I-BET151 blocked MMP1, MMP3, IL-6, and IL-8 production in response to TNF, IL-1β, or TLR ligands. I-BET151 also reduced proliferation and chemoattractant properties of RA FLS [52]. Similar results were seen with another BET inhibitor, JQ1, suggesting that this family of proteins may be promising therapeutic targets [53].

RHEUMATOID ARTHRITIS AND MICRORNA

Noncoding RNA are RNA molecules that are transcribed from DNA but are not translated into protein. They are grouped by size; microRNA (miRNA) are usually 22–23 nucleotides whereas long noncoding RNA (lncRNA) are over 200 nucleotides [54]. miRNA can be encoded within intergenic regions, introns, or exons of protein coding regions. miRNA associates with RISC to regulate transcription by binding and cleaving mRNA and by blocking access to the translation machinery [54]. A summary of miRNA expression in RA FLS has been previously described [4]. A brief description of key miRNAs implicated in disease is provided below.

A recent study identified over 380 differentially expressed miRNAs in RA and OA FLS [55]. Of these, miR-10a was highly expressed in OA but was markedly reduced in RA FLS and synovial tissue. Pro-inflammatory cytokines such as TNF and IL-1β downregulated miR-10a expression through the NF-κB pathway. miRNA-10a targeted several genes in the TNF/IL1 signaling pathway such as *TAK1*, *IRAK5* and *BTRC* [55]. Mimics of miR-10a inhibited expression of IL-6, IL-8, MCP1, MMP1, and MMP13 and reduced FLS proliferation, migration, and invasion. Another study showed that miR-10a also targeted *TBX5*, a transcription factor in RA FLS [56]. As noted above, the *TBX5* promoter is hypomethylated in RA FLS, which correlates with its overexpression, and contributes to induction of pro-inflammatory cytokines such as IL-8, CXCL2, and CCL20 [21].

miR-27a expression was also markedly reduced in RA synovial tissue, FLS and serum compared with normal controls [57]. An miR-27a mimic significantly inhibited migration and invasion of RA FLS by

decreasing expression of MMP2, MMP9 and MMP13 and invasion-related proteins, Rac1, Cdc42, and RhoA. Also, miR-27a inhibited TLR4 and NF-κB p65 protein levels. miR-27a targets follistatin-like protein 1, a pro-inflammatory mediator that is overexpressed in RA synovium and serum, particularly in ACPA+ patients [58]. Interestingly, another study demonstrated that miR-27a expression is suppressed by the lncRNA ZFAS1, which was overexpressed in RA synovial tissue and FLS compared with normal [59].

In contrast to miR-10a and miR-27a, miR-34a is overexpressed in RA FLS [60]. Two studies showed that miR-34a deficiency decreased incidence and clinical symptoms of CIA in mice [61,62]. Treatment with miR-34a antagomir reduced of TNF, IL-17A, IL-6, IL-21, IL-35, IFNγ, and IL-10 expression in the joint and serum of the arthritic mice [61].

SYSTEMIC LUPUS ERYTHEMATOSUS

Aberrant DNA methylation in peripheral blood $CD4^+$ T cells is potentially associated with dysregulated adaptive immunity and the loss of self-tolerance in SLE. Candidate gene analysis showed that immune-associated genes such as ITGAL (CD11a), TNFSF7 (CD70), perforin, and killer Ig-like receptor molecules (KIR) in $CD4^+$ T cells are overexpressed [63]. Studies have shown that gene expression can be enhanced by the loss of repressive histone marks such as H3K27me3. For instance, ITGAL expression is enhanced by JMJD3, a histone demethylase that is overexpressed in lupus CD4+ T cells (Fig. 4) [64▪]. The loss of histone methylation on H3K27 is inversely related to JMJD3 expression and positively correlated with higher disease activity.

Many X-linked genes such as *CD40LG* and *CXCR3* are also hypomethylated and might contribute to female predominance of the disease [65]. Genome-wide DNA methylation studies show profound promoter hypomethylation in other genes, most notably in the TLR and type I interferon response pathways [66,67]. Abnormal interferon epigenetic marks could play a role in the well described interferon signature in SLE. Differential methylation correlates with increased expression *IFIT1*, *STAT1*, *MX1*, *IFIT3*, and *IFI44L* and is associated with autoantibody production and higher disease activity [68–70]. Naive peripheral blood $CD4^+$ T cells in SLE also have transcriptomes with higher expression of interferon-regulated genes and are poised for hyper-responsiveness prior to activation [71]. Hypermethylated genes have also been observed in SLE, including CD3ζ in peripheral blood $CD4^+$ T cells [72], and correlate with lupus-related thrombocytopenia and hemolytic anemia. These methylation data have potential clinical implications, and IFI44L and CD3ζ are being evaluated as diagnostic markers for lupus [73▪].

DNA hypomethylation and DNMT expression in lupus peripheral blood $CD4^+$ T cells can be regulated by MAPKs, GADD45α, PP2A, and RFX1 [63,66,74]. Recent data indicate that ultraviolet B exposure reduced DNA methylation by inhibiting DNMT1 activity, suggesting that UV light might decrease methylation and increase expression of genes associated with SLE [75,76]. Others have shown that lupus T cells expressed lower levels of DNMT1 and DNMT3a, also resulting in a loss of methylation [77]. Recent data show that lupus T cells have increased 5-hydroxymethylation, which is an intermediate epigenetic mark between DNA methylation and demethylation [78]. This study showed that over 2700 genes were differentially hydroxymethylated in lupus $CD4^+$ T cells, many of which are involved in immune regulation. In addition, lupus T cells expressed higher levels of TET2 and TET3, which are demethylases that actively catalyze the conversion of 5-methylcytosine to 5-hydroxymethylcytosine [78]. Active demethylation further inhibits DNMT1 activity in lupus T cells. Finally, noncoding RNAs, which regulate many facets of disease pathogenesis, also contribute to DNA hypomethylation. MicroRNAs such as miR-126, miR-21, and miR-148a are markedly overexpressed in lupus $CD4^+$ T cells. These miRNAs can reduce DNMT1 expression and activity directly by binding DNMT1 mRNA or indirectly through the Ras–MAPK pathway [79,80].

ANKYLOSING SPONDYLITIS

DNA methylation studies in ankylosing spondylitis have identified over 1600 hypermethylated loci in the peripheral blood of patients with ankylosing spondylitis, most of which are located in HLA genes [81]. Genes such as *DNMT1* and *BCL11B* were hypermethylated but their expression did not correlate with clinical manifestations of ankylosing spondylitis [82,83]. miRNA expression profiles in ankylosing spondylitis blood showed 19 DEGs. Of these, miR-146a and miR-155 levels were increased compared with control and only miR-155 expression correlated with disease index [84].

OSTEOARTHRITIS

OA is traditionally thought of as a degenerative disease, but it often has a prominent inflammatory component. Several studies have determined differentially methylated genes in OA chondrocytes but there is little or no overlap between them [85,86]. A

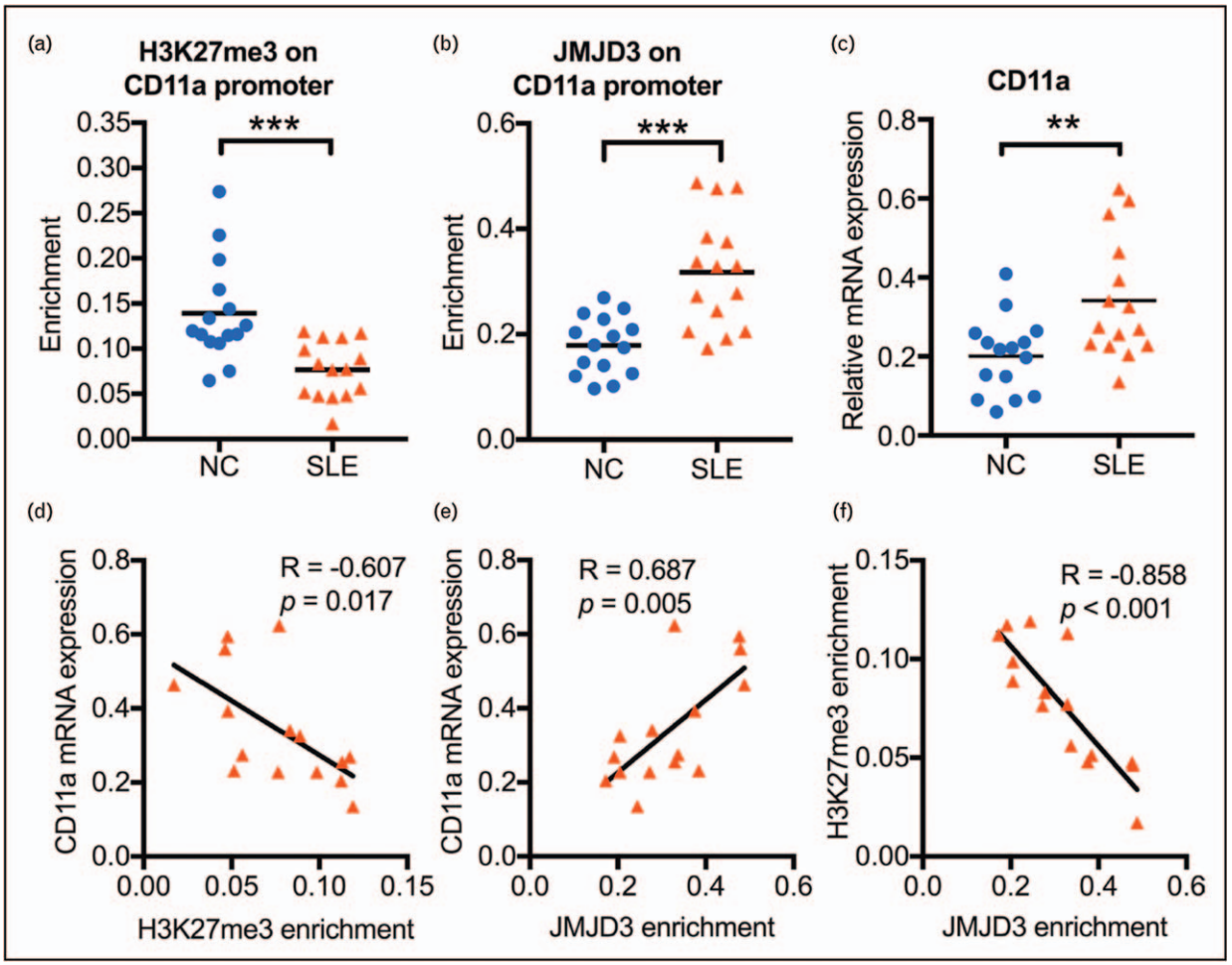

FIGURE 4. Regulation of CD11a gene expression by loss of the promoter repression mark H3K27me3 and increased JMJD3 in lupus CD4$^+$ T cells. (a, b) Relative enrichment of H3K27me3 and JMJD3 within the CD11a promoter. (c) CD11a gene expression in lupus and normal CD4$^+$ T cells. (d–f) Correlation analysis of H3K27me3 enrichment, JMJD3 enrichment, and CD11a mRNA expression levels. HeK27me3 and JMJD3 appear to have opposite effects on CD11a expression. Source: [64▪].

recent study took an integrative approach to analyze methylation, gene expression, and proteomic data from paired, intact, and degraded OA tissue chondrocytes [87▪▪]. This proof of concept study identified three differentially regulated genes namely, *AQP1*, *Col1A1*, and *CLEC3*, in intact and degraded chondrocytes in all three datasets. miRNA and lncRNA expression in OA chondrocytes have been shown to regulate genes involved in matrix degradation, chondrocyte homeostasis, and inflammation pathways [86]. Increased expression of HDACs 1, 2, and 7 has been observed in OA chondrocytes, which suggests that class-specific HDACi might be useful in OA therapy [88].

CONCLUSION

Epigenetics is still a relatively young field in rheumatic disease, but the data already implicate DNA methylation, noncoding RNA, and histone marks as key participants in disease mechanisms. Persistent epigenetic marks in cells suggests that they are imprinted, and the information can be mined to understand disease pathogenesis and the key pathways that contribute to inflammation and matrix destruction. These pathways could be leveraged to identify novel therapeutic targets that would not be readily apparent by simply reading the literature. Alternatively, epigenetic modulators that regulate DNMTs or HDACs could potentially remodel the chromatin and revert the imprinted cells to a more normal state. This intriguing possibility takes advantage of the plasticity in the distribution of marks and could help return a pathogenic cell to homeostasis.

Acknowledgements

None.

Financial support and sponsorship

This work was supported, in part, by grants from the Rheumatology Research Foundation and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (R01 AR065466).

Conflicts of interest

There are no conflicts of interest.

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REVIEW

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Mechanisms of vascular comorbidity in autoimmune diseases

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Purpose of review
Persuasive statistics support the clinical observation that because of cardiovascular comorbidities patients with inflammatory joint disease die significantly earlier despite anti-inflammatory therapy.

Recent findings
The reason for this earlier death is multifactorial and involves a combination of a complex genetic background, environmental influences, classical cardiovascular risk factors and the impact of anti-inflammatory therapy. We will describe the importance of several new mechanisms, especially the diverse intercellular communication routes including extracellular vesicles and microRNAs that support the development of cardiovascular comorbidities.

Summary
The aim of this review is to give an updated overview about the known risk factors in the development of cardiovascular comorbidities with the latest insights about their mechanism of action. Furthermore, the impact of newly identified risk factors and significance will be discussed.

Keywords
cardiovascular comorbidities, extracellular vesicles, microRNA, psoriatic arthritis, rheumatoid arthritis, systemic lupus erythematosus

INTRODUCTION

Before the appearance of the first disease-modifying drugs (DMARDs), the diagnosis of rheumatoid arthritis inevitably lead to a painful, progressive inflammatory arthropathy with joint erosion, deformation and loss-of-function. Nowadays with aggressive treatment (treat-to-target strategy), low disease activity or even remission have become realistic goals, improving the quality of life of these patients. Despite significant advances in treatment, patients die significantly earlier than the general population because of cardiovascular comorbidities, mostly in connection with accelerated atherosclerosis [1▪]. This clinical finding was underpinned by several epidemiological studies, which were followed by a new era of investigations aiming to understand the underlying pathophysiological mechanisms of this phenomenon. Lindhardsen *et al.* [2] examined the risk of acute myocardial infarction (AMI) in rheumatoid arthritis and stated that the risk of AMI was as high as the risk of AMI in patients with diabetes mellitus. Further results were recently published by Ruscitti *et al.*, presenting the results of a one-year prospective single centre study of patients suffering from rheumatoid arthritis. They quantified the increased risk for cardiovascular events (CVEs) and showed that the percentage of patients suffering a CVE and/or displaying subclinical atherosclerosis doubled within 12 months [3]. Another epidemiological study from Spain measured comorbidities in rheumatoid arthritis patients with a mean disease duration of 10 years and demonstrated a 51% prevalence of a Framingham Risk Score over 20%, resulting in a frequency of 5 and 1% of AMI and stroke, respectively [4▪].

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Curr Opin Rheumatol 2018, 30:197–206

DOI:10.1097/BOR.0000000000000483

KEY POINTS

- Despite significant improvements in the treatment of autoimmune diseases, patients die earlier than the general population, mainly because of cardiovascular comorbidities.
- Important new data are available about the complex interactions of genetic and environmental risk factors.
- Emerging data support the role of extracellular vesicles and microRNAs in the development of cardiovascular comorbidities.

With a mean follow-up of 5.8 years in an international cohort, diverse risk factors and CVD outcomes were collected from 5638 patients with rheumatoid arthritis and found that a total of 70% of CVD events were attributable to classical cardiovascular risk factors, Disease Activity Score and seropositivity combined. This demonstrates how important it is to closely monitor disease activity and cardiovascular risk factors in rheumatoid arthritis patients, but it also shows the need for defining the 'missing' 30% responsible for cardiovascular comorbidities [5].

The present review aims to summarize current knowledge about the contributing factors for cardiovascular comorbidities, from the genetic background and known cardiovascular risk factors through to the newest research results, highlighting particularly those related to extracellular vesicles, microRNAs (miRNAs) and their synergy, resulting in the higher morbidity and mortality rates in these patients.

GENETIC BACKGROUND OF CARDIOVASCULAR COMPLICATIONS IN AUTOIMMUNE JOINT DISEASE

The investigation of the genetic background of complex diseases is challenging. The search for genetic components for comorbidities of these autoimmune disorders (which are also of multifactorial origin) is even more challenging. The genetic basis of autoimmune joint disease is confirmed by classical genetic studies, for example twin and family studies [6]. A twin study conducted in 2000, which included over 13 000 twin pairs from Finland and the United Kingdom, estimated a contribution of genetic factors of around 60% [7].

A large number of candidate gene studies investigated the most different genes and their single nucleotide polymorphisms (SNP) in the development of cardiovascular comorbidities in patients with rheumatoid arthritis [8–10]. Starting points of candidate gene association studies are the physiology and pathophysiology of genes encoding for proteins with known function and their involvement in the development of a given phenotype. Thus, genetic loci are selected upon their potential biological function. There is a recent excellent summary of the results of these studies [1▪] showing that in addition to the well known HLA-DRB1* 01/04 shared epitope, several other genetic variants located inside and outside of the HLA region on the sixth chromosome may be of influence on the risk of cardiovascular disease (CVD) in rheumatoid arthritis. In addition, most variants outside the HLA region with a positive correlation to the elevated cardiovascular risk among rheumatoid arthritis patients on the basis of this review, are connected to genes encoding for proteins of cells and molecules of the immune system, including the tumor necrosis factor (TNF) superfamily genes, cytokines and related genes, chemokines, or adipokines [1▪]. Furthermore, correlations have also been found with variants of genes involved in nitric oxide synthesis [11] and vitamin D levels [12]. Finally, there are some additional exciting potential associations with other, seemingly unrelated genes, such as *MTHFR*, important in the homocysteine plasma level homeostasis [13].

Ten genes (*CRP, HNF1A, LEPR, GCKR, NLRP3, IL1F10, PPP1R3B, ASCL1, HNF4A,* and *SALL1*) known to have an impact on the serum level of CRP in nonrheumatic Caucasians were genotyped in rheumatoid arthritis patients. It was assessed whether they were of influence on the development of CVEs and subclinical atherosclerosis in this special clinical subgroup. Interestingly, no association could be shown between these genes and CVEs in rheumatoid arthritis [14].

CLASSICAL RISK FACTORS OF CARDIOVASCULAR DISEASES ARE MORE COMMON AMONG PATIENTS WITH AUTOIMMUNE DISORDERS

Smoking

Smoking is a well known risk factor of both autoimmune diseases and accelerated atherosclerosis. In autoimmune diseases, smoking was shown to modulate the immune system in various ways, namely the induction of the inflammatory response, alteration of cytokine balance, induction of apoptosis, and DNA damage resulting in the formation of anti-DNA antibodies [15]. There are a variety of studies that have addressed this area [16–18]. The harmful effect of smoking has been described in early atherogenesis especially on endothelial cells [19]. Effects are mediated through low NO bioavailability, followed by increased adhesion molecule expression and

subsequent endothelial dysfunction. A procoagulant and inflammatory milieu is generated by the increased adherence of platelets and macrophages. Macrophages migrate under the endothelial cells, take up oxidized lipoproteins and transform into foam cells.

Several studies reported interactions between smoking and different factors that are predictive of the cardiovascular outcome [rheumatoid factor; anti-citrullinated protein antibodies (ACPA) positivity, rheumatoid nodules, anti-TNF treatment, rheumatoid cachexia] [20]. This complicates the estimation of the extent of contribution of smoking to cardiovascular risk in patients with rheumatoid arthritis. Importantly, not only smoking, but also second-hand (passive) smoking has an impact on disease activity in women with rheumatoid arthritis [21▪].

Insulin resistance

Despite the updated recommendations from European League Against Rheumatism (EULAR) for the management of cardiovascular risk factors in patients with inflammatory arthritis, type 2 diabetes (T2D) is still underdiagnosed und undertreated. Ruscitti *et al.* [22] claim the poor clinical response for this as the main risk factor. A recent cross-sectional study demonstrated that the prevalence of both T2D and impaired fasting glucose (IFG) was higher in patients with rheumatoid arthritis compared with age-matched and sex-matched controls [23]. Furthermore, they were associated with both rheumatoid arthritis-specific features and traditional cardiovascular risk factors [23].

Dyslipidaemia

Adverse changes in the lipid profile are one of the main risk factors of cardiovascular morbidity and mortality. However, it is not evident to which level targeting the different lipoprotein subpopulations reduces the risk of CVEs. In a recently published prospective study based on data from over 50 000 patients with hypertension, dyslipidaemia or diabetes mellitus, an association was found between high-density lipoprotein (HDL)-cholesterol, total/HDL-cholesterol and triglyceride/HDL-cholesterol ratios, and a higher risk for CVD, in contrast to other common lipid profile biomarkers [24]. Recent observations show that small dense low-density lipoprotein (LDL) particles (sdLDL) are elevated not only in diverse metabolic disorders, but also in rheumatoid arthritis and psoriatic arthritis (PsA) [25]. This lipoprotein subgroup is especially important as it seems to be particularly atherogenic, and seems to be a good predictor of significant coronary artery stenosis. This is because of its high susceptibility to oxidation, high endothelial permeability, and decreased LDL receptor affinity [26].

Sudden cardiac death is twice as common among rheumatoid arthritis patients as in the general population. Regarding this, the importance of close lipid management is highlighted by the recent results of Turk *et al.* [27], showing a close relationship between prolonged QRS time and elevated total cholesterol.

Arterial hypertension

A study of cross-sectional design with multistage sampling, involving 2455 Chinese hypertensive patients, clearly demonstrated the importance of patient compliance. The percentage of non-compliant patients and the rate of suboptimal blood pressure control were both above 45%. In addition, multimorbidity was also more frequent in these patients, accentuating the importance of more clinical attention to this subgroup of patients [28▪▪].

Among classical cardiovascular risk factors, hypertension has the highest incidence and prevalence both in rheumatoid arthritis (74 cases per 1000 patient-years; 18.6% of patients) and psoriatic arthritis (79.8 cases per 1000 patient-years; 19.9% of patients) [29]. Not only blood pressure itself but arterial inflammation is more prevalent in patients with rheumatoid arthritis and is independently associated with both traditional cardiovascular risk factors and rheumatoid arthritis-disease characteristics [30▪▪].

Another important aspect of close cardiovascular risk management is demonstrated in a recent analysis of retrobulbar blood flow and choroidal thickness of rheumatoid arthritis patients, which showed a significantly higher peak systolic velocity of the ophthalmic and central retinal artery in rheumatoid arthritis patients compared with healthy controls [31].

Physical activity

Carlsson *et al.* stimulated peripheral blood mononuclear cells from children with high versus average physical activity. The authors found that high physical activity was associated with lower immune reactivity toward autoantigens GAD65, HSP60, and IA-2 and also with lower spontaneous pro-inflammatory immune activity [32▪].

However, physical activity in juvenile idiopathic arthritis (JIA) patients can be a double-edged sword as at times of acute flare, exercise may be very painful for these patients. Also, physical activity may exacerbate underlying inflammatory

processes. Through exercise, the secretion of various hormones, miRNAs, and peptides are influenced and it seems that muscle cell-derived IL-6 has a central role in the fine balancing of anti-inflammatory and pro-inflammatory cytokines [33].

Hyperhomocysteinaemia

Taking into consideration that the risk for cardiovascular comorbidities is still underestimated in patients with rheumatoid arthritis, it is thought-provoking that in the *Journal of Rheumatology* in 1998, attention had already been drawn to the importance of folic acid supplementation to prevent folate deficiency and hyperhomocysteinaemia and, if necessary, to prevent Methotrexate (MTX) toxicity [34]. Essouma and Noubiap [35] emphasized the importance of the bidirectional link between immunoinflammatory activation and hyperhomocysteinaemia. Hyperhomocysteinaemia may lead to nuclear kappa B enhancement and vice versa, chronic immune activation causes hyperhomocysteinaemia through vitamin B (including folic acid) depletion. The authors also underline the importance of folic acid supplementation in preventing cardiovascular complications in rheumatoid arthritis [35]. In cutaneous lupus erythematosus, the level of homocysteine is correlated with disease severity [36]. The C677T polymorphism in the *MTHFR* gene, important in the re-methylation of homocysteine, varies depending on geography and ethnicity [37].

Vitamin D level

The CIMESTRA trial has recently shown the importance of optimal vitamin D serum levels in patients with rheumatoid arthritis. The study found that low baseline vitamin D metabolite levels associate with long-term CVEs in patients suffering from rheumatoid arthritis [38▪]. Neuropathic pain is often a therapeutic challenge in chronic inflammatory diseases. In a recent cross-sectional study, patients suffering from rheumatoid arthritis filled out the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) questionnaire and their serum vitamin D levels were measured. An association was shown between low-serum vitamin D levels and increased neuropathic pain, which underlines again the importance of optimal vitamin D serum levels [39].

Obstructive sleeping apnoea

A current population-based study showed that obstructive sleep apnoea has a higher incidence in patients with rheumatoid arthritis as compared with age-matched and sex-matched controls. Considering the importance of obstructive sleep apnoea in predicting the future CVD risk, it may be important to screen patients for obstructive sleep apnoea [40▪].

Diet

The higher risk of cardiovascular comorbidities among patients with inflammatory joint disease consuming higher amounts of sodium is not the only consequence: sodium has an impact on the Th17 pathway activation and it can, thus, promote autoimmunity. A recent study shows an increased sodium excretion in patients with early rheumatoid arthritis [41]. Not only in-vitro evidence shows an anti-inflammatory effect of *trans*-resveratrol, the major cardioprotective component of red wine, but in preclinical models of osteoarthritis and rheumatoid arthritis. A joint protective effect through decreased production of pro-inflammatory and pro-degenerative soluble factors of *trans*-resveratrol was shown [42]. Fish consumption seems to be protective not only in decreasing the CVD risk through, for example, lowering triglycerides and increasing HDL serum levels [43], but has also been shown to impact on rheumatoid arthritis, associated with lower disease activity [44].

INFLAMMATION

Neutrophil to lymphocyte ratio is not only a reliable marker for inflammation in neoplastic and cardiovascular disorders, but a recent study shows its reliability also for disease activity in rheumatoid arthritis [45]. Low disease activity, defined by a disease activity score (DAS, 28) lower than 3.2 results in a reduced risk in cardiovascular complication in patients suffering from rheumatoid arthritis [46▪]. The magnitude and period of time of elevated CRP serum levels correlates with an increased risk of cardiovascular complications in rheumatoid arthritis [47]. Myocardial infarction is one of the main complications of accelerated atherosclerosis in rheumatoid arthritis patients and CRP serum level is also associated with AMI [48]. Thus, Meissner *et al.* declare that it is seemingly irrelevant which DMARD is administered but the goal must be the quickest effective disease control.

Symmetric dimethylarginine (SDMA) and asymmetric dimethylarginine (ADMA) emerge as novel biomarkers of CVDs. Their levels are also abnormal in patients with rheumatoid arthritis. Dimitroulas *et al.* [49] analyzed their presence in

rheumatoid arthritis patients and the results revealed that these molecules may promote endothelial injury in rheumatoid arthritis patients as a result of systemic inflammation during active disease periods.

DOES TREATMENT INFLUENCE CARDIOVASCULAR RISK?

Treatment of inflammatory joint disease should aim to reduce the cardiovascular risk accompanied with the disease, which is best achieved with a treat-to-target approach [50]. This is underpinned by a time-dependent Cox regression analysis of the Nijmegen early rheumatoid arthritis inception cohort, which showed that low disease activity was significantly associated with reduced risk of first CVE [46▪]. The effect of glucocorticosteroids on the cardiovascular risk is still questionable. On the one hand, glucocorticosteroid-induced hypertension, insulin resistance, and metabolic effects (especially insulin resistance and obesity) increase the cardiovascular risk, but on the other hand, attenuating inflammation is beneficial [51,52]. Nonsteroidal anti-inflammatory drugs (NSAIDs) increase the risk of CVD in the general population; diclofenac has a similar cardiovascular risk to rofecoxib [53]. The cardiovascular safety profile of COX2 selective and nonselective NSAIDs in rheumatoid arthritis and osteoarthritis was recently published; celecoxib was found to be noninferior to naproxen or ibuprofen in this study [54]. NSAIDs, especially COX2 inhibitors, increase the cardiovascular risk in rheumatoid arthritis [51].

Probably because of a blood pressure lowering and anti-inflammatory effect, methotrexate therapy seems to decrease the cardiovascular risk in rheumatoid arthritis [55].

Although TNF inhibitors frequently increase the total cholesterol, triglyceride, HDL and LDL cholesterol levels, accumulating evidence suggest the beneficial effect of these biologicals on cardiovascular risk [51]. Interestingly, whenever compared with TNF inhibitors, tocilizumab is associated with an even higher increase in blood cholesterol and triglyceride levels [56]. A recently published multidatabase cohort study suggests that the cardiovascular risk of rheumatoid arthritis patients treated with tofacitinib versus TNF inhibitors is similar [57]. These observations suggest that glucocorticosteroids and NSAIDs should be tapered as soon as possible. Appropriate combinations of synthetic and biological DMARDs, in addition to optimizing lipid levels and hypertension, may provide the best cardiovascular outcome in rheumatoid arthritis.

NEW PARTICIPANTS IN THE COMPLEX BACKGROUND OF CARDIOVASCULAR COMORBIDITIES IN AUTOIMMUNE DISEASES: EXTRACELLULAR VESICLES

In addition to cytokines and chemokines, extracellular vesicles are new mediators of intercellular communication [58]. Extracellular vesicles are highly diverse, heterogeneous, membrane-surrounded, subcellular structures that can be found in all body fluids. Currently, there is no molecular marker or marker panel that precisely discriminates extracellular vesicle subpopulations; based on their size, extracellular vesicles can be classified as small extracellular vesicles/exosomes (30–150 nm), intermediate sized extracellular vesicles/microvesicles/microparticles (100–1000 nm) and large extracellular vesicles such as apoptotic bodies (1–5 μm). Extracellular vesicles may target both neighbouring or remote cells, and by transferring DNA, RNA or proteins, extracellular vesicles may regulate multiple functions of target cells [58,59].

Extracellular vesicles are secreted by all human cells; blood-derived extracellular vesicles mainly originate from platelets, red blood cells, monocytes, lymphocytes, granulocytes, and endothelial cells. In addition to their broad physiological functions, extracellular vesicles play a central role in the pathogenesis of several diseases including cardiovascular and immunological conditions [60,61]. Although the lack of standardized isolation and characterization methods still hampers the widespread use of extracellular vesicles as diagnostic and prognostic biomarkers, a characteristic extracellular vesicle profile has been described in autoimmune diseases [60,62]. Increased levels of both phosphatidylserine-positive and phosphatidylserine-negative microvesicles, without association with the disease activity, was recently described in SLE [63].

Numerous observations support the multifaceted role of extracellular vesicles in CVD as well [64▪]. Extracellular vesicles have been claimed to promote plaque stability [65]. Small extracellular vesicles containing insulin-like growth factor 1 receptor (IGF-1R) and miR-29a have been found to have a cardioprotective effect in rats [66]. On the other hand, mainly platelet-derived human microvesicles are thrombogenic [67]. Elevated levels of endothelial cell-derived and platelet-derived extracellular vesicles were observed in acute coronary syndrome [68]. Interestingly, according to recently published observations, although smoking promoted both extracellular vesicle release by leukocytes, platelets and endothelial cells, and vascular inflammation, these effects were prevented by red wine [69]. Extracellular vesicles may also significantly modulate the effect of cytokines [70].

A highly unexpected observation was recently found by Sodar *et al.* [71], namely that LDL mimics

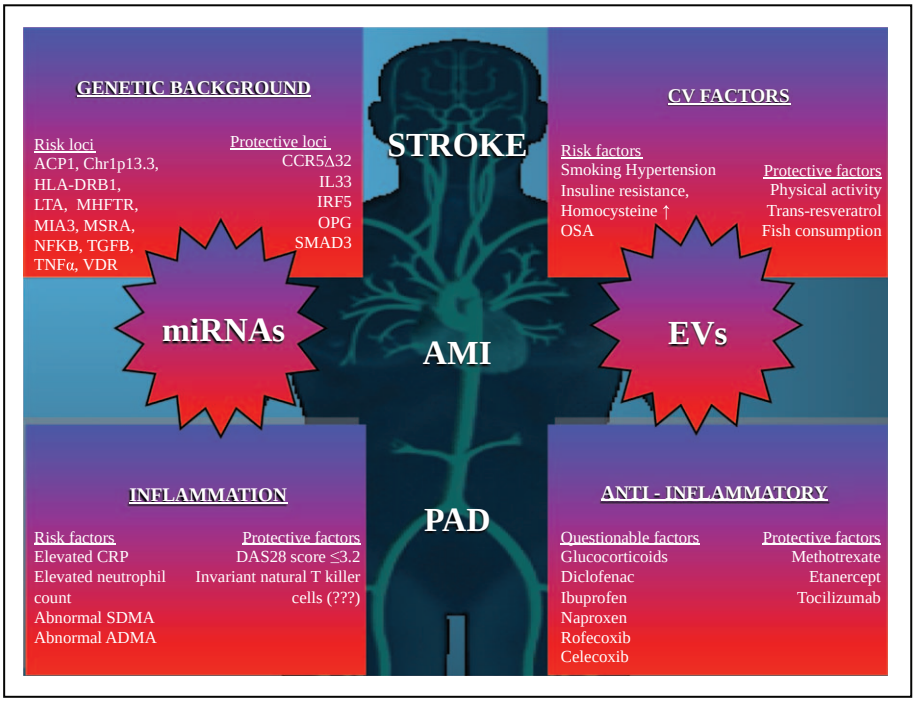

FIGURE 1. The figure demonstrates the known factors to our best current knowledge being of influence on the development of cardiovascular comorbidities such as stroke, acute myocardial infarction or peripherial arterial disease. PAD, peripherial arterial disease.

extracellular vesicles derived from blood plasma and may be copurified, which underlines their potential role whenever examining factors contributing to the development of CVD in rheumatic conditions/disorders.

Although there is little direct evidence, these data strongly support the potential role of extracellular vesicles in vascular comorbidity of autoimmune diseases. Extracellular vesicles may provide a link between inflammation and thromboembolic risk (Fig. 1).

ANOTHER NEW PARTICIPANT: MICRORNAS

Estimates show that as high as 10–30% of protein coding genes are regulated by micro-RNAs [72], which are small regulator RNA molecules composed of 21–24 nucleotides. Salmena *et al.* [73] introduced the term 'competing endogenous RNAs,' describing the complex communication system between the different subtypes of RNA molecules. During CD4 T-cell activation, posttranscriptional urydylation by the enzymes TUT4 and TUT7 are responsible for the fine tuning of miRNA levels [74]. MiRNAs are relatively stable molecules and their measurement is reliably reproducible [75]. It also now known that the most diverse illnesses are all characterized by specific changes in the miRNA profile, which makes them a very promising tool for diagnostic purposes [76,77].

Serum miR-210 and miR-155 levels could be shown to be reliable biomarkers for the diagnosis of rheumatoid arthritis [78]. There have been studies looking for miRNA biomarkers for subclinical atherosclerosis in rheumatoid arthritis, but until now only little or no association was found, whenever assessing miR-15a-5p, miR-24-3p, miR-26a-5p, miR-125a-5p, miR-146a-5p, miR-155-5p, and miR-223-3p [79].

An interesting link between different risk factors was found in a study measuring vitamin D levels in SLE patients and correlating them with certain miRNA levels in patients' T cells. An association between vitamin D concentrations and measured miRNA levels (miRNA-377, miRNA-342, miRNA-10a, miRNA-374b, miRNA-125a, and miRNA-410) was observed – not only comparing SLE patients with healthy controls, but also between patients differing in their vitamin D serum levels and also in cultured T cells from SLE patients, wherever the correlation was dose-dependent and time-dependent [80▪▪].

COOPERATION OF DIFFERENT MESSENGERS? EXTRACELLULAR VESICLES TRANSPORT IMPORTANT MICRORNAS

In atherosclerosis, Nguyen *et al.* [81▪▪] have demonstrated that extracellular vesicles originating from

Table 1. List of risk factors influencing the development of cardiovascular comorbidities in inflammatory joint diseases

Factors	Effect	References
Genetic background		
ACP1 – ∗C haplotype	Risk factor	Teruel *et al.* [84]
CCR5Δ32	Protective factor	Rodrígúez-Rodríguez *et al.* [85]
Chr1p13.3 – rs599839 – G allele	Risk factor	López-Mejías *et al.* [86]
HLA-DRB1*01*04	Risk factor	Mattey *et al.* [87]
IL33 – rs3939286 – T allele	Protective factor	López-Mejías *et al.* [88]
IRF5 – GTG haplotype	Protective factor	Garcia-Bermúdez *et al.* [89]
LTA – 252GG	Risk factor	Panoulas *et al.* [90]
MHFTR – rs1801131 – C allele	Risk factor	Abd El-Aziz *et al.* [91]
MIA3 – rs17465637 – A allele	Risk factor	Garcia-Bermúdez *et al.* [92]
MSRA – rs10903323 – G allele	Risk factor	Garcia-Bermúdez *et al.* [93]
NFKB – rs28362491 – -94ATTG ins/del	Risk factor	López-Mejías *et al.* [94]
OPG – CGA haplotype	Protective factor	Genre *et al.* [95]
SMAD3 – rs17228212 – C allele	Protective factor	Garcia-Bermúdez *et al.* [96]
TGFB – rs1800470TC	Risk factor	Chen *et al.* [97]
TNFα – rs1800629 – A allele	Risk factor	Rodríguez-Rodríguez *et al.* [8]
VDR – GATG haplotype	Risk factor	López-Mejías *et al.* [12]
ZC3HC1 – rs11556924 – TT genotype	Risk factor	Lopez-Mejias *et al.* [98]
Classical cardovascular risk factors		
Smoking	Risk factor	Murphy *et al.* [20]
Insulin resistance	Risk factor	Ruscitti *et al.* [22]
Dyslipidaemia	Risk factor	Gerber *et al.* [25]
Arterial hypertension	Risk factor	Radner *et al.* [29], Geraldino-Pardilla *et al.* [30▪▪]
Physical activity	Protecting factor	Carlsson *et al.* [32▪], Antunes *et al.* [33]
Hyperhomocysteinaemia	Risk factor	Morgan *et al.* [34], Essouma and Noubiap [35]
Low baseline vitamin D level	Risk factor	Herly *et al.* [38▪]
Obstructive sleeping apnoe	Risk factor	Wilton *et al.* [40▪]
Sodium intake	Risk factor	Marouen *et al.* [41]
Trans-resveratrol	Protective factor	Nguyen *et al.* [42]
Fish consumption	Protective factor	Alhassan *et al.* [43], Tedeschi *et al.* [44]
Therapy		
Corticostreoids	Complex effect	Roubille *et al.* [51], van Sijl *et al.* [52]
NSAIDs		
Celecoxib	Complex effect	Nissen *et al.* [54]
Naproxen	Complex effect	Nissen *et al.* [5]
Ibuprofen	Complex effect	Nissen *et al.* [54]
Methotrexate	Protective factor	Mangoni *et al.* [55]
TNF inhibitors	Protective factor	Roubille *et al.* [51]
Tocilizumab	Complex effect	Gabay *et al.* [56], Kim *et al.* [57]
New modalities		
Extracellular vesicles	Complex effect	No publication yet
miRNAs	Complex effect	No publication yet

atherogenic macrophages transfer certain miRNAs (in particular miR-146a). The important role of miRNA-126-3p and miRNA-126-5p, transferred by extracellular vesicles originating from endothelial cells after AMI, was also demonstrated by Akbar *et al.* [82] and showed that these messengers promote the

recruitment of transcriptionally activated splenic monocytes to the heart.

Systematic characterization of microvesicles and exosomes derived from T lymphocytes of healthy and SLE patients revealed that, depending on stimuli, extracellular vesicles carry a specific RNA profile and a deregulation of miR-155*, miR-34b, and miR-34a could be shown. This again underlines the importance of intercellular communication via extracellular vesicles and miRNAs in autoimmune diseases [83▪▪].

CONCLUSION

Cardiovascular comorbidities of autoimmune diseases are the result of different contributing factors and their synergistic effects

The present review contains numerous studies investigating multiple independent risk factors of cardiovascular comorbidities in autoimmune diseases, focusing on conditions involving the joints. We wish to underline the complex interactions and the importance of their total effect on the phenotype discussed in this review ([84–98]; Table 1). Our suggestion is to focus on new mechanisms emerging, especially the common intercellular communication system of extracellular vesicles and miRNAs as no study yet considers these factors together in the development of cardiovascular comorbidities in patients with inflammatory joint disease.

Acknowledgements

The authors would like to thank gratefully to David Darling for his valuable constructive comments.

Financial support and sponsorship

This work was supported by the National Research, Development and Innovation Fund of Hungary; with the following grants NVKP_16-1-2016-0017, OTKA NN 111023, OTKA-119459, PD-OTKA-121187, OTKA-111958 and OTKA-120237, Medinprot Synergy V grant, NKM-69/2016/CNR-HAS Joint Project 2016–2018 'NutriCargo: Characterization of plant secreted nanovesicles', B66D16000360005; VEKOP-2.3.3-15-2016-00016 and VEKOP-2.3.2-16-2016-00002.

Conflicts of interest

There are no conflicts of interest.

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- ▪▪ of outstanding interest

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REVIEW

OPEN

What are the dominant cytokines in early rheumatoid arthritis?

Laura A. Ridgley, Amy E. Anderson, and Arthur G. Pratt

Purpose of review
Rheumatoid arthritis is a systemic disease of evolving immune dysregulation that culminates in joint destruction and disability. The principle by which pro-inflammatory cytokines may be therapeutically targeted to abrogate disease is well established, but has yet to translate into reliable cures for patients. Emerging insights into cytokine-mediated pathobiology during rheumatoid arthritis development are reviewed, and their implications for future treatment strategies considered.

Recent findings
Accumulating data highlight cytokine perturbations before the clinical onset of rheumatoid arthritis. Some of these have now been linked to the arthritogenic activation of autoantibodies and associated pain and bone destruction in affected joints. These observations suggest cytokines may trigger the transition from systemic immunity to arthritis. Cytokine exposure could furthermore 'prime' synovial stromal cells to perpetuate a dominant pro-inflammatory environment. By facilitating cross-talk between infiltrating immune cells and even sustaining ectopic lymphoid structure development in some cases, cytokine interplay ultimately underpins the failure of arthritis to resolve.

Summary
Successful therapeutic stratification will depend upon an increasingly sophisticated appreciation of how dominant players amongst cytokine networks vary across time and anatomical space during incipient rheumatoid arthritis. The prize of sustained remission for all patients justifies the considerable effort required to achieve this understanding.

Keywords
chemokine, cytokines, interleukin, pathogenesis, rheumatoid arthritis

INTRODUCTION

Rheumatoid arthritis is a systemic inflammatory disease that primarily affects the synovial joints, and for which there is no known cure. Its heterogeneity, instantly recognizable to clinicians in the variability of its clinical presentation, is multilayered, confounding a unified description of pathogenesis. In particular, the concept that distinct subtypes of the syndrome are delineated by the presence or absence of circulating antibodies to citrullinated peptides (ACPAs) has gained traction recently [1,2]. In ACPA 'seropositive' disease, elegant epidemiological and translational work converges on a stepwise model for disease development [1] in which cigarette smoke exposure, other environmental effects and the microbiome act as principal risk factors for autoantibody development long before symptom onset [3–5]. Genetically determined amino acid sequences in the MHC binding groove of antigen presenting cells then gain influence in driving accelerated autoimmunity and the transition to arthritis in at-risk individuals [1,6]. Mechanisms behind the development of seronegative rheumatoid arthritis remain far less well understood, its heritability and association with smoking both apparently modest by comparison, but a recent familial aggregation study suggests the

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Curr Opin Rheumatol 2018, 30:207–214

DOI:10.1097/BOR.0000000000000470

KEY POINTS

- An increasingly sophisticated appreciation of how 'dominant' players within cytokine hierarchies may vary over time, across tissue boundaries and between individuals during incipient rheumatoid arthritis is now emerging
- Abnormal levels of pro-inflammatory and Th2-related cytokines are found in the circulation prior to symptom onset.
- New roles for cytokines of the IL-23/Th17 axis, type I interferons and IL-8 have been suggested in the progression of ACPA-positive arthralgia.
- An 'imprinted' pathological phenotype of stromal cells in the joint appears to respond aberrantly to cytokine stimuli at a critical phase in rheumatoid arthritis development.
- Pro-inflammatory mediators such as TNF, IL-6 and GM-CSF drive persistent synovitis and the systemic complications of rheumatoid arthritis.

aetiological overlap between these serotypes may be more important than yet fully appreciated [7]. Running through this complex backdrop of disease initiation, and orchestrating the common phenotype of persistent synovial hyperplasia, immune cell infiltration and joint destruction that ensues, the fundamental importance of cytokines in rheumatoid arthritis pathogenesis is long established (Table 1).

Cytokines are typically secreted by leukocytes to exert paracrine or autocrine effects, thereby regulating such diverse functions as cellular differentiation, activation, migration and survival. Exhibiting pleiotropy individually and synergy or redundancy in concert, the sensitivity of their combinatorial networks to perturbation is exquisite, and their individual potential for exploitation as therapeutic targets well recognized. Blockade of signalling by pro-inflammatory cytokines, such as tumour necrosis factor (TNF) and interleukin-6 (IL-6), using monoclonal antibodies has revolutionized outcomes for patients with severe rheumatoid arthritis but, in common with all currently available biologics, these drugs remain subject to a 'therapeutic ceiling', with true remission unattainable for the majority. Replicating even this degree of success in the clinic has proved difficult in clinical trials of alternative agents, for example blocking IL-1β, IL-17 and the IL-12/23 family in rheumatoid arthritis – despite their attractiveness as targets [8–10]. Rather than being interpreted as evidence that these cytokines are pathogenetically unimportant, such setbacks should prompt a more nuanced critique of our current therapeutic approach. An increasingly sophisticated appreciation of how 'dominant' players within cytokine hierarchies may vary over time, across tissue boundaries and between individuals during incipient rheumatoid arthritis is now emerging (Fig. 1). Developing and harnessing this understanding, perhaps guided by judicious sampling of blood or tissue at an individual patient level to more rationally map therapeutic strategies to disease endotypes, should one day pay dividends in the clinic. The present review will show how recent insights into the role of cytokines in the earliest stages of rheumatoid arthritis have advanced this endeavour.

CYTOKINES AS COORDINATORS OF PRE-CLINICAL RHEUMATOID ARTHRITIS

Genes encoding functional components of the immune system are enriched within loci associated with the development and natural history of rheumatoid arthritis; protein products pathogenetically implicated include cytokines themselves [IL-2, IL-21, G-CSF and granulocyte macrophage-colony stimulating factor (GM-CSF)], their receptor components [for IL-6, IL-20, interferon (IFN)-γ and IL-2] and elements of their downstream signalling machinery (e.g. TYK2, STAT4 and TNFAIP3). The range of epigenetic and other mechanisms via which such variants might disrupt cytokine homeostasis to confer disease risk is only beginning to be understood, together with an appreciation that they will best be dissected at a cellular level in relevant disease contexts [11,12]. This becomes pertinent when considering measurable alterations in a number of circulating cytokines that have, with some consistency, been observed prior to symptom onset amongst those who subsequently develop rheumatoid arthritis compared with healthy individuals. These include increased pro-inflammatory examples (TNF, IL-6, IL-1β and/or IL-1RA, GM-CSF) as well as IL-4, IL-12, IL-17 and the eosinophil chemotactic chemokine, eotaxin (Table 1). Against a facultative genetic background, such mediators may variously arise from the paucicellular joint itself, bone marrow or elsewhere in the periphery, but their presence reinforces the likely contribution of cytokines to systemic and general immune dysregulation prior to overt synovitis. In a recent study interrogating serum analyte profiles of ACPA seropositive patients with joint pain (arthralgia), the discriminatory value of the Th2-specific cytokine IL-5 for rheumatoid arthritis progression was highlighted [13▪]. Together with the elevated circulating IL-4 and eotaxin mentioned above, these data recall much earlier observations of transient Th2

Table 1. Overview of cytokines with established and emerging roles in early rheumatoid arthritis pathogenesis

Cytokine	Typical cellular source(s)	Cellular target(s) [and effect(s)]	Proposed role(s) in rheumatoid arthritis	Targeting strategy/ies
TNF	Monocytes/ macrophages.	SFs (pro-inflammatory cytokine production) Osteoclasts (differentiation, activation) Endothelium (neovascularization) - Lymphocytes (Treg inhibition)	Pro-inflammatory Bone erosion Systemic (?fatigue)	Anti-TNF (infliximab[a], adalimumab[a], golimumab[a], cerolizumab[a]), TNFR (etanercept[a]).
IL-6	Monocytes/ macrophages, stroma/SFs	SFs (activation, proliferation) Macrophage (osteoclast differentiation) T cells (proliferation, survival, Th17 differentiation) B cells (survival, antibody production). Hepatocytes (acute phase reactants)	Pro-inflammatory Systemic (atherosclerosis, impaired lipid metabolism, anaemia)	Anti-IL-6R (tocilizumab[a], sarilumab), anti-IL-6 (sirukumab)
IL-1α/β	Monocytes/ macrophages, DCs	Osteoclasts (activation) T cells (Th17 differentiation) Endothelium (vasodilation) Autocrine (pro-inflammatory)	Pro-inflammatory (contributory rather than dominant role)	IL-1RA (anakinra), anti-IL-1β (canakinumab).
IL-17A/F	Th17 cells, neutrophils, ILCs, iNKT cells.	SFs (proliferation, pro-inflammatory cytokine production, including IL-6) - Chondrocytes (metalloproteinase induction) Myeloid cells/neutrophils (chemotaxis) Endothelium (neovascularization)	Pro-inflammatory (?contributory *versus* dominant role depending on disease subset)	Anti-IL-17A (secukinumab), anti-IL-17RA (brodalumab).
IL-23	Macrophages, DCs	Th17 cells (development, maintenance and expansion; IL-21/IL-22 induction)	Th17 responses	Anti-p40 (common subunit of IL-23/12; ustekinumab), anti-IL-23 (guselkumab)
IL-21	Th17 cells, Th2 cells, NK cells, Tfh cells.	B-cell maturation, plasma cell development/antibody production	?Role in arthritogenic autoantibody glycosylation (Ref [16])	Anti-IL-21 in development
IL-12	Macrophages, DCs	Th1 cells (differentiation, autocrine)	?Cell-mediated immune resposes, Th17 plasticity.	Anti-p40 (common subunit of IL-23/12; ustekinumab)
GM-CSF	Monocytes/ macrophages, lymphocytes, stroma/ SFs	Myeloid cells (differentiation/ proliferation) Macrophages (pro-inflammatory phenotype) DCs (activation)	Pro-inflammatory, ?Pain	Anti-GM-CSF-Rα (mavrilimumab)
Th2 cytokines	Th2 cells, mast cells	Various	Awaits clarification [13▪,14,15]	Strategy to be determined.
Type I interferons	Plasmacytoid DCs	$CD8^+$ T cells and NK cells (cytotoxicity) Th1 polarization B cells (differentiation; IgG class-switching)	?pathogenesis of seropositive disease [16]	Anti-IFNα (sifalimumab)
IL-8 (CXCL8)	Macrophages, epi/ endothelial cells. Osteoclasts (?response to autoantibodies)	Neutrophils, leukocytes (chemotaxis) Osteoclasts (activation, including autocrine)	Leukocyte chemotaxis ?Bone erosion/pain in 'pre-RA' [19▪▪]	CXCR1/2 inhibitor (reparixin)

Typical cellular sources and effects in target cells are listed, and broadly accepted roles in rheumatoid arthritis pathogenesis are summarised, along with available/potential therapeutic targeting strategies (exemplar originator agents named).
[a]Only asterisked agents are currently licensed for use in rheumatoid arthritis). Less established roles indicated by '?' GM-CSF, granulocyte macrophage-colony stimulating factor; DC, dendritic cell; ILC, innate lymphoid cell; NK, natural killer; SF, synovial fibroblast.

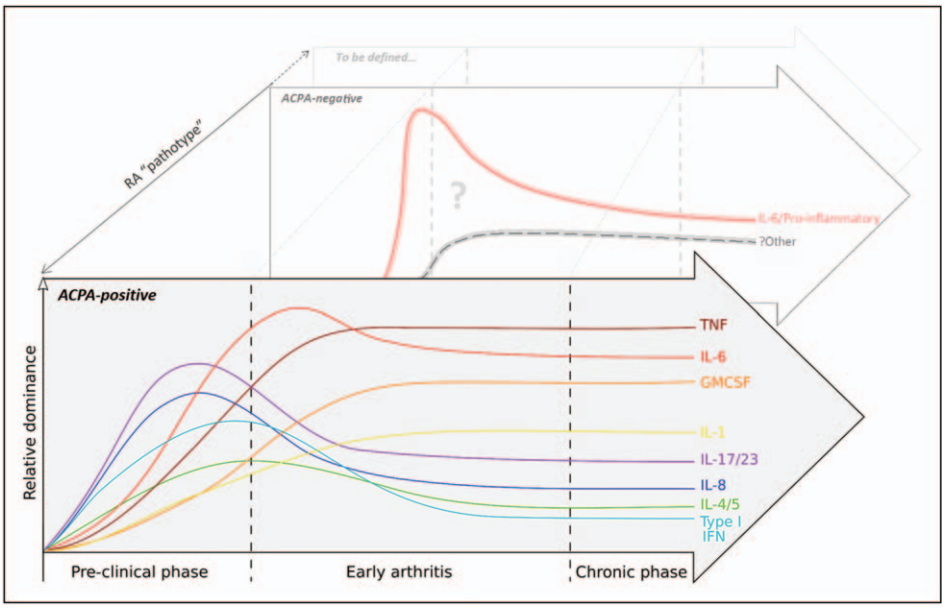

FIGURE 1. The hierarchical dominance of cytokines during rheumatoid arthritis development is dynamic. Recent insights permit a speculative depiction of how individual cytokines may exhibit distinct and evolving patterns of relative importance, even during the earliest phases of ACPA-seropositive rheumatoid arthritis. Whilst pro-inflammatory cytokines are clearly important drivers of seronegative disease, a paucity of equivalent data for this subset currently precludes a similarly granular representation of this or other, as yet undefined, rheumatoid arthritis 'pathotypes'.

cytokine profiles in synovial fluid of early seropositive synovitis patients who progressed to rheumatoid arthritis [14]. Th2 effector responses protect against inflammatory arthritis in certain contexts [15], and the extent to which such observations reflect 'failed regulation' or merely emphasize the role of humoral responses during preclinical rheumatoid arthritis remains to be clarified (Table 1).

The functional diversity of cytokines found in the circulation of individuals at risk of rheumatoid arthritis may be simplest to rationalize by viewing serum merely as a conduit between distant tissue sites, each harbouring an immunologically discrete niche; in acknowledgment of this it was proposed that measuring circulating mediators *en masse* to derive a summary 'cytokine score' for disease prediction might be their most practical application [16]. Nonetheless, examples of how specific cytokines actively shape antibody-mediated autoimmunity in the run-up to clinically manifest rheumatoid arthritis are now emerging. In the case of the IL-23-Th17 axis their propensity to do so appears greater during this 'prearticular' phase than after synovitis has developed (Fig. 1). Hence, recent data from mouse models of autoimmune arthritis show that IL-23-activated Th17 cells can, via IL-21 and IL-22, 'programme' germinal centre plasmablasts and plasma cells to alter the Fc glycosylation profile of secreted IgG autoantibodies [17▪▪]. Reduced terminal glycan sialylation at the asparagine-297 position thereby augments autoantibody affinity for osteoclast Fc receptors, impacting their propensity to localize to the joint and mediate bone loss [18]. Critically, these changes in autoantibody glycosylation directly mirror those seen to occur in circulating ACPAs of seropositive patients as their arthritis develops [17▪▪]. Recent experiments also support a nonredundant role for IL-8 in ACPA-mediated osteoclast activation as a mechanism of bone loss, and even arthralgia, prior to arthritis development [19▪▪,20▪]. Here it was shown that peptidyl arginine deiminase enzymes necessary for osteoclast differentiation had, as a result of their citrullinating activity, a secondary effect of generating additional targets for circulating ACPA within the joint; IL-8 was specifically produced by these cells in response to ACPA, feeding an autocrine loop that resulted in bone loss [19▪▪] and (in mice) pain-like behaviour [20▪]. Considered together these data are exciting as they point to a hitherto elusive model to explain how systemic autoimmune propensity manifests as joint-specific diseases; its confirmation is now eagerly awaited.

Type I interferons including the prototype IFNα, produced mainly by plasmacytoid dendritic cells, may provide a further example of cytokine-mediated autoantibody modulation. These factors are known to promote a number of functions linked to autoimmune pathology including B-cell differentiation and IgG class-switching. Up-regulation of

their target gene expression in whole blood (interferon gene signature, IGS), used as a surrogate of circulating cytokine levels, has been shown to predict IgG development in at-risk, ACPA+ individuals, as reflected predominately by its presence in polymorphonuclear granulocytes [21▪▪], and IGS elements were recently shown to correlate with ACPA titres in a Mexican population [22].

Studying the preclinical phase of seronegative rheumatoid arthritis poses a unique and important challenge now beginning to be addressed [23▪]. Of interest, patients with this subgroup of disease typically describe a shorter symptom duration when they present with arthritis, but with evidence for more prominent IL-6-mediated lymphocyte activation in the periphery, compared with their seropositive counterparts [24,25], consistent with a more 'explosive', pro-inflammatory component to the natural history of seronegative disease (Fig. 1). The knowledge that adaptive immune activation may be facilitated by pro-inflammatory cytokines in the absence of ongoing antigenic stimulus [26] suggests alternative mechanisms of sustained immune dysregulation that warrant further study in this subgroup.

CYTOKINES IN THE TRANSITION TO CHRONICITY

The pathological hallmarks of synovitis in rheumatoid arthritis include the proliferation of resident synovial fibroblasts, new blood vessel formation and the recruitment of a wide range of leukocytes including B and T lymphocytes, monocytes/macrophages and mast cells; in turn this leads to synovial hypertrophy and the invasion of cartilage and bone by activated inflammatory tissue. Cytokines are fundamental orchestrators of the development and maintenance of this lesion. Amongst them, TNF appears to hold a position of hierarchical dominance during the inflammatory disease phase, promoting the activation of osteoclasts, chondrocytes, vascular endothelium and fibroblasts, and so directly mediating synovial hypertrophy and damage whilst in turn upregulating the expression of other locally abundant pro-inflammatory cytokines. These include members of the IL-1 family, IL-6 and GM-CSF, the latter two of which clearly possess nonredundant functions, respectively in T-cell activation and the differentiation of inflammatory macrophages and dendritic cells. Furthermore, IL-6 and TNF exert potent systemic effects that help drive some of the co-morbidities seen in rheumatoid arthritis, including altered cholesterol metabolism, atherosclerosis and even mood disturbance [27▪]. Finally, in relation to adaptive immune dysregulation, these two cytokines were recently shown to induce the secretion of soluble programmed cell death-1 (sPD-1) by $CD4^+$ T cells, competitively compromising the normal PD-1-mediated regulation of these cells' activation in inflammatory arthritis patients [28▪].

The broad inflammatory features of rheumatoid synovitis are well described [27▪], but an emergent literature has now set 'early synovitis' apart as a distinct, transitional pathological phase in rheumatoid arthritis development, during which cytokine cross-talk between cells of the stroma, endothelium and the immune system may uniquely effect the failure of inflammation to resolve within the joint. Central to this concept is an appreciation that synovial fibroblasts, far from functioning merely as inert 'joint scaffolding', instead actively direct cellular interactions according to an epigenetically imprinted phenotype that is potentially more vulnerable to the cumulative effects of inflammation than stromal cells located elsewhere [29]. Building on this insight, Filer *et al.* recently demonstrated that an immune-protective effect exerted by TNF-exposed synovial fibroblasts from recent-onset arthritis patients in whom synovitis spontaneously resolves – whereby lymphocyte adhesion to endothelial cells in co-culture is prevented – was lost amongst synovial fibroblasts derived instead from patients with recent-onset rheumatoid arthritis, in whom synovitis persists [30▪▪]. The phenomenon appeared to be partly mediated by IL-6 which, although abundant in both 'resolving' and 'persistent' synovitis, mediated divergent effects during this circumscribed disease phase. On the other hand, only synovial fibroblasts from patients with advanced rheumatoid arthritis promoted lymphocyte adhesion even in the absence of TNF [30▪▪]. These data illustrate the importance of considering cytokine effects in the context of disease phase and diagnostic category, and may have consequences for the optimal therapeutic timing of cytokine blockade (Fig. 1). As with the preclinical disease phase, the autoantibody status should also be considered. For example, in patients with untreated early rheumatoid arthritis high circulating levels of IL-20 and IL-24 discriminate seropositive individuals and predict bony erosion – a property lost after treatment initiation; these cytokines appear to be produced by monocytes activated by immune complexes, and in turn mediate osteoclast activation [31▪].

Aside from the largely pro-inflammatory moieties discussed above, recent investigations into a number of 'regulatory' cytokines that shed light on means by which immune homeostasis might be restored during rheumatoid arthritis development are also considered. For example, the observation that spontaneous resolution of synovitis in a

mouse model is dependent on IL-9 raised the intriguing possibility that this cytokine could also regulate human RA persistence: an enrichment of IL-9-producing type 2 innate lymphoid cells (ILC-2s) was indeed present in the circulation and synovium of patients with active rheumatoid arthritis compared with those on effective treatment and controls [32▪▪]. Tertiary lymphoid organs (TLOs) that closely resemble lymphoid follicles (with segregated T- and B-cell zones, follicular dendritic cell networks and a supporting stroma) are observed in approximately 40% of patient with rheumatoid arthritis synovium, where they support local autoantibody responses and may be a marker of adverse prognosis. It was recently shown that IL-27 inhibits TLO development via the inhibition of podoplanin-expressing Th17 cells [33]. Any therapeutic gains in the light of these insights remain some way off, but they offer a rich field for future research.

CYTOKINE-TARGETED THERAPY: LESSONS AND FUTURE DIRECTIONS

Experience gained from the use of targeted therapies may teach us much about rheumatoid arthritis pathogenesis – including the hierarchical dominance of individual cytokines at its various phases. The value of achieving rapid and broad suppression of pro-inflammatory pathways during the earliest phase of arthritis by blocking TNF or IL-6-mediated signalling has been demonstrated, for example leading to sustained remission in about a third of patients [34,35]. Amongst patients with rheumatoid arthritis who fail to respond to 'traditional' nonbiological DMARDs these pathways clearly remain important drivers of disease for many, and GM-CSF blockade has now joined the above strategies as a rapidly effective treatment modality in this setting [36]. The efficacy of small molecular inhibitors of these cytokines' downstream signalling machinery (the Janus kinase family) further supports their importance in perpetuating the inflammatory joint disease. By contrast, unsuccessful therapeutic targeting of other pro-inflammatory cytokines, despite their evident participation in pathogenesis, likely reflects functional redundancy during the disease phase at which clinical trials have thus far been undertaken. In the case of IL-1 this is true in both early and established rheumatoid arthritis, but attempts to block the IL-23/17 axis have thus far tended to be limited to patient groups with established disease [8,9]. Conceivably, based on recent insights described above, inhibitors of IL-23, p40 (the common subunit of IL-23 and IL-12) and IL-17A, may be more rationally deployed in seropositive individuals before clinically overt arthritis develops – in which context the role of Th17 cells could be more pivotal [17▪▪]. Here, the potential role of agents that block IL-8 signalling (such as the CXCR1/2-inhibitor reparixin) or IFN-α (e.g. sifalimumab) has become the subject of similar conjecture [37].

The preponderance of ACPA and/or rheumatoid factor seropositive patients with rheumatoid arthritis amongst populations studied in most of the clinical trials alluded to here is notable. Where it is available, accumulating data identifies seronegative rheumatoid arthritis as subject to relatively unfavourable treatment responses, irrespective of the targeted cytokine. Perhaps this is unsurprising given the aetiological distinction of this subgroup, but it highlights persistent unmet needs: not only in pathophysiological understanding, but also in our ability to map therapeutic response to measurable markers of the heterogeneous disease process at an individual patient level. Pretreatment levels of circulating cytokines themselves have so far proved to be of little value for this purpose, and the ability to measure their effects at a cellular level and/or within synovial tissue holds promise for stratified treatment approaches [38▪].

CONCLUSION

Cytokines leave their footprint at all stages of the natural history of rheumatoid arthritis. Their signalling pathways are represented amongst genes encoded at disease risk loci; they regulate the immunological 'prodrome' that precedes clinically manifest arthritis – including autoantibody pathogenicity and joint pain; they mediate (and are mediated by) stromal dysregulation within the joint at the earliest stages of synovitis; and they define and perpetuate the chronic inflammation that ensues. Harnessing an understanding of how members of this diverse family of molecules variously dominate at each disease phase across disease subgroups should yield more rational and effective treatment strategies.

Acknowledgements

Ms Ridgley's work is supported by the Arthritis Research UK Centre of Excellence for the Pathogenesis of Rheumatoid Arthritis (RACE); all authors gratefully acknowledge constructive discussions with colleagues and collaborators within this Centre that have informed the content of this review. The authors have benefitted from infrastructural support from the National Institute of Health Research (NIHR) Newcastle Biomedical Research Centre.

Financial support and sponsorship

None.

Conflicts of interest

Dr Pratt has received funding from Pfizer towards an externally peer-reviewed research project. Honoraria he has received from Eli Lilly and Janssen-Cilag Ltd. for his time in preparing presentations for nonpromotional meetings have been paid directly to Newcastle University. The views expressed in this manuscript are his own.

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Current views on the pathogenesis of Sjögren's syndrome

Elena Pontarini, Davide Lucchesi, and Michele Bombardieri

Purpose of review
The purpose of this review is to provide an insight into the pathophysiological mechanisms involved in the pathogenesis of primary Sjögren's Syndrome (pSS), highlighting recent findings with potential therapeutic repercussions.

Recent findings
In the last 2 years, epigenetic analyses provided new insights into pSS pathogenesis. Characterization of DNA methylation patterns, chromatin structures and microRNA confirmed the importance of aberrant interferon and B-cell responses in the development of the disease. The formation of ectopic B-cell follicles with germinal centers is now a well recognized pathogenic mechanism within salivary glands of pSS. In the context of ectopic germinal centers reaction, T/B-cell interactions, that is regarding T-helper 17 and T-follicular helper cells, and their respective counterparts, T-regulatory and T-follicular regulatory cells, appear particularly relevant in pSS pathogenesis as their imbalance is associated with a dysregulation of B-cell dynamics and the production of autoantibodies.

Summary
Advances in the understanding of pSS pathogenesis have paved the way for clinical trials with novel biologic agents targeting immune pathways regulating T/B-cell interactions and downstream B-cell activation. Reverse translation from these studies provides invaluable novel information of the mechanisms sustaining autoimmunity and chronic inflammation in pSS.

Keywords
ectopic germinal centers, epigenetics, primary Sjögren's syndrome, T-follicular helper cells, T-follicular regulatory cells

INTRODUCTION

Primary Sjögren's syndrome (pSS) is a chronic autoimmune disease, with a prevalence of 0.2–0.5% in the adult population [1]. PSS, for which new classification criteria have been recently developed [2], is characterized by an autoimmune response localized in the exocrine glands, with a preferential immune cell infiltration in the salivary and lacrimal glands, ultimately leading to the loss of glandular secretory functions resulting in dry eyes (xerophtalmia) and dry mouth (xerostomia) [1]. In addition, a subset of pSS patients develops extra-glandular manifestations, including the involvement of joint, kidney, peripheral nervous system and blood vessels [3]. The extraglandular manifestations are frequently related to B-cell hyperactivity, characterized by increased levels of immunoglobulins, circulating autoantibodies and alterations in B-cell subpopulations [4]. Moreover, approximately 5% of patients with SS develop non-Hodgkin B-cell lymphomas of mucosal-associated lymphoid tissue (MALT-L), most commonly arising in the parotid glands [5]. The association between markers of immune cell activation and disease severity clearly indicates that a better understanding of the key immune abnormalities underlying pSS pathogenesis has the potential to lead to the development of novel therapeutics. This is of particular relevance as no disease-modifying drug is currently available for pSS, and the current treatment for pSS is unsatisfactory (reviewed in [6]). In addition, recent large randomized trials with the B-cell depleting agent Rituximab have

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Curr Opin Rheumatol 2018, 30:215–221
DOI:10.1097/BOR.0000000000000473

KEY POINTS

- Abnormalities in the epigenetic regulation of at-risk susceptibility *loci* are emerging as important regulators of autoimmunity and chronic inflammation in pSS.
- Cognate T/B-cell interactions appear critical for the development of the immune abnormalities observed in pSS.
- Both Th17 and T-follicular helper cells can interfere with the formation and function of ectopic germinal centers response in the salivary glands of pSS.

yielded disappointing results [7▪,8▪] highlighting the importance of a more refined approach to rebalance immune alterations in pSS.

Consistent with the current paradigm of rheumatic autoimmune diseases pathogenesis, autoimmunity and chronic inflammation in pSS can be considered the result of a series of multifactorial events, comprising genetic susceptibility and environmental factors; these yet undefined triggers result in an impairment of physiological immune checkpoints with breach of self-immunological tolerance and accumulation of autoreactive and polyreactive naïve and memory B cells in the systemic circulation [9] and in the salivary glands.

In this review, we will discuss recent findings of relevance to the pathogenesis of pSS in two main areas: first, epigenetics modifications regulating the transcription of key genes associated with pSS susceptibility and second, the emerging role of specialized CD4+ T helper cells in regulating immune cell infiltration and organization within the affected salivary glands.

For reason of space, we will not discuss the putative role of viruses as triggers of pSS, but we direct the reader to our recent review article on this topic [10].

EPIGENETIC REGULATION OF SUSCEPTIBILITY GENES IN PRIMARY SJÖGREN'S SYNDROME

Recent genome-wide association studies in pSS [11] identified novel single nucleotide polymorphisms conferring increased susceptibility to pSS and corroborated disease associations with previously described at-risk *loci* of genes related to key pathogenic pathways in pSS development. These include regulation of the innate immune system through type-1 interferon (IFN) axis; B-cell (and T-cell) trafficking mediated by C-X-C motif chemokine receptor 5 (CXCR5)-driven immune cell recruitment to ectopic B-cell follicles; B-cell lymphocyte kinase-mediated B-cell receptor activation; the IL-12-IFN-γ axis Th1-related pathway; and finally the cognate activation of T cells through major histocompatibility complex Human Leukocyte Antigen (HLA) – antigen D Related (HLA-DR) and HLA-DQ (reviewed in [12]).

Although genetic at-risk *loci* likely represent important contributors to develop pSS, there is emerging evidence that epigenetics alterations, including changes in DNA methylation, histone modifications and microRNA (miRNA) expression, also play a relevant role in the pathogenesis of pSS [13].

DNA methylation

DNA methylation, together with histone acetylation, is one of the main epigenetic mechanisms able to modulate gene expression by regulating the transcriptional accessibility of a gene's regulatory regions [14]. In particular, active transcription is associated with the hypomethylation of the gene promoter and hypermethylation of the body region. It is now clear that epigenetic deregulations, in particular DNA methylation, are present in pSS and restricted to specific cell subsets, such as lymphocytes and salivary glands epithelial cells. Significantly, a comprehensive analysis of DNA methylation in circulating B cells (CD19+) and in minor salivary glands biopsies from pSS patients, confirmed a prominent hypomethylation of IFN-regulated genes in the whole blood and in B cells, including in the genes MX1 (MX dynamin-like GTPase 1), IFI44L (Interferon Induced Protein 44 Like-an indicator gene of the type-I IFN signature) and PARP9 [Poly (ADP-ribose) polymerase 9] [15▪], confirming previous findings [16▪,17]. Moreover, hypomethylation of IFN-regulated genes in B cells corresponded to an increase in expression of the above listed genes [15▪]. Significantly, the IFN-induced gene 2′-5′ oligoadenylate synthase 2, a key IFN-induced antiviral factor that regulates the innate immune response to viruses [18], was hypomethylatated in pSS salivary glands biopsies. This is particularly relevant, as persistent and non-resolved viral infections have been frequently linked to the insurgence of pSS [10]. A recent genome-wide DNA methylation study [19] revealed both hypomethylated and hypermethylated gene regions in pSS salivary glands biopsies, including 57 genes with differential methylation in their respective promoter, and two pSS genetic risk *loci*. Of interested, extended hypomethylation surrounding the PSMB8 (Proteasome Subunit Beta 8) and TAP1 (Transporter Associated with Antigen Processing Type 1) genes suggests a role of DNA methylation in the control of antigen-presentation within the target tissue [19].

Although the characterization of the methylation pattern in whole salivary glands tissue does not allow the investigation of histone methylation in the different T-cell types involved, recent reports on the DNA methylation status in salivary glands epithelial cells demonstrated a decreased expression of mRNA transcripts encoding the methylating enzyme DNMT1 (DNA methyltransferase-1) in ductal epithelial cells which was associated with the degree of B-cell infiltrate. Significantly, the autoantigen SSB/La (Sjögren syndrome type B antigen/Lupus associated protein) and the cytoskeletal protein cytokeratin-19 were shown to be affected by the activity of DNMT, thus linking DNA methylation in epithelial cells with the release of autoantigens, the activation of B cells and the impairment of epithelial integrity/function [20].

MicroRNA expression

Although DNA methylation is an epigenetic alteration that regulates the transcriptional accessibility of a gene, miRNAs regulate the gene expression mainly at a post-transcriptional level. The presence of a complete or incomplete match between the miRNA and the 3′ untranslated region of the target mRNA sequence, can induce respectively direct mRNA degradation or preventing mRNA from being translated [14]. Differential miRNA expression patterns have been demonstrated in pSS, via the analysis of either salivary glands tissue [21] or peripheral blood mononuclear cells [22–24]. So far, miRNA expression profiles in T cells and B cells isolated from pSS peripheral blood showed to be more informative than the data obtained from whole tissue analysis [25▪]. A large-scale analysis of miRNAs in blood from pSS patients demonstrated a differential expression pattern for miRNA associated with IRF5 (Interferon Regulatory Factor 5), STAT1 (Signal transducer and activator of transcription 1) and IRAK1 (Interleukin-1 receptor-associated kinase 1) in blood-derived T cells versus B cells [25▪]. The same miRNAs have also been found associated with genetic variation or DNA methylation changes in pSS [11,16▪]. Significantly, miRNAs associated with pathways involved in B lymphocytes survival, including the PI3K-PKB (Phosphatidylinositide 3-kinases - Protein kinase B) signaling pathway and B-cell activating factor (BAFF) were shown to be differentially expressed in SS patients [25▪]. This is particularly relevant, as BAFF is a proinflammatory cytokine, involved in the preferential proliferation, maturation and survival of autoreactive B cells [26]. Expression of BAFF mRNA was shown to be inversely correlated with the expression of miRNA hsa-mir-30b-5p in B cells from patients with pSS and the inhibition of miRNA hsa-mir-30b-5p resulted in an increased expression of BAFF [25▪].

Overall, further clarification of the epigenetic regulation of the key pathways involved in pSS pathogenesis will not only contribute to our understanding of pSS disease mechanisms but may also provide important clues on the mechanisms underlying the response or lack thereof to novel biologics, particularly within the salivary glands tissue.

THE EMERGING ROLE OF SPECIALISED CD4 T CELLS IN REGULATING ECTOPIC GERMINAL CENTER RESPONSES IN SJOGREN's SYNDROME

The histological hallmark of pSS is a lymphocytic infiltration of the salivary glands which organize around salivary intercalated ducts, forming the classic pSS inflammatory *foci*. T cells, mainly $CD4^+$, and B cells represent the vast majority of the mononuclear cells infiltrate. In around 30–40% of pSS patients, B cells and T cells infiltrating the salivary glands organize in structures closely resembling the germinal centers of secondary lymphoid organs, and thus defined ectopic lymphoid structures (ELS, reviewed in [27▪]). ELS are characterized by the presence of T/B-cell segregation, high endothelial venules differentiation, expression of lymphoid chemokines C-X-C motif chemokine ligand 13 (CXCL13)/CCL19/CCL21 and differentiation of follicular dendritic cell network supporting an ectopic germinal centers response [27▪]. Our and other groups have consistently shown that ELS display functional features of germinal centers [28], which contribute to autoimmunity through the local differentiation of autoreactive plasma cells. Higher degree of immune cell infiltration and ectopic germinal centers are associated with higher prevalence of anti-Ro/La autoantibodies, increased disease severity, extraglandular manifestations and MALT B-cell lymphoma [29,30,31], although the latter evidence remains controversial [32▪,33].

Pathogenic role of Th17 and the balance with regulatory T cells in the pathogenesis of primary Sjögren's syndrome

The development and function of ectopic germinal centers appears to be largely dependent on an antigen-driven immune response, which requires cognate interactions between T and B cells and the release of key pro-inflammatory cytokines, including IL-17, IL-21 and IL-22. In particular, specific subsets of Th17 cells which express gp38/

podoplanin and the nuclear receptor retinoic acid-related orphan receptor gamma t-isoform (RORγt) contribute to ELS development, as originally demonstrated in experimental autoimmune encephalomyelitis [34].

Recently, in a model of sialoadenitis induced by immunization of C57BL/6 mice with salivary glands proteins, deficiency of IL-17A in IL-17$^{-/-}$ mice prevented disease onset, whereas adoptive transfer of Th17 cells restored disease severity, salivary glands infiltration and increased the frequency of GL7+ germinal centers B cells in draining lymph nodes [35]. Similarly, genetic ablation of IL-17 in the C57BL/6.NOD-Aec1Aec2 spontaneous model of pSS reduced sialadenitis and the differentiation of germinal centers B cells and plasma cells; an effect which was more prominent in female than male mice [36]. Moreover, RORγt transgenic was shown to develop severe spontaneous pSS-like sialadenitis, which could be transferred in Rag2$^{-/-}$ mice by the adoptive transfer of CD4+ T cells from Tg mice. Significantly, in this model disease appeared to be independent from the sole effect of IL-17 deficiency but rather the result of the concomitant decrease in CD4+CD25+ transcription factor forkhead box P3 (Foxp3)+ regulatory T cells (Treg) [37]. This is in line with the critical role of maintaining a correct balance between Th17 and Treg cells to prevent autoimmunity and/or chronic inflammation. In this regard, it has been recently shown that the transcriptional coactivator TAZ [transcriptional coactivator with PDZ (postsynaptic density 65-discs large-zonula occludens 1-binding)] motif play a critical role as a coactivator of RORγt in promoting Th17 differentiation and, in parallel, reducing Treg cell development [38▪▪]. Significantly, the same authors demonstrated that retinoic acid-related orphan receptor C (which encodes RORγt) and TAZ had higher coexpression in circulating CD4+ memory T cells of pSS patients [38▪▪].

In keeping with the possibility that in certain experimental conditions, the formation of ectopic germinal centers in the salivary glands is not dependent on IL-17, in a model of viral-induced sialoadenitis with lymphoid neogenesis, IL-22, a member of the IL-10 superfamily biologically related to IL-17 (as it can also be released by Th17 cells) was required for the development and maintenance of ELS in the salivary glands. Il22$^{-/-}$ mice were protected from ectopic germinal centers development and autoimmunity through reduced B-cell recruitment to the salivary glands despite preserved levels of IL-17; moreover IL-22, which was expressed by both γδ and αβ T cells, was able to directly induce CXCL13 production in gp38+ stromal cells [39].

The dichotomic role of T-follicular helper cells and T-follicular regulatory cells in controlling germinal centers responses: recent evidence in primary Sjögren's syndrome

In physiological conditions, germinal centers responses require the presence of T-follicular helper (Tfh) cells, a highly specialized CD4$^+$/CXCR5$^+$ memory T helper cells subset, that migrate into the B-cell follicles thanks to their expression of CXCR5, the specific receptor for CXCL13 [40]. In the mantle zone and within germinal centers, Tfh interact with B cells through T-cell inducible costimulator (ICOS) molecule and ICOS-ligand (ICOSL) ligation, and release high amount of the Tfh signature cytokine, IL-21 (Fig. 1). IL-21 is a potent cofactor for B-cell survival, proliferation and plasma cell differentiation, particularly when associated with CD40-CD40L costimulation and in synergy with BAFF [26,41]. It has now been shown that high affinity plasma cells generation requires the presence of Tfh both for the differentiation process and for the plasma cells egress from the germinal centers [42].

The Tfh compartment is particularly relevant to pSS pathogenesis [43], as the regulation of its frequency, and thus its impact on germinal centers B-cell development and function, is crucial for the quality of the humoral immune response [44]. An overexpansion of Tfh in pSS has been associated with a dysregulation of B-cell dynamics and the production of autoantibodies [45] as result of a reduced selection pressure on germinal centers B cells, leading to the emergence of low-affinity B-cell clones. In fact, expression of IL-21, IL-4 and CXCL13 as well as Tfh frequency is increased in the salivary glands of pSS patients. Tfh are also increased in the peripheral blood of pSS patients and their frequency correlates with the presence of autoantibodies, the disease severity and an aberrant activation of memory B cells and plasma cells. It is important to note that circulating Tfh show a partially differentiated phenotype, as they have a lower expression level of Tfh-associated markers in comparison with their tissue counterparts, but they are still able to maintain their pro-B-cell differentiation function [46]. Recently, an alternative subset of Tfh-like cells which differ from traditional Tfh for the expression of CCR9, the receptor for the mucosa-associated chemokine CCL25, was shown to circulate at increased frequency and infiltrate the salivary glands of pSS patients; additionally, CCR9+ T cells from pSS patients were able to release higher levels of IL-17 and IL-21 compared with CXCR5+ Th cells. Both CCR9+ and CXCR5+ Th cells potently induced IgG production in B cells confirming their

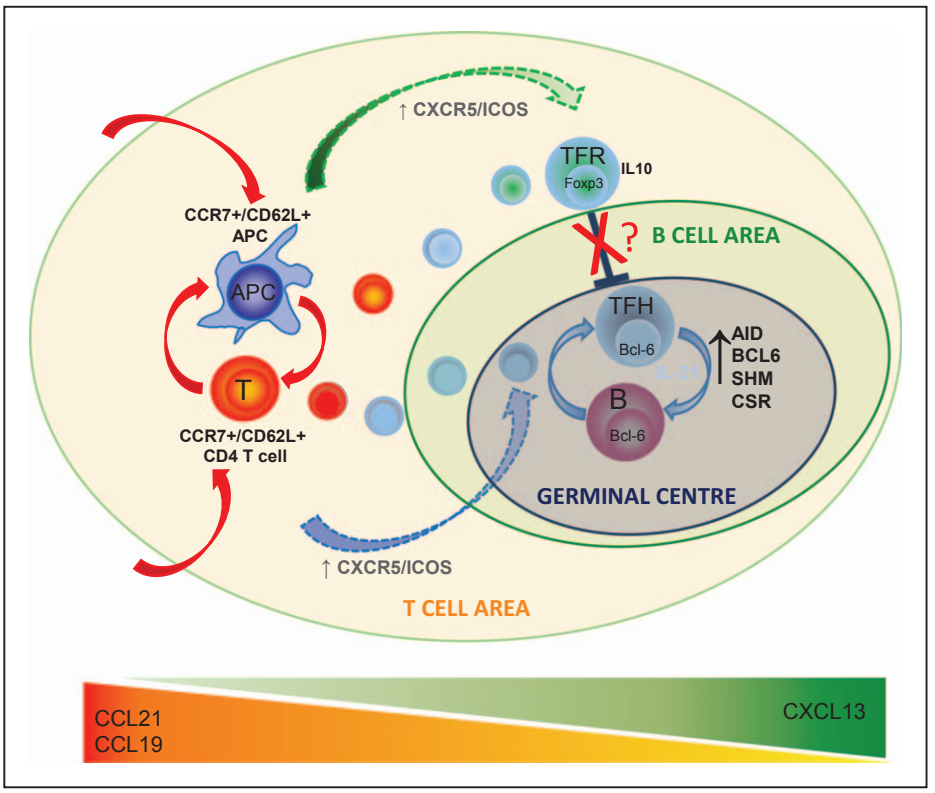

FIGURE 1. Schematic representation of the balance between T-follicular helper and T-follicular regulatory cells as putative regulators of the germinal center response in primary Sjögren's syndrome salivary glands. Within the T-cell area of ectopic germinal centers forming in the salivary glands of primary Sjögren's syndrome, T-follicular helper, a subset of T helper CD4+ cells activated by the interaction with antigen presenting cells, upregulate ICOS, transcription factor Bcl-6 and CXCR5 to migrate within the B-cell follicles, sensing the CXCL13 gradient. The interaction between T-follicular helper and germinal centers B cells induce the IL-21 production by T-follicular helper, responsible for class switch recombination and somatic hypermutation of germinal centers B cells. The control of germinal centers activation in secondary lymphoid organs is regulated by T-follicular regulatory cells which are identified by the expression of Foxp3 and the upregulation of CXCR5 which also drive their migration within the B-cell follicles. Although their inhibitory function is well described in secondary lymphoid organs, its role in ectopic germinal centers in general and in primary Sjögren's syndrome in particular remains to be investigated.

potential relevance in the observed B-cell hyperactivation in pSS [47▪].

The importance of Tfh in the response to novel biologics in pSS has emerged on the basis of the recent evidence that in a proof of concept clinical trial Abatacept (CTLA-4-Ig fusion protein) selectively reduced circulating Tfh cell numbers and the expression of ICOS on both circulating and lesional T cells. Lower numbers of activated circulating Tfh cells contributed to an attenuated Tfh cell-dependent B-cell activation, as shown by the reduction of serum levels of IL-21, CXCL13 and anti-SSA/SSB (Sjögren syndrome type A antigen/Sjögren syndrome type B) antigen [48▪]. Of relevance, also B-cell depletion was able to normalize the increased frequency of circulating Tfh cells, together with serum levels of IL-21. The decrease in circulating Tfh cells was also associated with lowering disease activity and serum IgG [49▪]. The above evidence highlights the bidirectional importance of cognate B/T-cell interactions not only for germinal centers B-cell activation but also for Tfh differentiation. It will be of extreme interest to investigate the effect on Tfh and Th17 in the ongoing clinical trials with novel biologics targeting immune pathways intimately linked with Tfh/B-cell costimulation such as the ICOS/ICOSL (Trial NCT02334306) and theCD40/CD40L (Trial NCT02291029) pathways which have entered phase II clinical development in pSS.

On the opposite spectrum of Tfh, a newly described subset of CD4+ T cells, termed T-follicular regulatory cells (Tfr) has been shown to regulate Tfh function during the germinal centers reaction. Tfr cells are thought to develop from thymic-derived Treg that express lineage-associated markers such as Foxp3, CD25, and low levels of CD127 [50]. Tfr cells migrate into the follicles of lymph nodes in response to CXCR5 (and down-modulation of CCR7) and, similarly to Tfh, express PD1 (programmed cell death protein 1) and ICOS. Significantly, germinal

centers Tfh and Tfr pools are generated from distinct T-cell receptor (TCR) repertoires, with Tfh cells expressing antigen-responsive TCRs to promote antibody responses, and Tfr cells expressing potentially autoreactive TCRs to suppress autoimmunity [51]. Tfr can inhibit germinal centers responses through controlling the number of Tfh and self-reactive germinal centers B cells (Fig. 1), via coinhibitory receptors such as CTLA-4 and secretion of IL-10 and TGF-β [50,52]. Recently, an increase in circulating Tfr cells in pSS has been reported [53▪▪]; however, circulating Tfr cells compared with tonsil-derived Tfr were not fully competent, as they were able to suppress T proliferation, but they lacked full B-cell suppressive capacity [53▪▪]. It is currently unknown whether the balance between Tfh and Tfr is impaired in the circulation and/or in the salivary glands of pSS and plays a role in the aberrant germinal centers reaction observed in pSS; nevertheless, it is intriguing to speculate that targeting B/T-cell costimulation with novel biologics may affect the degree of salivary glands inflammation and the formation and function of ectopic germinal centers.

CONCLUSION

Recent research on pSS summarized in this review, highlighted on the one hand the relevance of previously undefined epigenetic modifications in pSS pathogenesis and on the other confirmed the pivotal role of known players, such as INFs and B cells, in the development of the disease. In addition, the emerging evidence that cognate T/B-cell interactions, with Th17 and Tfh cells in the front line, are critical for the development of sialoadenitis and regulate ectopic germinal centers responses fosters the hope that new therapeutics targeting biologically related pathways will show efficacy in ameliorating disease in pSS patients.

Acknowledgements

None.

Financial support and sponsorship

The work was supported by project grants to M.B. from the Medical Research Council (MRC, grant MR/N003063/1) and the EU H2020 funded HarmonicSS study (Project ID: 731944).

Conflicts of interest

M.B. has received consultancy fees and/or from Medimmune, GSK and UCB. The other authors declare no conflict of interest related to this work.

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Recent developments in systemic lupus erythematosus pathogenesis and applications for therapy

Mindy S. Lo[a,b] *and George C. Tsokos*[c,d]

Purpose of review
Systemic lupus erythematosus (SLE) pathogenesis is complex. Aberrancies of immune function that previously were described but not well understood are now becoming better characterized, in part through recognition of monogenic cases of lupus-like disease.

Recent findings
We highlight here recent descriptions of metabolic dysfunction, cytokine dysregulation, signaling defects, and DNA damage pathways in SLE. Specifically, we review the effects of signaling abnormalities in mammalian target of rapamycin, Rho kinase, Bruton's tyrosine kinase, and Ras pathways. The importance of DNA damage sensing and repair pathways, and their influence on the overproduction of type I interferon in SLE are also reviewed.

Summary
Recent findings in SLE pathogenesis expand on previous understandings of broad immune dysfunction. These findings have clinical applications, as the dysregulated pathways described here can be targeted by existing and preclinical therapies.

Keywords
anifrolumab, cholesterol homeostasis, DNA damage repair, monogenic lupus, systemic lupus erythematosus, TREX1, type I interferon

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease defined by the presence of autoantibodies, particularly antibodies directed against nuclear antigens. These autoantibodies, which unify the many different clinical presentations of SLE, reflect a breach of central tolerance. Defects in the clearance of apoptotic debris and aberrant presentation of self-antigens are major mechanisms that contribute to this breach. Excessive plasmacytoid dendritic cell (pDC) activation and interferon production amplify the inflammatory response in SLE. Finally, end-organ tissue damage is mediated by immune complexes and abnormal activation of T lymphocytes and other immune cells. These mechanisms are all known to be influenced by genetic, environmental, and hormonal factors.

The last few years have seen some interesting developments in our understanding of SLE pathogenesis. The spectrum of abnormalities that have been characterized continues to expand, currently including metabolic derangements, signaling and biochemical defects in immune cells, and impaired sensing and repair of DNA damage (Fig. 1). Correlation of these dysregulated pathways with specific clinical and pathophysiologic aspects of SLE has been aided by the study of monogenic forms of lupus-like disease. Further, characterization of these pathway defects in SLE has allowed identification of new targets for therapeutic intervention.

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Curr Opin Rheumatol 2018, 30:222–228
DOI:10.1097/BOR.0000000000000474

KEY POINTS

- Defects in multiple metabolic pathways contribute to immune dysregulation in SLE.
- Impaired DNA damage repair leads to lupus-like disease, in part by inducing type I interferon overproduction.
- Interferon signaling may be an effective therapeutic target in SLE.
- Monogenic cases of lupus-like disease may inform further understanding of pathologic mechanisms in SLE.

METABOLIC DEFECTS

Signaling through the T-cell receptor (TCR) is dysregulated in SLE in multiple ways, including aggregation of lipid rafts around TCR clusters, downregulation of the CD3ζ chain, and decreased upregulation of IL-2 in response to TCR activation [1].

The CD3ζ in SLE T cells is downregulated, and its function is substituted by FcεRIγ, which signals through Syk rather than Zeta-associated protein 70, resulting in a stronger signal of the TCR [1]. The lysosomal degradation of CD3ζ is aggravated by the increased activity of the mammalian target of rapamycin (mTOR) in these cells, resulting in upregulated endosomal trafficking and turnover of cell surface markers [2]. mTOR is a sensor of mitochondrial polarization which coordinates multiple cellular pathways as a component of mTOR complex 1 (mTORC1) and mTOR complex 2. T cells from SLE patients treated with rapamycin, which inhibits mTOR activity, showed restored levels of CD3ζ and normalized signaling through the TCR [2].

Mitochondrial hyperpolarization and increased mTORC1 activity likely influences the T-cell phenotype in SLE in many other ways, including altered follicular helper and regulatory T-cell profiles [3,4]. CD3+CD4−CD8− double negative T cells are thought to play a pathogenic role in SLE through the secretion of IL-17. Treatment of SLE T cells with rapamycin decreases in-vitro IL-17 production and promotes the development of regulatory T cells (Tregs) [3]. The expression of IL-17 and other proinflammatory cytokines in double negative T cells appears to be especially dependent on mTORC1 activity [3]. In Tregs, IL-2 signaling induces mTORC1 activity, which in turn influences cholesterol metabolism and upregulates inhibitory

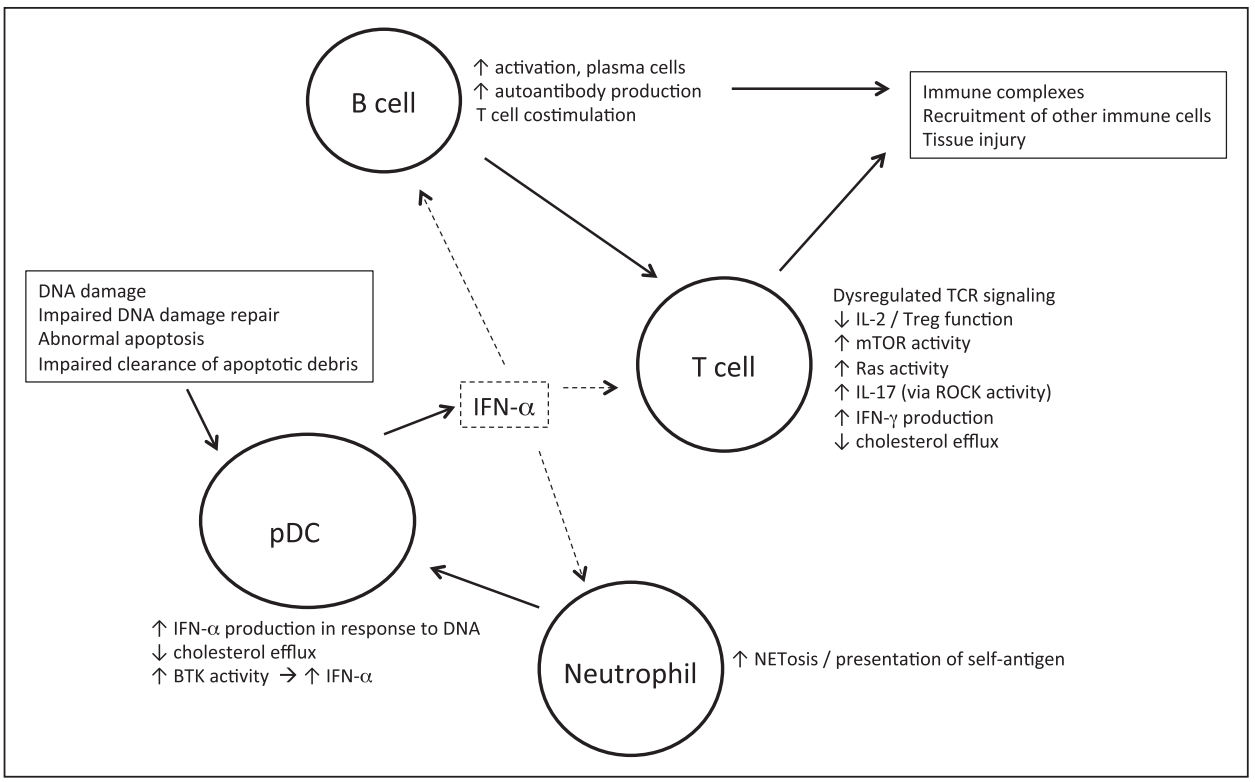

FIGURE 1. Schematic of immune abnormalities known to contribute to systemic lupus erythematosus pathophysiology. This diagram greatly underestimates the complexity of interactions that are dysregulated in systemic lupus erythematosus to highlight recent findings described here.

pathways important for Treg function [5]. This mTOR activation pathway in Tregs is reliant on activation of protein phosphatase 2 (PP2A) [6]; abnormalities of PP2A expression and activation have been described in SLE patients [7].

Clinical evidence for the role of mTOR activity in SLE is further supported by the coexistence of SLE and tuberous sclerosis, described in recent case reports [8–10]. Tuberous sclerosis is a rare neurologic condition associated with benign tumor growths due to mutations in either *TSC1* (hamartin) or *TSC2* (tuberin). Hamartin and tuberin form a complex that inhibits mTORC1; immune profiling of one of the described tuberous sclerosis patients with SLE demonstrated significant mitochondrial hyperpolarization and increased mTOR activity *in vitro* [10].

CHOLESTEROL HOMESTASIS

The glycosphingolipid profile within lipid rafts is altered in SLE, with increased expression of lactosylceramide and other species of glycosphingolipids when compared with T cells from healthy controls [11]. This increase is associated with increased TCR activation and appears to be due to upregulation of liver X receptor β (LXRβ), a nuclear regulator of glycosphingolipid homeostasis. LXRα polymorphisms have been associated with SLE [12], and mice deficient in LXRα and LXRβ develop lupus-like disease [13]. These LXRs influence immune cell function in multiple ways. LXR activity promotes cholesterol efflux through upregulation of the ATP-binding cassette transporters ABCA1 and ABCG1. In murine T cells, deficiency of ABCG1 results in intracellular cholesterol accumulation with consequent T-cell activation and proliferation [14]. Notably, in Tregs, intracellular accumulation of ceramide increases activity of PP2A, linking cholesterol pathways again back to T-cell activation [6].

However, a recent study in mice suggests that it is impairment of cholesterol efflux in dendritic cells, but not T cells, that contributes to lupus-like immune activation. Dendritic cells from mice with double deficiency of ABCA1 and ABCG1 showed marked cholesterol accumulation and also NLRP3 inflammasome activation with increased secretion of IL-1β and IL-18 [15▪]. Selective deficiency of the ABCA1/ABCG1 transporters in dendritic cells was sufficient to induce a lupus-like phenotype with lymphadenopathy and glomerulonephritis [15▪]. It is not clear how intracellular cholesterol accumulation leads to inflammasome activation. One proposed mechanism is that cholesterol increases stability of Toll-like receptors (TLRs) in lipid raft clusters, enhancing the TLR signal response [16].

REGULATORY T CELLS AND LOW-DOSE IL-2

T-cell production of IL-2 is impaired in SLE due to abnormal TCR signaling responses as well as repressed IL-2 transcription [17]. IL-2 is generally a proinflammatory cytokine, but is also critical for the development and function of Tregs [18]. Deficiency of IL-2 likely contributes to the Treg abnormalities observed in SLE [19]. In mouse models of lupus, treatment with IL-2 has resulted in variable levels of improvement [20,21].

In humans, low-dose IL-2 therapy was first trialed with good success in two other conditions characterized by Treg dysfunction, graft-versus-host disease and hepatitis C-induced vasculitis [22,23]. There have now been several reports of low-dose IL-2 therapy in SLE. In one case report, an SLE patient experienced remarkable improvement in skin rash and myositis after a 2-month treatment course with recombinant IL-2 [24]. The same researchers then described five patients with active SLE treated with daily subcutaneous injections of IL-2 administered over 5 consecutive days [25]. Treatment with just this single course resulted in significant increases in Treg numbers as well as in CD25 expression on Tregs [25].

In a larger uncontrolled study, recombinant IL-2 administered over a 12-week treatment period resulted in increased number and function of Tregs, whereas follicular helper T cells and double negative T-cell populations declined [26▪▪]. Clinically, 90% (34/38) of patients showed a 4-point drop in their SLE disease activity index score over the 12-week treatment period [26▪▪]. These reports claiming impressive therapeutic efficacy should await the results of controlled studies. Recombinant IL-2 is currently approved for the treatment of select malignancies, and its efficacy in autoimmunity remains under investigation.

INTERFERON

SLE patients characteristically show increased serum IFN-α levels and a pattern of increased expression of type I interferon-stimulated genes in peripheral immune cells, known as the interferon signature [27]. This is in part related to expanded numbers of pDCs, the primary producers of IFN-α in response to nucliec acid. IFN-α, in turn, has a number of effects that drive lupus pathophysiology, including increased expression of B-cell activating factor (BAFF), IL-6, and other cytokines, as well as increased autoantibody production [27–29].

Monogenic cases of lupus-like disease have also emphasized the importance of type I interferon in effecting these immune abnormalities. Familial

chilblain lupus and Aicardi–Goutieres syndrome are both syndromes characterized by autoantibodies and systemic inflammation, and are both due to mutations in the gene encoding three-prime exonuclease 1 (*TREX1*) [30,31]. Lack of the TREX1 exonuclease allows accumulation of nucleic acid fragments during the DNA damage response; these fragments ultimately stimulate type I interferon production [32]. Mutations in other components of the DNA damage sensing and repair pathways also result in upregulation of type I interferon and a lupus-like phenotype. Examples of these 'interferonopathies' include *RNASEH2A/B/C*, *SAMHD1*, *ADAR*, and *IFIH1* [33]. Outside of these monogenic cases, polymorphisms in these genes may also contribute to the interferon signature and to SLE disease risk. As an example, *TREX1* polymorphisms were found at a frequency of 0.5% in one SLE cohort.

Type I interferon may play a particular role in the central nervous system (CNS) manifestations of lupus, as suggested by the severe neurologic phenotype of Aicardi–Goutieres. In one case report, *TREX1* mutation was found to underlie the development of CNS lupus in a young child, whereas in a very large cohort of SLE patients, a *TREX1* haplotype was associated with risk for neurologic involvement [34,35]. IFN-α was shown recently to activate microglial cells which then engulf neuronal structures, pruning synapses [36▪▪]. Interferon-mediated synapse loss probably represents a mechanism responsible for CNS manifestations in patients with SLE.

These findings, among others, suggest the type I interferon signaling pathway as an appropriate therapeutic target. Anifrolumab is a mAb directed against the IFN-α receptor subunit 1. The first clinical trial of anifrolumab was recently published [37]. In a phase IIb trial, 305 patients were randomized to receive placebo, low-dose (300 mg), or high-dose (1000 mg) infusions every 4 weeks. The primary endpoint was a composite of the SLE responder index and reduction in corticosteroid use. Patients who received anifrolumab had significantly higher rates of reaching the primary endpoint, with the greatest response seen in patients with a high interferon signature [37].

Type II interferon (IFN-γ) may also play a role in SLE pathogenesis. IFN-γ is secreted by both T cells as well as by macrophages and other innate immune cells, and induces upregulation of a distinct but overlapping set of genes as compared with type I interferon. A recent study examined interferon activity, autoantibodies, and cytokine levels in serum samples collected longitudinally before and after diagnosis of SLE [38▪▪]. In this cohort, 75% of patients showed elevated serum IFN-α activity prior to diagnosis of SLE. However, in all patients, development of autoantibodies preceded significant IFN-α activity. Significantly, serum levels of IFN-γ and the IFN-γ-induced protein 10 (also known as CXCL10) were elevated in SLE patients even before the development of autoantibodies [38▪▪]. This finding suggests that IFN-γ, more so than IFN-α, may influence the initial loss of tolerance and development of autoantibodies that characterizes early lupus pathogenesis. T cells from patients with SLE have previously been noted to produce more IFN-γ in response to stimulation, and this in turn promotes higher secretion of BAFF by monocytes [39].

Both types I and II interferon signaling pathways can be targeted with Jak inhibitors. Studies of tofacitinib in murine lupus models have been promising, and there are at least two phase I clinical trials in progress [40,41]. Jak inhibitors have also been used in the treatment of monogenic interferonopathies with reported success [42,43].

DNA DAMAGE REPAIR AND CHROMATIN REMODELING

The report of defects in DNA damage repair genes causing lupus-like disease has led to increased scrutiny of this pathway. Repair of DNA damage in response to oxidative stress is impaired in SLE neutrophils, whereas lymphoblastoid cells lines from SLE patients show defective repair of radiation-induced DNA damage [44,45]. A recent study similarly showed impairment of both nucleotide excision repair and double-strand break repair in SLE mononuclear cells treated with an alkylating agent [46▪]. Even in cells taken from SLE patients with quiescent disease, DNA damage repair was decreased compared with healthy controls, and the degree of impairment correlated with higher apoptotic susceptibility [46▪]. Significantly, treatment with vorinostat, a histone deacetylase (HDAC) inhibitor, improved the efficiency of DNA damage repair; the authors hypothesize that vorinostat reverses the abnormal chromatin compaction in SLE that impedes access to sites of DNA damage [46▪].

HDACs may be therapeutic targets for other reasons. Epigenetic dysregulation is well documented in SLE, particularly global hypomethylation in T cells [47]. HDAC inhibitors ameliorate disease in multiple mouse models of lupus [48,49]. *In vitro*, HDAC inhibitors directly inhibit B-cell proliferative responses to T-cell activation and TLR4 stimulation [50]. Specific inhibitors targeting different classes of HDACs have variable effects on B-cell differentiation and antibody production [50]. Treatment of lupus-prone mice with a nonspecific HDAC inhibitor, panobinostat, dramatically reduced circulating naïve B and plasma cell numbers as well as

autoantibody levels [50]. Significantly, treatment of immunized mice with panobinostat did not affect the memory B-cell compartment, suggesting that humoral autoimmunity might be treated with HDAC inhibitors while preserving B-cell immunocompetence [50].

RHO KINASES

Rho kinases (ROCK) 1 and ROCK2 are serine/threonine kinases activated by the GTPase RhoA. The ROCK kinases participate in multiple signaling pathways in both hematopoietic and nonhematopoietic cell types [51]. In T cells, ROCK2 can directly activate interferon regulatory factor 4, a transcription factor necessary for Th17 differentiation [52]. Lupus-prone mice show increased ROCK2 activation, and treatment of these mice with fasudil, a ROCK inhibitor, ameliorated both Th17 dysregulation and their lupus-like disease [52]. ROCK activity in T cells is augmented by PP2A, which as discussed above is upregulated in SLE [7,53]. A recent study demonstrated that IL-17A and IL-21 production due increased ROCK activity in SLE T cells can be blocked using ROCK inhibitors [54]. The authors found that selective and nonselective ROCK inhibitors have overlapping but similar effects, concluding that selective ROCK2 inhibition may be sufficient to modulate the Th17-axis dysfunction seen in SLE [54]. KD025, a selective ROCK2 inhibitor, is in early-phase clinical trials for several different immune-related conditions.

BRUTON'S TYROSINE KINASE

Bruton's tyrosine kinase (BTK), a critical factor in the B-cell receptor signaling cascade, has long been an attractive therapeutic target in SLE. BTK signaling is necessary for B-cell activation, and congenital deficiency of BTK results in agammaglobulinemia and immunodeficiency. As SLE is often thought of as an autoantibody-driven disease, it is perhaps not surprising that BTK inhibition decreases autoantibody production and ameliorates nephritis in multiple different murine models of lupus [55–58]. However, BTK also mediates signaling through the Fcγ receptor and TLR. The production of IFN-α by pDCs in response to nucleic acid is dependent on BTK signaling through TLR9 [59]. BTK inhibition may thus interrupt SLE pathophysiology in multiple ways. In a recent murine study of IFN-α-accelerated lupus nephritis, a BTK inhibitor was more effective than BAFF or Syk inhibition at decreasing autoantibody levels, reducing plasma cell numbers, and improving survival [60▪]. There is currently one BTK inhibitor approved for treatment of B-cell malignancy; in autoimmunity, a phase 2 study of the BTK inhibitor LY3337641 is currently in progress for treatment of rheumatoid arthritis (ClinicalTrials.gov, NCT02628028).

RAS

The role of Ras/mitogen-activated protein kinase (MAPK) signaling in SLE T-cell dysfunction has been highlighted by several clinical associations. Ras is a small GTPase that exists in three isoforms – K-ras, N-ras, and H-ras. These enzymes are involved in many different signaling and cell cycle pathways, including mTOR and MAPK. Noonan syndrome is a neurodevelopmental disorder associated with various gene mutations in the Ras/MAPK pathway; some of these genes have also been implicated in SLE genome-wide association studies, and there have been several case reports of SLE in Noonan syndrome patients [61]. Somatic gain-of-function mutations in Ras genes have been implicated in both malignancies as well as nonmalignant lymphoproliferative syndromes. More recently, an unusual presentation of SLE in a young boy was also associated with a somatic gain-of-function mutation in *KRAS* [62].

Due to their role as oncogenes, the RAS GTPases have been an intensive area of interest in cancer therapy. However, targeted inhibition of these enzymes has proved challenging, and there are currently no approved Ras inhibitors on the market [63].

CONCLUSION

SLE is a heterogeneous disease and the underlying mechanisms may vary among patients, further increasing the complexity in understanding pathogenesis (Fig. 1) [64]. With this complexity in mind, this review is not intended to be a comprehensive list of new findings in SLE. Recognition that monogenic forms of lupus may yield important insights in pathophysiology suggest that there are likely to be many more advances in understanding in the years to come, allowing further identification of potential targets for therapy.

Acknowledgements

None.

Financial support and sponsorship

The work described here was supported in part by R01AI049954 and R01AI068787 (GCT).

Conflicts of interest

There are no conflicts of interest.

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