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

Atul A. Deodhar

Atul A. Deodhar, MD, is Professor of Medicine and Medical Director of rheumatology clinics at the Division of Arthritis & Rheumatic Diseases in Oregon Health & Science University, Portland. He is Board Certified in Internal Medicine and Rheumatology; and is a fellow of the American College of Rheumatology, and also American College of Physicians.

Dr Deodhar is the immediate past-chair of SPARTAN (Spondyloarthritis Research and Treatment Network), an organization of North American Rheumatologists dedicated to education and research in the field of axial spondyloarthritis. He also serves on the American College of Rheumatology's (ACR) treatment guidelines sub-committee, and is the associate editor of the Advanced Rheumatology Course by Association of Health Professionals in Rheumatology (ARHP). He has served the ACR in various other capacities as a vice chair of the annual meeting planning committee, member of the peripheral MRI task force, Association of Rheumatology Health Professionals (ARHP) nominating committee and developer of the ARHP online advanced rheumatology course. Dr Deodhar serves on the Rheumatology Board of the American Board of Internal Medicine (ABIM)

Dr Deodhar is a reviewer for *Arthritis & Rheumatology*, *Annals of the Rheumatic Diseases*, *Annals of Internal Medicine*, among several other journals. His research interests are axial spondyloarthritis, and psoriatic arthritis. He has authored 3 books, over 150 peer-reviewed articles; several book chapters, and editorials. Dr Deodhar has been a guest editor for Best Practice and Research Clinical Rheumatology, and Current Opinion in Rheumatology. He has been a principal or co-investigator in more than 100 clinical trials, mostly focused on therapies for ankylosing spondylitis, psoriatic arthritis, and rheumatoid arthritis.

He completed his fellowship in rheumatology at Oregon Health & Science University, and before that, a research fellowship in rheumatology at the Royal Cornwall Hospital, Truro, England. He completed his residency in internal medicine and geriatrics at the Royal Cornwall Hospital, Truro, as well as in the Sassoon General Hospital and King Edward Memorial Hospital, Pune, India. He received his MBBS and MD degrees from the University of Pune, India; and the MRCP from the Royal College of Physicians, London, England.

Yehuda Shoenfeld

Prof. Yehuda Shoenfeld is the founder and head of the Zabludowicz Center for Autoimmune Diseases, at the Sheba Medical Center which is affiliated to the Sackler Faculty of Medicine in Tel-Aviv University, in Israel. Dr Shoenfeld is the Incumbent of the Laura Schwarz-Kipp Chair for Research of Autoimmune Diseases at the Tel-Aviv University.

His clinical and scientific works focus on autoimmune and rheumatic diseases, and he has published more than 1920 papers in journals such as *New Eng J Med, Nature, Lancet, Proc Nat Acad Scie, J Clin Invest, J Immunol, Blood, FASEB, J Exp Med, Circulation, Cancer* and others. His articles have had over 55 000 citations. He has written more than three hundred and fifty chapters in books, and has authored and edited 40 books, some of which became cornerstones in science and clinical practice, such as 'The Mosaic of Autoimmunity', 'Infections and Autoimmunity' and the textbook

'Autoantibodies' and 'Diagnostic criteria of autoimmune diseases', all of which were published by Elsevier and sold by the thousands.

He is on the editorial board of 43 journals in the field of rheumatology and autoimmunity and is the founder and the editor of the IMAJ (Israel Medical Association Journal) the representative journal of science and medicine in the English language in Israel, and also is the founder and Editor of the 'Autoimmunity Reviews' (Elsevier) (Impact factor 7.095) and Co-Editor of 'Journal of Autoimmunity' (Impact factor 7.018). He has organized over 20 international congresses on autoimmunity.

Prof. Shoenfeld received the EULAR prize in 2005, in Vienna, Austria: 'The infectious etiology of anti-phospholipid syndrome'. In UC Davis, USA, Dr Shoenfeld received the Nelson's Prize for Humanity and Science for 2008. In 2009 he was honored as Doctoris Honoris Causa, from Debrecen University (Hungary). He has recently been awarded the ACR Master Award in 2013.

Prof. Shoenfeld has described two new syndromes: the ASIA syndrome (Autoimmune Syndromes Induced by Adjuvants) and the Hyperferritinemic Syndrome.

Prof. Shoenfeld was head of department of internal medicine for 27 years and has educated a long list of students (>40) being heads of departments and institutes.

Christian Roux

Christian Roux is Professor of Rheumatology and Head of Bone Unit at Cochin Hospital, Paris Descartes University, Paris, France.

He received his medical training at the University of Paris. He has published works in the areas of primary and secondary osteoporosis, malignant bone diseases, and Paget's disease. He is author and co-author of 260 original papers, and chapters of books. He is Past President of GRIO, the French Society of Osteoporosis. He is a member of the Editorial Board of Osteoporosis International.

The field of spondyloarthritis coming of age

Atul A. Deodhar

Within the last few years, immune-mediated rheumatic diseases have seen spectacular progress in all areas – from discoveries in genetics and cellular mechanisms underlying pathogenesis of autoimmunity, to translation of this knowledge in developing novel therapies. This progress is not more evident in any particular disease area than in spondyloarthritis. After tumor necrosis factor inhibitors first got approved by the U.S. Food and Drug Administration (FDA) in 2005, last year a new cytokine inhibitor therapy got approved by the FDA [1]. We witnessed multiple articles being published, from new understanding of epidemiology of chronic back pain and ankylosing spondylitis within the United States [2–4], to possible new biomarkers for ankylosing spondylitis [5,6]; and from new treatment guidelines from the American College of Rheumatology, Spondylitis Association of America, Spondyloarthritis Research and Treatment Network, and from the Assessment of Spondyloarthritis International Society (ASAS) and European League against Rheumatism [7,8] to a phase II trial on a small molecule oral therapy blocking the intracellular signaling heralding a new class of drugs that could be effective in treating the signs and symptoms of ankylosing spondylitis [9]. This issue of the Current Opinion in Rheumatology highlights some of these, and other areas, where real progress is being made in spondyloarthritis. Apart from recounting the progress being made, these articles also discuss where further research is necessary and even suggest a research agenda.

Neerinckx and Lories (pp. 287–292) chronicle our understanding of the pathogenesis of new bone formation in spondyloarthritis – from clinical trials and prospective cohort studies to translational laboratory investigations. They also discuss a new paradigm that is developing in the field of spondyloarthritis, in which sustained and effective suppression of inflammation could possibly inhibit the structural disease progression. Deodhar, Kumthekar, and Dubreuil (pp. 293–297) discuss the concept of 'minimal disease activity' (MDA) in the context of rheumatoid arthritis and psoriatic arthritis (PsA) and argue the need for development of MDA in axial spondyloarthritis (axSpA). They suggest a possible methodology for development of MDA in axSpA, with input from patient research partners, experts in the field, and give guidance for using multiple sources for candidate items to be included in such an instrument.

In this issue of Current Opinion in Rheumatology, the reader will find two articles dealing with recognizing and managing common comorbidities – acute anterior uveitis (AAU), the commonest comorbidity in patients with spondyloarthritis, and fibromyalgia the most commonly missed comorbidity in these patients. Rosenbaum (pp. 298–303) highlights the advances made in the field of HLA-B27-related uveitis within the last year in his article 'New developments in uveitis associated with HLA B27'. These advances range from documentation of the world-wide prevalence of AAU, the genetics of uveitis, and include the progress being made in the treatment of uveitis. The second article deals with fibromyalgia, the comorbidity that is most commonly missed in patients with spondyloarthritis. Mease (pp. 304–310), in his essay on 'Fibromyalgia, a missed comorbidity in spondyloarthritis', discusses central sensitization – the underlying pathophysiology of chronic widespread pain, or fibromyalgia. He then discusses the prevalence of fibromyalgia in spondyloarthritis patients, and its impact on the commonly used disease activity measures, many of which have subjective elements. These can be exaggerated in patients with fibromyalgia and may not reliably assess true inflammatory disease. He argues that recognizing this comorbidity is essential when evaluating the impact of immunomodulatory therapy in spondyloarthritis patients. Raychaudhuri's (pp. 311–316) article on JAK-STAT pathway in spondyloarthritis is very timely, and it describes the translational research in the area of intracellular signaling cascade inhibition. He discusses the pathophysiologic role of intracellular signaling of IL-23 and IL-17 cytokines

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in PsA and axSpA, and latest clinical trials on tofacitinib, a JAK1 and JAK3 inhibitor in PsA and ankylosing spondylitis.

Lastly in a special article, Dubreuil and Deodhar (pp. 317–322) tackle the controversial issue of the sensitivity and specificity of the 2009 ASAS Classification Criteria for axSpA. They recount the tremendous progress made in the field of axSpA that can be directly accounted for by the development of these classification criteria. They also narrate the areas of controversy and suggest one of many possible ways forward. They argue that improving the sensitivity and specificity of these classification criteria can only help to refine the axSpA populations definitions for research and ultimately improve axSpA patient care and outcomes.

It is not possible to cover all the hot topics in the field of spondyloarthritis in a single issue of a journal. Apart from the topics mentioned above, we are making rapid progress in novel imaging techniques, from whole-body MRI to low-dose computed tomography scans, helping us in earlier diagnosis of axSpA. We are finding new biomarkers for spondyloarthritis, a real unmet need so far. We stand on the cusp of inventing several new therapies for axial spondyloarthritis, from agents that block IL-17 to selective JAK inhibitors, and soon to selective IL-23 inhibition. We also look forward to 'strategy trials' such as 'treat-to-target' in axSpA, and finding if such aggressive strategies will prevent new bone formation and change the natural course of the disease.

We hope that this issue of Current Opinion in Rheumatology will give the reader a glimpse of the excitement in the field of spondyloarthritis, and the suggested research agenda will give an indication where this field is heading.

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Mechanisms, impact and prevention of pathological bone regeneration in spondyloarthritis

Barbara Neerinckx[a,b] *and Rik Lories*[a,b]

Purpose of review
To discuss different aspects of new bone formation in patients with spondyloarthritis based on emerging data from clinical trials, prospective cohort studies and translational laboratory investigations.

Recent findings
New bone formation potentially leading to ankylosis of the spine and sacroiliac joints remains an important concern for patients with axial spondyloarthritis. New therapeutic strategies, in particular targeting of interleukin-17, have emerged in addition to the antitumor necrosis factor drugs, but we still fail to fully understand the mechanisms of structural disease progression. A new paradigm is developing in which sustained and effective suppression of inflammation likely inhibits this structural disease progression. Biomechanical factors, in particular changes in bone microarchitecture in the vertebrae, and the need for core stability could provide a new framework to understand the relationship between bone remodeling and inflammation and to develop long-term strategies.

Summary
New bone formation leading to ankylosis remains a hallmark of axial spondyloarthritis and should be further investigated. The clinical data that progressively become available support the concept that effective and sustained therapy will be beneficial for the patients not only in short-term, but also in long-term outcomes.

Keywords
ankylosing spondylitis, ankylosis, bone, spondyloarthritis

INTRODUCTION

Spondyloarthritis is a chronic inflammatory skeletal disease that covers different diagnostic entities that share clinical, genetic, pathophysiological and radiographic characteristics [1]. Currently, the location of the main clinical presentations helps to distinguish axial spondyloarthritis, including ankylosing spondylitis and nonradiographic axial spondyloarthritis, and peripheral spondyloarthritis. In axial spondyloarthritis, the dominant symptom is inflammatory back pain and stiffness. Peripheral spondyloarthritis covers more heterogeneous presentations. Many patients in this group are diagnosed with psoriatic arthritis and with inflammatory bowel disease-associated arthritis. Here, oligoarthritis of the lower limbs and clinical enthesitis, for example at the Achilles tendon insertion or the plantar fascia, are key manifestations. However, polyarticular disease involving small joints of the hand is not uncommon, in particular in the group of patients with psoriatic arthritis.

Structural damage to the skeleton as a consequence of chronic arthritis is clinically important as it contributes strongly to loss of function and disability. In axial spondyloarthritis, the sacroiliac joints and the spine are typically sites wherein such damage occurs. Progressive disease potentially translates into bridging of the sacroiliac and the facet joints and the formation of bridging syndesmophytes between vertebral bodies. Bone destructive lesions also occur, in particular erosion of the sacroiliac joints or end-plates of the vertebra but appear to represent a more transient phase followed by the bone remodeling process that leads to ankylosis. Equally important from a clinical and

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KEY POINTS

- Long-term follow-up data of patients with spondyloarthritis treated with anti-TNF drug indicate slow but successful effects of the drugs on ankylosis.
- Loss of bone with changes in microarchitecture could be the drivers of the ankylosing process.
- Early data with IL-17 blocker secukinumab warrant optimism for effects on radiographic progression in axial spondyloarthritis.
- Further research on the relationship between inflammatory cytokines, growth factors and target cells is required to move the field forward.

pathophysiological perspective is the inflammation-associated bone loss that occurs in the spine, increasing strongly the risk for fractures in patients with axial spondyloarthritis. As further elaborated below, this bone loss and the associated changes in the bone microarchitecture have been proposed as a potential driving mechanism for the ankylosing process [2▪]. In peripheral joints, both bone erosion and bone remodeling can be found. Many affected joints show varying degrees of new bone formation, but the development of full joint ankylosis is rare, in particular in the larger joints.

The management of spondyloarthritis and the prospects for the individual patients have dramatically changed after the turn of the century. The introduction of targeted strategies that aim to neutralize the cytokine tumor necrosis factor (TNF) has led to unprecedented control of inflammation in a large number of patients [1]. More recently, a second wave of drug development seems to finds its way into clinical practice. A novel strategy directed at neutralization of proinflammatory interleukin-17 (IL-17) spearheads the arrival of new treatments [3,4▪]. In addition to market-approved anti-IL-17, there are also early data available and clinical trials underway evaluating the effect of anti-IL12/23 [5] as well as studying small molecules such as Janus kinase (JAK)/Signal Transducer and Activator of Transcription (STAT) inhibitor tofacitinib [6▪] or phosphodiesterase 4 inhibitor apremilast [7].

Although the clinical effect of anti-TNF strategies has been undisputable for a large number of patients, the effect of such interventions on structural disease progression is less clear [8,9]. In particular, the early postclinical trial cohort studies comparing long-term follow-up of anti-TNF treatment with a historical cohort casted doubts about a structure-modifying effect on these drugs [10]. However, novel data from studies with TNF inhibitors and with the new drugs available are slowly bringing evidence that prevention of structural damage may not be an unachievable goal anymore.

THE IMPORTANCE AND IMPACT OF PROGRESSIVE STRUCTURAL DAMAGE IN AXIAL SPONDYLOARTHRITIS

Individual variation in the extent, speed of progression and impact of structural damage, in particular in the axial forms, is highly variable [11]. Nevertheless, it is an important concern and point of attention for many patients and physicians for various reasons. The distinction between ankylosing spondylitis and the nonradiographic forms is largely made by the presence of specific changes in the radiographic evaluation of the sacroiliac joints. The newly developed classification criteria for axial spondyloarthritis [12] and the delineation of nonradiographic axial spondyloarthritis as a specific entity have stirred up some controversy [13▪▪,14]. From a practical and patient-focused point of view, the distinction between ankylosing spondylitis and nonradiographic axial spondyloarthritis should be best abandoned in diagnosis and management of disease and only used for classification in clinical and translational studies [13▪▪]. The debate did identify the important remaining concern that we do not sufficiently understand the time-course of disease in individual patients and in particular ignore the answer to the question which patients will ultimately develop ankylosis.

Progressive ankylosis strongly contributes to the burden of the disease and resulting disability. Older data presented by Machado *et al.* [15] clearly identified that both inflammation and structural damage define the effect of axial spondyloarthritis on the patient. Inflammation appears to be most important in the early disease phase, whereas structural damage takes steps to the foreground as disease duration increases. Over the last couple of years, further insights have been provided into specific features of the disease and their impact on the patient. Poddubnyy *et al.* [16▪▪] studied a cohort of patients from open-label extensions of clinical trials testing the effects of either infliximab or etanercept in patients with ankylosing spondylitis. Despite the observation that this cohort of successfully treated patients did show radiographic progression, their functional status and the assessment of the spinal mobility remained stable over time. This supports the view that sustained control of inflammation results in disease modification at the clinical level even if the definition of structural modification at the radiographic level is not met [17].

IS TREATMENT OF INFLAMMATION CAPABLE OF PREVENTING STRUCTURAL DISEASE PROGRESSION?

The great clinical success associated with the introduction of different TNF inhibitors in clinical practice has sparked expectations that structural damage, and in particular new bone formation leading to ankylosis in the spine, would also be prevented by the successful intervention. This initial expectation resulted in disappointment. Two-year follow-up studies with different TNF antagonists did not find a difference in radiographic progression compared to the historical prospective OASIS cohort [18–20]. However, more recent data strongly suggest that sustained TNF inhibition over a much longer time period may result in effective inhibition of radiographic progression. Baraliakos *et al.* [21] reported on a cohort of ankylosing spondylitis patients treated with infliximab. Although by the end of their prospective evaluation, the sample number of patients became low, curves between treated and nontreated patients became clearly different. Haroon *et al.* [22] also suggested that anti-TNF treatments in particular when started early would have an impact on radiographic progression. More recently, Maas *et al.* [23▪] also reported their prospective cohort follow-up with patients being exposed to anti-TNF treatment for up to 8 years. Remarkably, structural disease progression continued in a linear way up to 4 years after the initiation of anti-TNF therapy. However, in the next phase, the measured disease progression was strongly reduced and interrupted the linear course. Taken together, these novel data could provide support for an emerging view that we proposed earlier in this journal on structural disease progression in patients with axial spondyloarthritis [2▪] (Fig. 1).

Inflammation at the spine leads to trabecular bone loss and increased fracture risk, in particular when there is osteitis in the vertebral bodies [24,25▪]. Inflammation therefore likely affects the bone's microarchitecture. Loss of this bone microarchitecture in a part of the body where dynamic loading is important is hypothesized to trigger a regenerative or reparative response [2▪]. As restoring bone quality in the trabecular bone may be difficult if inflammation persists, stabilizing new bone formation occurs at the vertebral corners and the facet joints. In this hypothesis, progressive ankylosis is mainly driven by bone instability and will improve after sustained treatment of inflammation. This would also imply that, in addition to continued and efficacious treatment to control inflammation, dedicated physiotherapy aiming at increasing core stability and proprioception are important factors for intervention [2▪]. The importance of rapid stabilization as driving force for ankylosis appears to be confirmed in another recent study by Maas *et al.* [26▪▪]. Here, the authors show that structural disease progression in the cervical spine even under anti-TNF therapy, rather involved the cervical facet joints than the vertebral bodies.

Among the new strategies, secukinumab, a monoclonal antibody directed against IL-17A, is currently used in the clinic for the treatment of axial spondyloarthritis [3,4▪], psoriasis [27] and

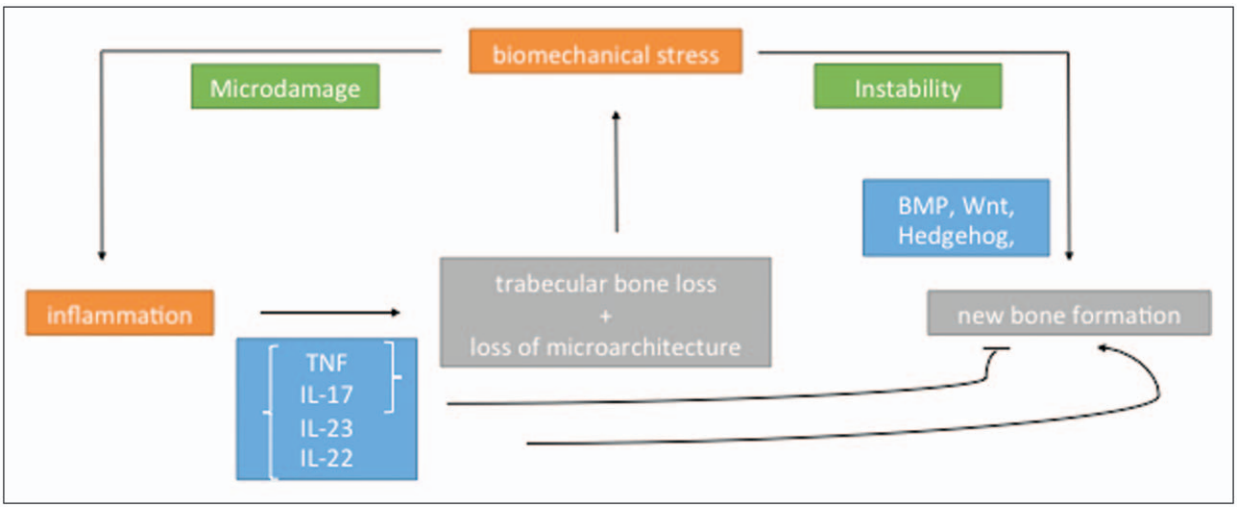

FIGURE 1. Impact of biomechanical factors in spondyloarthritis. Biomechanical stress can contribute to inflammation by causing microdamage. Cytokines produced can lead to bone loss and instability resulting in a different type of biomechanical stress that triggers new bone formation to stabilize the spine or joint. Cytokines such as TNF and IL-17 negatively affect bone formation *in vitro*, whereas IL-22 can stimulate bone formation. Bone morphogenetic proteins (BMPs), Wnts and Hedgehog (HH) proteins directly stimulate ankylosis. IL-17, interleukin-17; TNF, tumor necrosis factor.

psoriatic arthritis [28]. The clinical effect size at the group level of secukinumab treatment appears comparable to that of TNF inhibitors and the drug appears to be effective in a significant proportion of patients that failed anti-TNF therapy [3,4▪]. A first analysis after 2 years did not document significant structural disease progression in axial spondyloarthritis [29]; however, there are different caveats that should be considered before claiming that anti-IL-17A has stronger effects than TNF on structural disease progression. Although classical parameter comparisons do not suggest strong differences in selected patient populations, patients with spondyloarthritis are likely better diagnosed and treated in this decennium that in the previous one. Patients with high risk of radiographic progression may be treated earlier and better than before. Thus, it is unclear if the observed data with anti-I7 represent an effect of shifts in the patient population included in trials or a drug effect. Additional data will be necessary to fully understand the impact of novel drugs on radiographic progression.

Data on nonsteroidal anti-inflammatory drug (NSAID) use in patients with axial spondyloarthritis, still the first-line treatment, also remain somewhat controversial. Continuous NSAID intake could have a significant effect on structural disease progression [30,31]. However, the ENRADA trial did not confirm this observation [32▪▪]. Here, radiographic progression was not statistically different between patients receiving continuous or on-demand diclophenac. Again, differences in patient population included in clinical trials from different decades may explain this inconsistency. Patients with severe inflammation and high risk for radiographic progression may more rapidly be considered for advanced treatments. A poststudy analysis of the trial from Wanders *et al.* [30] indeed indicated that the patient population who benefited most from continuous NSAID treatment were those patients with elevated C reactive protein probably reflecting severe disease [33].

INFLAMMATION AND NEW BONE FORMATION, STILL A DIFFICULT QUESTION?

The relationship between inflammation and new bone formation has been strongly debated since the first data on radiographic progression in patients treated with anti-TNF became available [8,10]. Increasing evidence supports the view that inflammation and ankylosis are linked but molecularly and cellular uncoupled processes [8,34,35]. Many aspects of this view are based on the sequential analysis of disease sites by nuclear MRI [36,37]. Fatty lesions have been proposed as a transitional phase between active inflammation and new bone formation [35,38▪] [39], and the tissue metaplasia seen in these lesions has recently been confirmed by histology [40▪▪].

The molecular pathways that stimulate new bone formation appear clearly distinct from the classical inflammatory cascades that are associated with the disease and that are currently targeted by available and upcoming drugs. When discussing new bone formation, growth factor signaling cascades such as bone morphogenetic proteins (BMPs), Wnts and Hedgehogs come into the focus [8]. Inhibition of Dickkopf-1 (DKK1), an antagonist of the Wnt signaling pathway, shifts erosive arthritis in mice toward ankylosing disease [41]. Inhibition of BMP signaling by overexpression of its antagonist noggin was earlier shown to protect against the development of joint ankylosis in mice [42]. Hedgehog signaling has been specifically associated with chondrocyte hypertrophy [43]. A chemical antagonist of the pathway inhibits new bone formation in different mouse models [44].

The impact of inflammatory cytokines on these processes remains largely unclear. Sherlock *et al.* [45] suggested that IL-22 production triggered by systemic overexpression of IL-23 is a key player in new bone formation, but further evidence for this hypothesis has only come from specific in-vitro experiments that lack further in-vivo validation [46]. Other in-vitro experiments have further investigated the link between inflammatory cytokines, growth factor cascades and cell differentiation assays. TNF and IL-17 have a mostly negative impact on setups focused on chondrogenic or osteogenic differentiation, an in-vitro observation that appears to be confirmed *in vivo*. High levels of TNF expression, such as seen in the human TNF transgenic mouse model, appear to complete inhibit bone remodeling and repair [41]. Nevertheless, in some experimental setups, negative effects of IL-17 and TNF on the bone forming process appear to be inversed. The differentiation status of the cells used in such setups appears to be a key determinant of the outcome. For instance, in cells that have already committed to bone formation, IL-17 and BMP2 appear to have remarkable synergistic effects in stimulating the process [47▪▪].

MONITORING OF BONE REMODELING IN SPONDYLOARTHRITIS

Biomarker studies are facing many challenges in this context. Many of the available reports are based on cross-sectional sampling and do not provide sufficient follow-up to allow a full prospective view on

the data. There is an unmet need for large prospective evaluations that set high standards for sample taking, its timing and storage. Any evaluation of markers associated with bone remodeling needs to take into consideration that effects on bone at the systemic level, associated with inflammation, can strongly impact the potential to measure events at a smaller scale, for instance in the developing syndesmophyte. There is a need for combined and innovative biomarker and imaging studies as growth factor concentrations at the local level are much more relevant than their systemic presence. Indeed, molecules associated with embryonic skeletal development such as BMP and Wnts exert their effects by local concentration gradients established in complex connective tissues that are rich in extracellular matrix molecules, thus representing an enormous challenge for systemic sampling and analysis.

Some data are available, however, and suggest that further investment in these questions may be warranted. DKK1 and Wnt signaling have been best studied. The original report on DKK1 from Diarra *et al.* [41] indicated that spondyloarthritis patients would have very low levels of DKK1. Additional data demonstrated that high levels of functional DKK1 predict protection against radiographic progression [48]. However, Daoussis *et al.* [49] intriguingly showed that levels of DKK1 are elevated in patients with axial spondyloarthritis but that DKK1 itself is not functional. Indeed, functional DKK-1 levels appear to be lower in the serum of patients with ankylosing spondylitis compared to controls, and levels are inversely correlated with progression of ankylosis [50]. Such data were also reported for sclerostin, another Wnt antagonist [48,51]. Data on BMPs are less convincing and consistent, mostly because of the small cohort sizes.

CONCLUSION

The opportunities to effectively treat patients with spondyloarthritis are still growing and control of inflammation and associated symptoms is an increasingly achievable goal. Nevertheless, progressive ankylosis remains a concern. As patients are treated earlier and more consistently, these therapies also appear to have an impact on structural disease progression. Inflammation resulting in bone loss may be the driving factor of bone remodeling in this disease. Further research is still required in particular to better understand the relationship between the key inflammatory cytokines that play a role in spondyloarthritis and the growth factors that steer bone remodeling. From a clinical perspective, carefully designed prospective cohorts will be necessary to confirm the evolving hypotheses.

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Conflicts of interest

There are no conflicts of interest.

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Minimal disease activity in axial spondyloarthritis: the need of the hour and a proposal for development

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Purpose of review
Axial spondyloarthritis (axSpA) is a chronic inflammatory condition with articular and extra-articular manifestations. Remission, a state of absence of clinical and imaging signs of disease activity over time, is the goal of management. This review addresses the concept of minimal disease activity (MDA) in axSpA, which is less stringent than remission, and is closer to patient and provider acceptable low disease state.

Recent findings
Existing axSpA treatments improve physical function and quality of life, and lead to remission in a minority of patients. A consistent MDA state decreases disease progression in rheumatoid arthritis and psoriatic arthritis. We argue a need to develop MDA in axSpA for clinical practice and clinical trials and propose methodology. Considering that MDA will be used in clinical practice, its elements must be easy to collect and cover both musculoskeletal and extra-articular domains. MDA will complement current disease activity measures in axSpA.

Summary
Defining an MDA target in axSpA would provide an outcome measure that is less stringent than remission, and will likely predict function and quality of life. We propose methods to develop MDA in axSpA and that further research be performed to determine if treating to an MDA target in axSpA improves patient outcomes.

Keywords
axial spondyloarthritis, minimal disease activity, outcome measure, remission

INTRODUCTION

Minimal disease activity (MDA), as defined by the Outcome Measure in Rheumatology Clinical Trials (OMERACT) 6 conference, encompasses both remission and low disease activity. MDA is a state that is deemed 'a useful target of treatment by both patient and physician, given current treatments and knowledge'. MDA allows a small amount of residual disease activity, and is not a state of complete remission. MDA criteria have been developed for rheumatoid arthritis (RA) and for psoriatic arthritis (PsA) [1,2]. Development of MDA in RA and PsA has taken advantage of the OMERACT core sets. It has been shown that maintenance of an MDA state decreases the progression of joint damage [3,4]. One study has also demonstrated that early achievement of MDA can be considered a predictor of treatment efficacy with tumour necrosis factor (TNF) inhibitors (TNFi) in PsA [5].

DISEASE ACTIVITY IN AXIAL SPONDYLOARTHRITIS IS CORRELATED WITH BOTH RADIOGRAPHIC AND FUNCTIONAL OUTCOMES

In RA, greater disease activity, as measured by the DAS28, is correlated with both functional loss and radiographic damage [4,6]. In ankylosing spondylitis (AS), parallel relationships have been demonstrated between disease activity and both function and spinal radiographic changes. The OASIS study, which followed 184 AS patients for 12 years, found

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KEY POINTS

- A minimal disease activity (MDA) state encompasses both remission and low disease activity, and is described as 'a useful target of treatment by both patient and physician, given current treatments and knowledge'. It has been previously established in both rheumatoid arthritis and psoriatic arthritis.
- Disease activity in axial spondyloarthritis (axSpA) is associated with both functional and radiographic outcomes, thus MDA would be a valuable outcome measure in treatment studies of axSpA, and MDA assessment at the point-of-care would inform shared decision making.
- Considering the multisystem involvement of axSpA, there is a need to establish MDA criteria that include assessments of extra-articular features for use in clinical practice as well as in clinical trials. Future 'treat-to-target' studies will establish if maintenance of MDA will improve long-term outcomes in patients with axSpA.

that for every unit increase in disease activity (Ankylosing Spondylitis Disease Activity Score; ASDAS), the radiographic damage as measured by modified Stoke Ankylosing Spondylitis Spine Score (mSASSS), worsened by 0.72 units over 2 years. At study end, those with high disease activity had nearly twice the radiographic damage as those with inactive disease [7]. Similarly, the German cohort, GESPIC, demonstrated associations in a combined population of AS and nr-axSpA ($n = 178$) [8▪]. In GESPIC, the mSASSS increased by more than 2 units per unit increase in the time-averaged ASDAS. Disease activity was associated with syndesmophyte formation; no patients with low disease activity developed syndesmophytes, but 29% of those with very high disease activity had new syndesmophyte development or syndesmophytes progression.

Function in axSpA may reflect accrued damage over time, but evidence also shows that greater disease activity is associated with impaired function. Analysis of 2-year data from OASIS found that AS disease activity (BASDAI) was correlated with two patient-reported functional indices: BASFI ($r = 0.66$) and the Dougados Functional Index (DFI; $r = 0.59$), independent of structural changes [9]. Similarly, a meta-analysis of clinical trials of TNF-inhibitors in AS demonstrated consistent improvements in disease activity and physical function, despite the fact that trials have not shown reductions in structural changes over periods up to 2 years [10].

MINIMAL DISEASE ACTIVITY DEVELOPMENT IN OTHER FORMS OF ARTHRITIS

Minimal disease activity measurement tool has been developed for rheumatoid arthritis and psoriatic arthritis.

Rheumatoid arthritis

The need for a definition of MDA in patients with RA was based on the conclusions from the TICORA study, which showed that intensive control of disease activity in RA reduced radiographic progression of disease, and improved physical function and quality of life [11]. It was therefore thought that achieving and maintaining a low disease activity or remission state was important in the long-term management of RA.

The MDA definition for RA was developed in a three-step process [2]. Firstly, an MDA discussion group was convened at the American College of Rheumatology (ACR) meeting in 2003. At this meeting, agreement was reached on candidate measures to consider in the initial definition of MDA, and an opinion-based stakeholder survey on possible operational definitions of MDA was developed. The second step in early 2004 was the stakeholder survey to derive a limited set of possible definitions for MDA. At the OMERACT 7 meeting, participants discussed this limited set of candidate definitions and chose an agreed definition. A database of 730 consecutive RA patients in 40 clinics around the US and Canada was used to obtain 60 individual profiles for inclusion in a subsequent questionnaire. The measures in the profile were from the RA core set as developed by OMERACT [i.e. pain, swollen joints, tender joints, Health Assessment Questionnaire (HAQ), physician global, patient global and ESR]. For each profile, respondents were asked 'Is the patient described in the profile in MDA?' If at least 80% of respondents classified the profile as MDA, then the profile was considered to correspond to a patient in MDA. Thirty-eight respondents reviewed the profiles and there was at least 90, at least 80 and at least 70% agreement that 15, 17 and 22 profiles, respectively, were representative of MDA. In the end, the 80% consensus was selected as the threshold for the remainder of the project, and final MDA definitions were agreed upon, based on either DAS28 score of 2.85 or less or the core set definition. The core set MDA definition could be met if a patient had no tender or swollen joints and an ESR of 10 or less, *or* if at least five out of seven of the following criteria were met:

(1) Pain 2 or less (VAS 0–10)
(2) Swollen joint count 1 or less
(3) Tender joint count 1 or less
(4) HAQ 0.5 or less
(5) Physician global 1.5 or less (VAS 0–10)
(6) Patient global 2 or less (VAS 0–10)
(7) ESR 20 mm/h or less

Psoriatic arthritis

One rationale for developing MDA criteria in PsA was the broad disease spectrum and complexity, which affects domains beyond the joints. The OMERACT 8 agreed upon a core set of measures for PsA in 2006 and these were used as an anchor to develop the MDA criteria [1]. A questionnaire was compiled consisting of 40 PsA patient profiles that included the following measures: tender joint count, swollen joint count, enthesitis count, psoriasis area and severity index (PASI), psoriasis body surface area (BSA), VAS pain, patient global disease activity and HAQ. The questionnaire included the OMERACT definition of MDA and was sent electronically to rheumatologists and dermatologists identified through membership of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA). The respondents were told 'This patient comes to see you in the clinic. He/she has been on a stable dose of disease modifying antirheumatic drug (DMARD) therapy for over 6 months. Do you consider this patient to be in a 'minimal disease activity' state?' A 70% agreement was selected as a reasonable consensus, and profiles were classified as MDA if that threshold of agreement was reached between respondents. The final PsA MDA definition required at least five out of seven of the following criteria to be met:

(1) Tender joint count 1 or less
(2) Swollen joint count 1 or less
(3) PASI 1 or less or BSA 3 or less
(4) Pain 15 or less (VAS 0–100)
(5) HAQ 0.5 or less
(6) Patient global 20 or less (VAS 0–100)
(7) Tender entheseal points 1 or less

INSTRUMENTS FOR DISEASE ACTIVITY MEASUREMENT IN AXIAL SPONDYLOARTHRITIS

The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the ASDAS are the most widely adopted disease activity instruments in axSpA [12,13]. BASDAI can be simply calculated as a weighted average of six patient-reported questions regarding fatigue, spinal pain, pain originating in peripheral joints, entheseal pain and morning stiffness. ASDAS includes four patient-reported questions, but additionally requires an ESR or CRP measurement and calculation of a complicated formula using a dedicated application or web-based calculator for most users (available on the ASAS website, http://www.asas-group.org/mission-statement.php). There is no validated definition for disease remission using BASDAI, although a threshold of 3 or less has been used in clinical trials for low disease activity [14]. In ASDAS, remission is defined as a score under 1.3, moderate disease activity 1.3–2.1, high disease activity 2.1–3.5 and very high disease activity more than 3.5 [15]. ASAS also has developed treatment response criteria, five out of six (domain) improvement criteria and partial remission criteria. Each of these instruments *additionally* includes an assessment of function (BASFI). The functional assessment, though critically important to patients, does not necessarily reflect current disease activity, as prior damage may have led to functional loss that may not be restored even with complete disease remission [16,17].

LIMITATIONS OF EXISTING DISEASE ACTIVITY MEASURES

Although thresholds for disease activity in axSpA have been established using rigorous methodology, and have been validated for the ASDAS, both the ASDAS and the BASDAI have important limitations, including their focus on only the musculoskeletal manifestations of axSpA. Given that axSpA commonly has extra-articular manifestations, such as uveitis, skin disease, nail disease and inflammatory bowel disease, the lack of any assessment of these features in existing disease activity instruments is notable. For example, a man with a 40-year history of AS and a fused spine may have low BASDAI and ASDAS scores indicating 'remission' on treatment with a TNF-inhibitor, despite recurrent attacks of acute anterior uveitis leading to vision loss. Failure to account for extra-articular disease activity in axSpA may lead to inappropriately optimistic assessments using the existing axSpA disease activity instruments. The other drawback of the ASDAS is that, neither the ESR nor the CRP required to calculate the ASDAS is readily available at point-of-care, when the patient is being seen by the rheumatologist in the United States. To make a treatment decision based on the patient's disease activity as measured by ASDAS is therefore not always possible. The BASDAI is solely patient driven, with no objective input from the physician. The following proposed MDA measure in axSpA, which addresses extra-articular manifestations of axSpA

and would be available at the point-of-care, will not replace any of the existing disease activity measures, but will complement them.

THE NEED FOR A MINIMAL DISEASE ACTIVITY MEASURE IN AXIAL SPONDYLOARTHRITIS

Developing MDA criteria in axSpA would allow the assessment of important extra-articular manifestations that are associated with loss of function, as well as those affecting patients' quality of life. The goal of such an MDA assessment should be to incorporate disease features of importance to patients' function and radiographic progression, within an easy to calculate outcome measure. An important goal of establishing axSpA MDA would be its use in treatment trials as a measure that addresses the spectrum of axSpA disease and allows important comparisons of treatment effects across disease domains (e.g. eyes, skin, bowel). An MDA measurement that incorporates extra-articular manifestations may provide an additional basis for payers to cover treatments, which previously required evidence of spinal or peripheral arthritis activity, thereby improving patient access to effective treatments. Another equally important goal of the MDA criteria development would be application of MDA criteria in clinical care; such availability at the point-of-care may inform shared decision making between patients and clinicians. This MDA measure would have the potential to improve patient outcomes by allowing a treat-to-target strategy that ultimately prevents functional loss due to both articular and extra-articular manifestations.

PROPOSED METHOD OF DEVELOPMENT OF MINIMAL DISEASE ACTIVITY IN AXIAL SPONDYLOARTHRITIS

Development of MDA criteria in axSpA should involve both clinician and patient stakeholders, with methods similar to those used in the RA and PsA efforts (Fig. 1).

As was done for RA and PsA, a list of candidate measures for the axSpA MDA could be derived from several sources, including existing axSpA disease activity instruments, the ASAS/OMERACT core domains (Table 1)[18,19], expert clinicians and patient focus groups. An electronic stakeholder survey can subsequently reduce the set of candidate measures.

A sample of actual patient profiles (N~100) from existing axSpA cohorts representing the spectrum of axSpA disease will be required to evaluate if the patient is in an MDA state, or not in MDA using

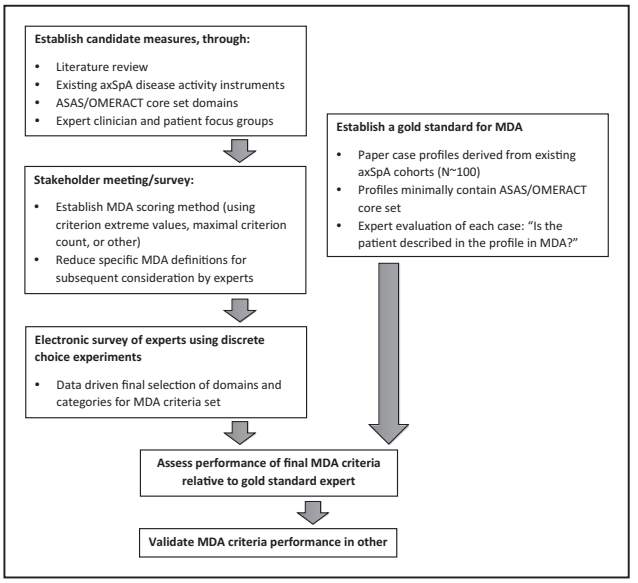

FIGURE 1. Flow diagram for axial spondyloarthritis minimal disease activity development methodology.

an electronic survey of expert clinicians from multiple disciplines (e.g. rheumatology, ophthalmology, dermatology and gastroenterology). The experts will need to define the maximum tolerated value for each measure that they would consider for the patient to remain in MDA methods for scoring MDA, including cut points for extreme values for each measure, and/or a maximum count of

Table 1. ASAS/OMERACT core set domains for studies on symptom-modifying anti-rheumatic drugs disease controlling anti-rheumatic treatments and physical therapy

Domain	Instrument
Function	BASFI
Spine pain	VAS/NRS
Spinal mobility	Chest expansion, modified Schober and occiput to wall distance, lateral spinal flexion or BASMI
Patient global	VAS/NRS
Spine stiffness	Duration of morning stiffness in spine
Peripheral joints	Swollen joint count
Entheses	Validated enthesitis scores such as Berlin, MASES
Acute phase reactants	ESR and CRP
Spine radiographs	Lateral lumbar spine and lateral cervical spine
Fatigue	Fatigue question BASDAI

BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; DFI, Dougados Functional Index; NRS, Numeric rating Scale; VAS, Visual Analogue Scale. Adapted from [18,19].

measures allowable for axSpA MDA. Discrete choice experiments will allow a data-driven final selection of the domains and categories for the axSpA MDA criteria set. Specific candidate formulas for MDA will then need to be tested with different cut points, their sensitivity/specificity and ROC curves plotted. The final preliminary MDA criteria will need to be established through expert consensus, and will require validation in a separate longitudinal axSpA cohort, as well as in prospective clinical trials in axial spondyloarthritis.

As noted above, an easy-to-calculate MDA assessment would be very valuable in daily clinical care, but another important goal of these MDA criteria would be for use as an endpoint in clinical research. Novel treatment modalities in axSpA are rapidly being developed; therefore, any MDA criteria would need periodic reassessment, as would other outcome criteria.

CONCLUSION

Axial spondyloarthritis is a multisystem disease with the potential to affect extra-articular sites, in which patients may experience significant functional impairment even when the musculoskeletal inflammatory process is quiescent. Establishment of MDA criteria using a rigorous process that involves a multidisciplinary group of clinicians and patient stakeholders would be of great value. The development of axSpA MDA would primarily allow treatment comparisons across multiple disease domains in treatment trials, but will also be useful at the point-of-care to inform shared decision making between axSpA patients and clinicians.

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Conflicts of interest

None.

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New developments in uveitis associated with HLA B27

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Purpose of review
Uveitis is the most common, clinically apparent, extra-articular manifestation of axial spondyloarthritis. This review summarizes recent publications related to this form of uveitis.

Recent findings
Studies published since the start of 2015 address the worldwide prevalence of human leukocyte antigen (HLA) B27-associated uveitis, the prevalence of axial spondyloarthritis among patients with B27-associated acute anterior uveitis (AAU), the genetics of AAU and some of the clinical implications of AAU. Progress has been made in the treatment of uveitis in general and in the treatment of uveitis in association with spondyloarthropathy in particular. The pathogenesis of AAU might derive clues from the above as well as from an understanding of the microbiome and possibly from knowledge derived from uveitis in association with Ebola.

Summary
Although HLA B27-associated uveitis has been recognized since 1973, a variety of recent observations shed new light on this common clinical association with spondyloarthritis.

Keywords
ankylosing spondylitis, HLA B27, iritis, uveitis

INTRODUCTION

Uveitis is the most common, clinically apparent, extra-articular manifestation of spondyloarthritis. The uveal tract is composed of the iris anteriorly, the choroid posteriorly and the ciliary body juxtaposed between the two. As such, uveitis can be subdivided anatomically as anterior, intermediate, posterior or panuveitis. When a portion of the uvea is inflamed, an adjacent structure is usually affected as well. For example, a chorioretinitis is arguably more common than simply a choroiditis. In epidemiologic studies, about 85% of the uveitis in the United States is anterior [1]. The uveitis associated with human leukocyte antigen (HLA) B27 is also typically anterior [2]. HLA B27 is associated with about 50% of instances of acute anterior uveitis (AAU) based on a classic British study [3]. Conversely, if the follow-up is sufficiently long, about 50% of patients with known ankylosing spondylitis will have at least one episode of AAU [4▪▪].

In order to provide an update on the relation between uveitis and spondylitis, in January 2017, we performed a literature search on the key term, uveitis, using the database of the National Library of Medicine. The titles of the 1100 most recent entries were reviewed. Articles were selected for further assessment if they were written in English, were relevant to spondyloarthritis and if they appeared to contain novel observations rather than simply represent a review of prior publications. Not all the selected publications could be discussed because of space considerations. In addition, we have elected to include a limited number of publications from 2015 because their importance warranted discussion. We have divided these selected reports into five categories: epidemiology, genetics, clinical characteristics, treatment and cause.

In this review and as is commonly practiced by many ophthalmologists, uveitis is frequently diagnosed as 'HLA B27-associated'. This phrase is misleading because HLA B27 is not a disease in contrast

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KEY POINTS

- In many countries of the world, HLA B27-associated uveitis is the most frequent cause of uveitis.
- Over a lifetime, a patient with ankylosing spondylitis has about a 50% chance of having at least one episode of AAU.
- HLA B27-positive patients who have an attack of AAU usually have spondyloarthritis and frequently are unaware of this diagnosis.
- Many genes that predispose to ankylosing spondylitis also predispose to AAU, but several genes have been identified which predispose to AAU without influencing susceptibility to ankylosing spondylitis.
- Adalimumab is now approved in the United States to treat noninfectious intermediate, posterior or panuveitis, but this is not the phenotype of uveitis most commonly associated with spondyloarthritis.

to a designation such as ankylosing spondylitis-associated or sarcoidosis-associated uveitis. In addition, the majority of individuals who are HLA B27 positive do not develop either ankylosing spondylitis or uveitis. On the contrary, the uveitis associated with HLA B27 has a distinct phenotype: unilateral, anterior, sudden onset (also known as acute), self-limited (an episode usually resolves within 2 months) and recurrent (sometimes in the contralateral eye but rarely in both eyes simultaneously) [2]. Thus, while 'HLA B27' is not a disease, 'HLA B27-associated' uveitis designates a phenotype which is recognized by many ophthalmologists. For want of a better term, HLA B27-associated uveitis is used throughout this article.

EPIDEMIOLOGY

A study based on insurance claims analyzed data on 4 million adults [5]. This study reached conclusions similar to a report based more than a decade ago on the Kaiser medical care delivery system in northern California [1]. The prevalence of noninfectious uveitis among adults was 121 per 100 000. Eighty-one percentage of these patients had anterior uveitis. This is germane to spondyloarthritis because uveitis associated with HLA B27 is predominantly anterior.

In 2016, the journal, *Ocular Immunology and Inflammation*, elected to publish diagnostic surveys from uveitis clinics around the world. These studies along with a small number published in 2016 in other journals are summarized in the table [6–19]. The studies confirm that in many parts of the world ranging from Korea to New Zealand, HLA B27-associated disease and/or ankylosing spondylitis are common causes of uveitis. A tertiary referral clinic generally sees a different spectrum of disease compared with a community clinic. As noted above, the majority of all cases of uveitis are anterior. Anterior uveitis can often be managed with just topical corticosteroids. Uveitis which is posterior to the lens or which is chronic is more likely to be referred. As HLA B27-associated uveitis is typically anterior and self-limited [2], patients with HLA B27-associated uveitis are less likely to be referred compared with many other diagnoses. Despite the prevalence of B27-associated uveitis as shown in Table 1 [6–19], B27-associated uveitis is presumably under-represented compared with results that would be obtained from an epidemiologic study. In some centers, such as in Myanmar [15] or Sao Paolo [17], infectious causes of uveitis are quite common. Obviously, ethnicity influences the frequency of HLA B27-related uveitis and in Japan [16], Saudi Arabia [19], Brazil [17], Nepal [18], Myanmar [15] and northern China [14], B27 appeared less frequently as the underlying diagnosis for the uveitis. But in the majority of centers, HLA B27 was a common diagnosis for uveitis, just as it would be in North America or throughout most of Europe.

A related question is: if you have ankylosing spondylitis, how likely are you to develop AAU. Although many publications have addressed this issue, the report by Robinson *et al.* [4▪▪] is arguably the best because of the size of the series (1711 with AAU) and the duration of the follow-up. Robinson *et al.* concluded that if you followed patients with ankylosing spondylitis (AS) for at least 40 years, more than half will report having had at least one episode of AAU.

An important issue which relates to both epidemiology and clinical management is how often is AAU the initial clinical manifestation of spondyloarthritis? The answer is that AAU is rarely the first clinical manifestation of spondyloarthritis, but it is often the first symptom that brings spondyloarthritis to clinical attention. This conclusion was reached by two prospective studies, one in Dublin [20▪▪] and one in Spain [21▪▪]. Both studies evaluated patients with AAU for evidence of axial spondyloarthritis. Both excluded patients who had known spondyloarthropathy. Both relied on the assessment of ankylosing spondylitis (ASAS) criteria to classify axial spondyloarthritis [22]. In the Irish study, a discovery set and a validation set were evaluated. In the validation phase, 42% of consecutive patients in the emergency department with AAU were diagnosed with spondylitis. The presence of HLA B27 made it far more likely that a patient had inflammatory sacroiliac disease, but this inflammation was

Table 1. Vogt–Koyanagi–Harada syndrome

Location	Size of series	Conclusions
Northern Spain [6]	500	65.4% anterior; 10.8% of total series had AS
Sydney, Australia [7]	1165	63% anterior; 22.8% B27 positive
Seoul, South Korea [8]	602	46.7% anterior; AS and Behcet's most common systemic diseases
New Zealand [9]	1260	70.3% anterior; HLA B27 most common diagnosis
Turkey [10]	4863	24.9% Behcet's, 9.7% AS B27-related
Taiwan [11]	450	HLA B27-associated most common cause among noninfectious uveitis
Hokkaido, Japan [12]	?	Sarcoidosis most common systemic disease
Singapore [13]	1397	HLA B27 most common cause of anterior uveitis
North China [14]	606	Panuveitis most common diagnosis; VKH, Behcet's or idiopathic most common cause
Myanmar [15]	131	54.7% had infectious uveitis; idiopathic and then HLA B27 most common causes of noninfectious uveitis
Tokyo [16]	695	Leading diagnoses were scleritis, sarcoidosis, herpetic, Behcet's, VKH, AAU, Posner–Schlossman, lymphoma
Sao Paolo, Brazil [17]	1053	Posterior uveitis most common location; toxoplasmosis most common cause
Nepal [18]	1113	53% anterior; HLA B27 not among three leading causes
Saudi; Arabia [19]	888	Common causes included TB, VKH, Behcet's, HSV and toxoplasmosis and idiopathic

AAU, acute anterior uveitis; AS, ankylosing spondylitis; HLA, human leukocyte antigen; HSV, herpes simplex virus; VKH, Vogt–Koyanagi–Harada.

not strictly limited to those who were HLA B27 positive.

The Spanish study was a collaboration between rheumatologists and ophthalmologists. Nearly, 800 individuals were evaluated. All HLA B27+ individuals with AAU were included. If an individual was negative for HLA B27, the uveitis had to be recurrent for inclusion. The authors found that 71.2% of the 475 individuals who were B27+ had axial spondylitis and 21.9% had peripheral joint disease. Among the 323 in the B27 negative group, 19.5% had axial disease and 11.1% had peripheral disease. Although it is remarkable in both studies how commonly individuals were unaware that their chronic back pain represented an inflammatory disease, the data are consistent with a prior report from Paris on the prevalence of spondyloarthropathy among B27+ patients with AAU [23] and my own observation in a uveitis referral clinic [2]; the majority of patients with AAU and spondyloarthritis are unaware of the relationship.

A study from Denmark reported on MRI results from 1020 consecutive individuals with low back pain. Two hundred seventeen of these individuals met ASAS criteria for sacroiliitis on MRI [24]. Although sacroiliitis correlated with features such as the presence of HLA B27, inflammatory low back pain or peripheral arthritis, a history of uveitis did not predict sacroiliac changes on MRI scan. Eleven of the 1020 individuals or about 1.1% had a history of uveitis. As noted above, the prevalence of uveitis is closer to 0.1%, so uveitis is likely increased among patients with low back pain. It is surprising that this increase was not more common among those with MRI changes indicating sacroiliitis.

GENETICS

The study just cited by Robinson *et al.* [4▪▪] compared genes associated with AAU either with or without ankylosing spondylitis. The investigators concluded that some genes such as HLA B27, IL-23R and ERAP-1 predispose to both diseases. Some genes such as IL-10–19 and IL-18R1-IL-1R1 predispose to both uveitis and inflammatory bowel disease. And a few genes such as IL-6R, KIF21B and EYS appear to predispose only to AAU.

A Chinese study examined the role of gene copy number in predisposing to AAU with AS. This study found that a high copy number of either GATA-3 or T-Bet predisposed to AAU with AS [25▪]. Both GATA-3 and T-bet code for transcription factors that have a marked effect on the cytokines produced by T cells. In women only, a high copy number of the gene for FOXP3 predisposed to AAU either with or without AS [25▪].

Another study from China concluded that HLA B*2704 was a stronger risk factor for uveitis than HLA B*2705 [26▪].

CLINICAL CHARACTERISTICS

The clinical characteristics of HLA B27-associated uveitis have been well characterized as sudden onset, unilateral, anterior and recurrent as noted above. Typically, the intraocular pressure falls with

the attack. Either posterior synechiae and/or hypopyon may complicate the attack. Chorioretinal involvement does not occur. Disease in both eyes concurrently and persistent disease are both described but not common. Despite the severity of attacks, less than 5% develop visual impairment in a recent series [27].

A study from Utrecht also confirmed that the visual prognosis was good, but among those who do lose visual acuity, glaucoma or glaucoma surgery was frequently the cause [28]. Another study from Holland examined the effect of B27-associated uveitis and quality of life [29]. Although vision-related quality of life was relatively good, it was not as good as in a healthy, working population. A concomitant systemic disease like ankylosing spondylitis further lowered the vision-related quality of life.

Another observation derived from a study from China which correlated the risk of uveitis in patients with ankylosing spondylitis with having either hip disease or peripheral arthritis [30]. Uveitis was also more common if circulating immune complexes were detectable [30]. In a previous study with a similar purpose, we had correlated uveitis with heel or lower jaw involvement as well as with a history of inflammatory bowel disease [31].

HLA B27-associated uveitis is rare in the elderly, but a series from the Cleveland Clinic noted three patients with new onset, HLA B27-associated uveitis after age 70 and a particularly severe course [32].

The Scotland Registry for Ankylosing Spondylitis evaluated the role of smoking in disease severity. Interestingly, relative to current smokers, ex-smokers had more mild back disease, but they were more likely to provide a history of uveitis [33]. As correlations like this do not establish cause and effect, one possible interpretation is that an episode of uveitis served as an inducement to quit smoking.

TREATMENT

Until 2016, the only medications specifically approved to treat uveitis were corticosteroids in various forms. In the summer of 2016, adalimumab was approved in the United States by the Food and Drug Administration for the treatment of noninfectious, intermediate, posterior or panuveitis. This approval was based on two well-designed, randomized controlled trials that demonstrated efficacy in uveitis which was either active [34▪▪] or controlled but requiring oral corticosteroids [35▪▪]. As uveitis in association with HLA B27 is usually anterior and not persistent, the approval affects only patients with spondyloarthropathy who have persistent inflammation behind the lens. Often, these are patients who will have either psoriatic arthritis [36] or inflammatory bowel disease [37] in association with uveitis and spondyloarthropathy.

Monoclonal antibodies that inhibit tumor necrosis factor (TNF) have been shown to reduce the likelihood to develop anterior uveitis in the future [38]. Recent studies have extended this conclusion to certolizumab [39] and golimumab [40▪].

Just as TNF inhibitors can paradoxically induce psoriasis, TNF inhibitors have been reported to trigger uveitis [41]. Etanercept is the most likely TNF inhibitor to cause this adverse event [41]. Further, some have found that etanercept is inconsistent in preventing attacks of AAU in patients with spondyloarthritis [42]. As etanercept-induced uveitis is extremely rare, this side-effect is not a contraindication to the use of etanercept in patients with ankylosing spondylitis. However, if uveitis is a major manifestation in a patient with spondyloarthritis, a monoclonal antibody is usually preferred over a soluble receptor.

CAUSE

Two notorious viruses, Zika and Ebola, have each been reported to be potential causes of uveitis [43,44]. Although this has no obvious relevance to spondyloarthropathy, a detailed case report of a physician who contracted Ebola, survived multiorgan failure and then developed uveitis during convalescence might be instructive [45▪▪]. In addition to his eye inflammation, his disease included sacroiliitis and bilateral Achilles tendonitis. The eye disease was not typical of HLA B27 because it was bilateral and associated with chorioretinitis. His systemic disease also had features not typical of HLA B27 including some transient cognitive decline. Still, it is fascinating that a well-documented viral illness resulted in inflammation that showed clinical overlap with spondyloarthropathy.

The microbiome is emerging as a potential cause of many diseases including ankylosing spondylitis [46], psoriatic arthritis [47] and inflammatory bowel disease [48]. Although no direct evidence that the microbiome is the cause of uveitis has emerged [49], the microbiome is affected by HLA B27 [50]. At least, two murine models of uveitis are affected strongly by the microbiome. In a T-cell transgenic model of retinal autoimmunity, the investigators concluded that a bacterial antigen in the gut probably mimics the retinal autoantigen, although the identity of the bacterial product has not been successfully identified [51]. In a polyclonal model of retinal autoimmunity, broad spectrum antibiotics have been shown to ameliorate the disease when given orally but not systemically, thus implicating gut microbes [52]. Although both these observations point to a

role for the microbiome in uveitis, both deal with models of chorioretinitis which might differ substantially from the pathogenesis of anterior uveitis.

Another known bacterial trigger for uveitis is Bacille–Calmette–Guerin (BCG). In the rat model of adjuvant arthritis triggered in susceptible strains by the injection of killed mycobacteria, rats develop many aspects of spondyloarthritis including axial disease, periosteal new bone, uveitis and nongonococcal urethritis [53]. A Japanese study reported on the incidence of reactive arthritis over a 20-year span among 555 individuals who had been injected with BCG into the bladder to treat bladder cancer. Two percent of individuals developed reactive arthritis. Seven tenths of 1% developed uveitis and 5.9% developed conjunctivitis. HLA B27 was present in only 0.3% of controls reflecting that the study was from Japan. Among those who developed reactive arthritis, 9.1% were HLA B27 positive.

CONCLUSION

Although the association between HLA B27 and the development of AAU was first recognized in 1973 [3], new insights are still emerging. Two studies have shown how commonly spondylitis is associated with AAU [20▪▪,21▪▪]. A well-designed genetics study has shown that common genetic factors predispose to both AS and AAU, but there are also genetic factors that influence susceptibility specifically to AAJ [4▪▪]. The microbiome affects uveitis [51,52] and HLA B27 [50] affects the microbiome, but studies are still in progress to analyze specifically the association between the microbiome and HLA B27-associated AAU.

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Conflicts of interest

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Fibromyalgia, a missed comorbidity in spondyloarthritis: prevalence and impact on assessment and treatment

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Purpose of review
Fibromyalgia is a clinical representation of the neurobiological phenomenon of central sensitization, characterized by chronic widespread pain, fatigue, sleep disturbance, and other symptoms. Fibromyalgia may occur in conjunction with chronic rheumatic diseases, driven by the effects of chronic pain and inflammation and likely influenced by the patient's genetic and psychoemotional background. This article reviews the data on prevalence of concomitant fibromyalgia and its impact on disease assessment in patients with spondyloarthritis (SpA) and psoriatic arthritis (PsA).

Recent findings
Fibromyalgia occurs in 2–8% of the general population. In AxSpA cohorts the prevalence has been reported in 4–25%, and in PsA, 16–22%, the majority being female. Measures of disease activity which are comprised partly or wholly of patient-reported outcomes such as pain and patient global are significantly higher in patients with concomitant fibromyalgia and do not improve as much with treatment as more objective measures, a finding which has been observed in other diseases such as rheumatoid arthritis and lupus.

Summary
Fibromyalgia occurs in a significant proportion of patients with SpA and PsA. Disease activity measures with subjective elements are conflated in patients with fibromyalgia and do not reliably assess true inflammatory disease. This needs to be taken into account when evaluating the impact of immunomodulatory therapy.

Keywords
ankylosing spondylitis, axial spondyloarthritis, central sensitization, fibromyalgia, spondyloarthritis

INTRODUCTION: NEUROBIOLOGY OF PAIN IN RHEUMATIC DISEASE: INTRODUCTION TO PERIPHERAL AND CENTRAL SENSITIZATION

In rheumatic diseases characterized by inflammation and degeneration of joints and other musculoskeletal tissues, pain is traditionally considered to originate from nociceptive signaling from peripheral nerve endings present in innervated tissues near joints, muscle, connective tissue, and bone, induced by inflammatory, mechanical, chemical, or thermal stimuli [1,2,3▪]. Numerous neuropeptides, such as substance P, somatostatin, neurokinin A, neuropeptide Y, and so on are implicated in this signaling process. Persistence of the noxious stimulus, for example, with chronic inflammation, leads to a state of peripheral sensitization, characterized by increased production of nociceptive neuropeptides, reduction of activation thresholds, and increased neuronal excitability. Peripheral nerves project to multilevel dorsal horns, where many of the same neuropeptides, as well as glutamate and *N*-methyl-D-aspartic acid, are involved in spinal cord axonal signaling to multiple relay points in the brain such as the primary and secondary somatosensory cortices and insula which serve as principal pain processing areas. The affective motivational, emotional aversion, and autonomic reactions are centered in the limbic system, anterior cingulate cortex, and insula. The central nervous

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KEY POINTS

- Fibromyalgia occurs in a significant proportion of SpA and PsA patients who are genetically and psychoemotionally predisposed to central sensitization.
- Disease activity measures which include subjective elements such as pain and patient global may be inflated when fibromyalgia coexists with SpA and PsA, not reliably reflecting inflammatory disease activity, which needs to be taken into account when assessing the effect of treatment.

system has established a 'balancing' system which moderates and helps to turn off pain signaling in the form of descending neurons which serve an inhibitory/pain moderating role. Key neurotransmitters functioning in this pathway include norepinephrine, serotonin, γ-aminobutyric acid, cannabinoid receptors 1 and 2, and opioid receptors.

Central sensitization (CS) is defined as a state in which neurons activated by nociceptive stimuli become 'sensitized' by said stimuli and subsequently become hyperresponsive to stimuli in the neuron's receptor field. This results in the phenomena of temporal summation ('windup') and subsequent hyperalgesia and allodynia not only in the site of inflammation or mechanical nociception, but also in other parts of the body where no injury/inflammation has occurred. Prolonged and intense input from peripheral nociceptors modulates spinal cord pain transmitting neurons, resulting in increased synaptic excitability, decreased activation thresholds, alteration in neuropeptide receptor quantity, and increased gene expression of nociceptive neuropeptides. In addition, microglial cells cluster in the dorsal horn, release proinflammatory cytokines which enhance CS and pain. In some individuals, perhaps through the influence of genes regulating pronociceptive states, CS processes in the spinal cord and brain take on a life of their own, regardless of the activity of peripheral nociceptors. As discussed elsewhere in this article, this may partly account for the apparent disconnect between persistent pain experience by patients with conditions such as AxSpA and psoriatic arthritis (PsA) despite minimal objective inflammation or tissue destruction, especially with effective treatment of the rheumatologic condition.

FIBROMYALGIA

Fibromyalgia is a condition characterized by chronic widespread pain and frequently associated symptoms including fatigue, sleep disorder, cognitive dysfunction, and numerous other symptoms [4▪,5,6]. Depending on ascertainment methodology, it is present in 2–8% of the population, with similar prevalence in different countries, cultures, and ethnic groups [4▪]. Although a prominent symptom is muscle pain, and various groups have observed minor pathophysiologic changes in peripheral muscle tissues, the prevailing conception is that the multidomain symptoms of fibromyalgia represent a persistent state of CS, partly genetically determined, and influenced by psychosocial factors and concomitant illness. Genes controlling production and function of neuropeptides that regulate pain and other symptoms of fibromyalgia demonstrate increased expression in patients with fibromyalgia [4▪,7]. The 1990 Classification Criteria for fibromyalgia were not intended as diagnostic criteria but have often been used as such [8]. These emphasize widespread pain and palpated 'tenderpoints'. In 2010, Wolfe published diagnostic criteria which do not depend upon palpated tenderpoints, but do emphasize the presence of widespread pain and other cardinal symptoms of fibromyalgia including fatigue, sleep disturbance, and dyscognition as well as a number of other symptoms such as headache, irritable bowel syndrome, mood disturbance, and so on, which are frequently seen in patients with fibromyalgia [9]. Although the criteria are largely overlapping in the terms of the patients identified, the newer criteria more fully address the full clinical spectrum of the illness and are less likely to exclude male patients who may not fulfill tenderpoint criteria. Mease *et al.* [10] established an Outcome Measures in Rheumatology Clinical Trials (OMERACT) core domain set for the study of fibromyalgia. Patients with fibromyalgia experience significant chronic symptom burden, reduced function, and quality of life, with a large impact not only on the individual but also the family and society in terms of decreased participation and lost work productivity [4▪,5]. Optimal treatment approaches are multidisciplinary, nonpharmacologic including education, exercise, and cognitive behavioral therapy, and pharmacotherapy including nonnarcotic analgesics which downregulate nociceptive neuropeptides such as glutamate and upregulate pain inhibitory neuropeptides such as norepinephrine and serotonin, that is, reduce CS [4▪,11].

FIBROMYALGIA IN RHEUMATOLOGIC DISEASES

Numerous studies demonstrate the concomitant presence of fibromyalgia in patients with a variety

Table 1. Fibromyalgia as a comorbid condition in rheumatologic disease

Rheumatologic condition	Author	Prevalence of fibromyalgia (%)	Number of study participants in original study	FM diagnosis by 1990[8] or 2010[9] criteria or other
RA	Wolfe *et al.* (2004) [12]	17	1731	Symptom intensity scale [17]
	Wolfe *et al.* (2011) [13]	20	9739	Modified 2010 (survey) [18]
	Ranzolin *et al.* (2009) [14]	13.4	270	1990
	Lee *et al.* (2013) [15]	4.6	1487	Investigator judgement
	Lage-Hansen *et al.* (2015) [16▪]	15.4	162	2010
SpA	Azevedo *et al.* (2010) [19]	15	71 (AS)	1990
	Almodovar *et al.* (2010) [20]	4	462 (AS)	1990
	Haliloglu *et al.* (2014) [21]	12.6	119 (AS)	1990
	Salaffi *et al.* (2014) [22]	12.7	211 (AxSpA)	2010
	Aloush *et al.* (2007) [23]	25; 50 (Female)	36	1990
	Wallis *et al.* (2013) [24]	6 (AS); 14 (nrAxSpA)	639 (AS); 73 (nrAxSpA)	Investigator judgement
	Wach *et al.* (2016) [25]	17	103 (SpA)	1990
PsA	Husted *et al.* (2013) [26]	22	631	Investigator judgement
	Brikman *et al.* (2016) [27▪]	17.8	73	1990; 2010
	Salaffi *et al.* (2014) [22]	17.2 (Ax PsA)	191	2010
	Graceffa *et al.* (2015) [28]	16	74	1990
SLE	Torrente-Segarra *et al.* (2016) [29]	6.2	3591	1990
	Wolfe *et al.* (2009) [30]	22.1	834	Symptom intensity scale
Sjogren's	Torrente-Segarra *et al.* (2017) [31▪]	14.6	437	1990
OA	Wolfe *et al.* (2010) [32]	18.8	1888	Modified 2010 (survey)
	Haliloglu *et al.* (2014) [21]	10.1	238	1990

PsA, psoriatic arthritis; RA, rheumatoid arthritis; SpA, spondyloarthritis.

of rheumatic diseases, usually at a prevalence rate higher than expected in the general population (Table 1). A hypothesis is that a chronic pain stimulus and/or chronic inflammatory state, perhaps in a genetically and psychoemotionally predisposed individual, fuel the abnormalities that occur in central pain processing, including CS, loss of descending analgesia (loss of inhibitory modulation), and temporal summation [1,4▪,6,33]. Typically this phenomenon occurs more often in women than men; other characteristics, such as disease duration and severity of objective disease markers are often similar. Concerningly, disease measures which rely heavily on patient reported and more subjective measures tend to be negatively influenced by the presence of concomitant fibromyalgia/CS, thus rendering these measures to be less reliable in reflecting the 'true' severity of the primary rheumatologic disease being assessed. A corollary finding in some studies that have assessed treatment outcome is that it is more difficult for such patients to achieve low disease or remission states when these states are measured by largely patient-reported questionnaires, requiring the use of biomarkers or imaging to provide a more reliable picture of response. The following sections illustrate these points in spondyloarthritis (SpA) and PsA; space limitations do not allow discussion of other conditions such as rheumatoid arthritis (RA), lupus, Sjogren's, osteoarthritis, and so on, for which the reader can trace references noted in Table 1.

When considering data on 'presence or absence of concomitant fibromyalgia ', it is important to recognize that fibromyalgia and its neurobiologic basis, CS, likely represent a continuum of neuropathology rather than a discreet 'present or absent'. Wolfe *et al.* [34] applied the symptom intensity scale, a measure combining number of nonarticular painful sites and a fatigue visual analog scale in over 23 622 RA patients, a proportion of whom had fibromyalgia. He found that mean symptom intensity scale score for all RA patients was 3.75 and the mean for those who also had fibromyalgia was 7.25 and that there was a continuum of symptom intensity rather than being discreet sets of 'control RA' and 'RA and fibromyalgia ' patients. Wolfe *et al.* [34] coined the term 'fibromyalgianess' to reflect this continuum.

Development of more sensitive and feasible screening tools, such as patient questionnaires, can facilitate research on the question of concomitant fibromyalgia, as it is unlikely that highly sensitive neuroimaging technologies will be feasibly available for screening in the near future. Examples of patient reported measures include the symptom intensity scale [17] and the Fibromyalgia Survey Questionnaire developed by Wolfe *et al.* [18] from the 2010 fibromyalgia criteria, and the Fibromyalgia Rapid Screening Tool questionnaire developed by Perrot *et al.* [35]. The painDETECT questionnaire [36,37] was developed as a screening tool for neuropathic pain, which is not completely overlapping with CS but may be useful in assisting the identification of CS [38]. Koop *et al.* [39] applied the painDETECT questionnaire to 159 patients who were predominantly well controlled in remission or low disease activity using disease-modifying antirheumatic drug therapy. Despite this, 44% reported clinically significant pain in the previous 4 weeks. According to painDETECT scores, 21.4% of patients had possible neuropathic, that is, noninflammatory, pain, with scores of 13–18 and 17% had likely NP. This suggests that the pain of a substantial proportion of RA patients may be neuropathic in nature. Of those patients who had a painDETECT score of more than 12, 28% were diagnosed with fibromyalgia using the Fibromyalgia Survey Questionnaire, whereas only 6% with scores 12 or less were so diagnosed. An additional questionnaire that has been used is the London Fibromyalgia Epidemiologic Study Screening Quesionnaire [40]. Use of patient-reported questionnaires may be a more feasible way to distinguish noninflammatory and possibly central pain, and help steer the clinician away from intensification or change of immunomodulatory medicine and toward nonpharmacologic and/or pharmacologic treatments of central pain.

AXIAL SPONDYLOARTHRITIS

Prevalence

Recent studies have attempted to ascertain the prevalence of fibromyalgia within either ankylosing spondylitis (AS) or AxSpA populations and as in RA, find higher prevalence rates than the 2–4% expected in the general population. These include AS cohort studies in Brazil (fibromyalgia prevalence by 1990 criteria 15%, AS $n = 71$) [19], Spain (prevalence of fibromyalgia by 1990 criteria 4.11%, $n = 462$) [20], Turkey (prevalence of fibromyalgia by 1990 criteria 12.6%, $n = 119$) [21], Italy (prevalence by 2010 criteria 12.7%, $n = 211$) [22], Israel (prevalence by 1990 criteria 25%, $n = 36$) [23]. The percentage of women compared with men with fibromyalgia in these cohorts was higher: 54.5/45.5% in Brazil, 10.83% of female AS patients in Spain, 93/7% in Turkey, 31.3/9.3% in Italy, 50/0% in Israel, despite men predominance of AS in most of these studies. Although most studies have focused on AS, in the Toronto cohort, Wallis *et al.* [24] noted an fibromyalgia prevalence of 6% in AS and 14% in nonradiographic axial spondyloarthritis patients. Most recently, Wach *et al.* [25] identified 18 patients in a cohort of 103 SpA patients (81 axial, 22 peripheral).

Baraliakos *et al.* [41] studied 91 patients with AxSpA, 93 with fibromyalgia, and 30 with RA as an inflammatory control group. Classification criteria, including both 1990 and 2010 fibromyalgia criteria and 2009 ASAS AxSpA criteria, standard outcome measures, and MRI were performed. The study was partly performed because of concern that the AxSpA criteria, especially the clinical arm, might include patients with fibromyalgia without true AxSpA. Importantly, only two of the fibromyalgia patients fulfilled AxSpA criteria, whereas fulfillment of the 1990 and 2010 fibromyalgia criteria were fulfilled by 14.3 and 34.1% of the AxSpA and 30 and 46.7% of the RA patients, respectively. This helps dispel the notion that the AxSpA criteria may be too nonspecific too exclude pure fibromyalgia, but does raise the point that some fibromyalgia patients in whom AxSpA has not been investigated should be considered for this.

Neurobiology of central pain in AS

Wu *et al.* [42▪] applied painDETECT questionnaires and neuroimaging studies to 17 patients with AS compared with 17 healthy controls. Eleven AS patients, including three out of four women in the study, had painDETECT scores at least 12, considered to be consistent with the presence of neuropathic pain. MRI in AS patients showed cortical thinning in the primary somatosensory, insular, anterior cingulate and anterior mid-cingulate cortices, and the supplemental motor area, and increased gray matter volume in the thalamus and putamen. PainDETECT scores were correlated with thinning in the primary somatosensory cortex and increased gray matter in the motor cortex, the anterior cingulate cortex, prefrontal cortex, thalamus, and striatum. These findings are similar to MRI data from other chronic pain studies [43]. Taken together, these findings suggest that a central pain process exists in some patients with AS [42▪].

Impact of fibromyalgia on outcome measures in AS

Patient-reported outcomes are generally negatively affected by the presence of fibromyalgia. In the Brazilian study, bath ankylosing spondylitis disease activity index (BASDAI), bath ankylosing spondylitis functional index (BASFI), and ankylosing spondylitis quality of life results in the 11 study participants with AS and fibromyalgia were 7.2, 8.3, and 15, respectively, whereas in the 60 AS study participants without fibromyalgia, they were 3.9, 5.5, and 9.6, respectively, all statistically significantly different [19]. In AS patients in Israel, female patients (50% had fibromyalgia) had significantly higher BASDAI scores, tender joint, and enthesitis counts, but not health assessment questionnaire for the spondyloarthropathies, BASFI, or patient global assessment than men (0% with fibromyalgia) [23]. Almodovar *et al.* [20] also found patients with AS and fibromyalgia to have worse BASDAI and BASFI scores. There was generally no difference in physical exam measures between men and women. In contrast to these observations, Salaffi *et al.* [22] found no difference in total BASDAI, individual BASDAI questions, ankylosing spondylitis disease activity score (ASDAS), or acute phase reactants in Italian AxSpA patients with and without fibromyalgia. Wach *et al.* [25] observed that the BASDAI was nearly twice as high in their cohort of patients with SpA (both axial and peripheral) and fibromyalgia vs. SpA only, but that ASDAS-CRP scores were not statistically different, thus arguing for use of the ASDAS-CRP as a more reliable measure in a SpA cohort.

The diagnosis of AxSpA is heavily weighted on the presence of chronic inflammatory back pain as well as features such as morning stiffness, and symptoms such as fatigue, sleep disturbance, and depression can be prominently expressed. These same symptoms are characteristic of fibromyalgia. With the exception of the Salaffi *et al.* [22] study, most studies demonstrate that AxSpA disease activity measures that wholly or largely rely on patient report may be negatively influenced by the presence of fibromyalgia. Even if the inflammatory aspects and more objective parameters of AxSpA are well controlled on a patient's current therapy, the patient and clinician may feel that change of immunomodulatory therapy is needed as patient reported disease activity measures, such as the BASDAI, suggest the need for intensification or change of this therapy, when in fact, treatment approaches for fibromyalgia should be enacted instead. In a clinical trial, a study drug's clinical effectiveness may appear blunted in patients with concomitant fibromyalgia. Thus, it is important to try to distinguish the presence of fibromyalgia in AxSpA using criteria for fibromyalgia classification, emerging patient-reported measures [35–37]. Leung *et al.* [44] discusses the current OMERACT emphasis of taking into account 'contextual factors' such as fibromyalgia when evaluating rheumatologic disease and considering therapy, taking into account the 'amplification' of disease severity when using measures with a significant subjective/patient reported component, especially in AxSpA where more objective features such as swollen joints and psoriatic skin lesions are not palpable or visible, as in RA or PsA. In the future, more objective approaches for diagnosing fibromyalgia or CS, such as neuroimaging techniques or quantitative sensory testing, may be feasible in the clinical setting.

PSORIATIC ARTHRITIS

Prevalence

Husted found that 22% of 631 patients in the Toronto PsA cohort had fibromyalgia and its presence contributed significantly to decrement in short form-36 physical and mental component scores [26]. Brikman *et al.* [27▪] in Israel studied 31 men and 42 women with PsA. Of these, 13 (17.8%; 12 = 92.3% women) fulfilled either 1990 or 2010 fibromyalgia criteria [27▪]. Demographic features of the patients with and without fibromyalgia were similar, except for sex. The fibromyalgia criteria were largely overlapping; few patients failed to fulfill both. Salaffi *et al.* [22] in Italy evaluated 191 study participants with axial PsA and found that 33 met 2010 criteria for fibromyalgia (17.2%), 34.2% of the female study participants and 6.1% of the male study participants probability of achieving remission [28]. This latter is an important observation which suggests there may be a 'blunting' of effect of therapy, possibly because of diminished likelihood of change of patient-reported outcome measures used to assess disease severity. Using Wolfe's symptom intensity scale and the London Fibromyalgia Epidemiologic Study Screening Questionnaire (LFESSQ), Magrey *et al.* [45] observed a prevalence of 37.5 and 53.3% fibromyalgia in 34 PsA patients, a different approach than using fibromyalgia 1990 or 2010 criteria.

Impact of fibromyalgia on outcome measures in psoriatic arthritis

Brikman *et al.* [27▪] studied the disease severity measures in 60 PsA patients in Israel, 13 of whom (17.8%) had fibromyalgia. All measures which include patient-reported outcomes, that is, comprehensive psoriatic disease activity index, disease activity PsA, disease activity score 28, minimal disease activity, HAQ, BASDAI were significantly worse in the group with fibromyalgia. Of the 60 patients, 43% of the PsA patients without fibromyalgia were

in a state of minimal disease activity and 0% of those with fibromyalgia were so. Interestingly, there was also a statistical difference in the Leeds enthesitis index score, in which six enthesial sites are palpated, with worse results in those with fibromyalgia. More 'objective' measures such as swollen joint count, psoriasis area and severity index and C-reactive protein (CRP) were not statistically different between the two groups of patients. Thus, as in RA and AS, it appears that the presence of fibromyalgia exerts a significant negative influence on patient-reported disease activity measures, rendering them less valid and reliable to use as a true measure of inflammatory disease activity in PsA.

Because of the difficulty in distinguishing PsA enthesitis tenderness from fibromyalgia tender-point tenderness, Marchesoni *et al.* [46] studied 266 PsA and 120 fibromyalgia patients and found that by univariate analysis, fibromyalgia study participants had higher mean tender point and enthesitis scores, more somatic symptoms, and responded less well to nonsteroidal anti-inflammatory drugs. Multivariate analysis suggested that at least six fibromyalgia-associated symptoms and at least eight tender point sites helped discriminate the presence of fibromyalgia.

CONCLUSION

Numerous studies demonstrate that fibromyalgia is found in a higher prevalence in rheumatologic diseases (10–30%) than is seen in the general population (2–8%). Chronic pain and/or inflammation establish a state of peripheral sensitization and in some patients, a state of persistent CS, characterized by amplified pain sensation and potentially fatigue, sleep disturbance, and other symptoms, which collectively may be called fibromyalgia. This process is at least partially genetically determined, as well as influenced by psychological and environmental factors. Fibromyalgia can be objectively demonstrated by advanced neuroimaging and other objective techniques. However, these techniques are not yet available for general clinical practice, and so use of classification and diagnostic criteria and patient-reported questionnaires are currently used as surrogates. Also important is to be aware that a state of concomitant fibromyalgia/CS is not simply a matter of presence or absence of another disease process but is a continuum of neurobiologic dysregulation with variable severity. Taken as a whole, the data reviewed here suggest that the presence of fibromyalgia influences disease activity measures which rely partly or wholly on patient report which may negatively amplify the experience of pain, fatigue and physical disability well beyond causality by the 'primary' rheumatologic disease. Concomitant fibromyalgia has also been shown to reduce the ability to achieve low disease state or remission, again because of inadequate improvement of subjective, patient-reported items in outcome measures, even when more objective measures such as swollen joint count or CRP have improved. For these reasons, it is important to assess for the presence of fibromyalgia and exclude such patients from clinical trials lest unreliable outcome assessment lead to inaccurate conclusions about treatment effect on the primary disease being studied. Such exclusion should at least be based on the investigator's judgement about the presence of fibromyalgia but ideally would also include evaluation of the patient population using fibromyalgia criteria or validated questionnaires, as discussed above, which identify patients with fibromyalgia/CS. Disease severity measures are less reliable for the purpose of therapeutic decision-making in clinical practice and amplified disease severity scores may lead to intensification of or switching immunotherapy when it is not warranted. Being aware of the potential for and diagnosing concomitant fibromyalgia is important so that the clinician can make appropriate adjustments of disease assessment for purposes of anti-inflammatory and immunotherapy decision-making as well as instituting nonpharmacologic and/or pharmacologic treatment of fibromyalgia.

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- ■ of special interest
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Janus kinase/signal transducer and activator of transcription pathways in spondyloarthritis

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Purpose of review
Cytokines are major drivers of autoimmunity, and biologic agents targeting cytokines have revolutionized the treatment of immune-mediated diseases. Janus kinase/signal transducer and activator of transcription (JAK-STAT) pathway represents a group of several intracellular molecules with a key role in signal pathways activated by growth factors and cytokines. These kinase proteins are associated with the signaling process of multiple key cytokines, which regulates various T-cell subpopulations and their effector cytokines. Development of novel drugs to inhibit this kinase cascade is an emerging field in clinical immunology. Thus, it is essential to have insights about the regulatory role of the JAK-STAT cytokine signaling in relation to autoimmune diseases and its applications in spondyloarthritis.

Recent findings
JAK-STAT kinase signaling proteins have been extensively studied in rheumatoid arthritis. Initial observations suggest that JAK-STAT kinase signaling cascade regulates activation and proliferation of the $IL17^{+}$ effector memory T cells and thus has a potential role in the pathogenesis of psoriasis, psoriatic arthritis and ankylosing spondylitis.

Summary
Here, we provide an overview of the clinical rheumatologists about the significance of JAK-STAT signaling system in rheumatic diseases and introduce the potential application of JAK and STAT inhibitors in spondyloarthritis.

Keywords
Janus kinase/signal transducer and activator of transcription, spondyloarthritis, treatment

INTRODUCTION

Autoimmune diseases are characterized by persistent inflammation mediated by perturbation in the immune system. The cause of many inflammatory and autoimmune diseases still remains unclear. Genetic, immunologic, environmental and lifestyle stress/strains contribute to the pathogenesis of autoimmune disease [1]. Human leukocyte antigen phenotypes, cell trafficking mechanisms, nature of T-cell phenotypes, cytokine profiles and angiogenesis act in an integrated way to develop various unique autoimmune diseases [2]. Activation of T cells by antigen-presenting cells (APCs) requires two distinct signals. First, the trimolecular complex must be formed, consisting of the T-cell receptor, antigenic peptide and major histocompatibility complex class II molecule from the APC [3]. The engagement of costimulatory receptors with their respective ligands provides an essential 'second signal' for the optimal activation of T cells [4,5]. A number of costimulatory molecules have been shown to influence T-cell activation. The most well-characterized T-cell costimulatory ligands are CD28 and cytotoxic T lymphocyte-associated antigen-4 (CTLA4) (CD152), which engage CD80 and CD86 receptors on APCs [6].

Among these, a principal signal is delivered by engagement of CD28 on T cells with CD80 (B7-1) and CD86 (B7-2) on APCs. This process enhances T-cell activation by stabilization of cytokine mRNA and upregulation of antiapoptotic genes [6,7]. In contrast, CTLA4-Ig binds to B7-1 and B7-2 molecules on APC and blocks the CD28-mediated costimulatory

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KEY POINTS

- The JAK-STAT signaling kinase proteins play a vital role in immunity development and immune surveillance.
- JAK-STAT kinase cascade regulates proliferation and its associated cytokine network of various T-cell subpopulations such as Th17 cells and the IL-23/IL-17 cytokine axis.
- As IL-23/IL-17 cytokine axis plays a critical role in the pathogenesis of psoriasis, PsA and AS, it is expected that specific JAK-STAT inhibitors will be therapeutically effective in these autoimmune conditions.
- Initial results of ongoing clinical trials with JAK inhibitors in SpA are very promising and suggest that JAK inhibitors could be an effective therapeutic option for these chronic critical human autoimmune diseases.

signal for T-cell activation. These activated T cells secrete cytokines that activate other cells of the immune system, such as macrophage, natural killer cell and neutrophil that infiltrate the targeted tissue, causing the damage associated with these diseases [8,9▪,10]. Therefore, by orchestrating the intercellular communication in this process, cytokines play a central role in the inflammatory response.

Cytokines signal through a variety of cell surface receptors. Binding of a cytokine to the extracellular domain induces conformational changes at the intracellular domain of the receptor, this leads to phosphorylation of kinase proteins and triggers the signal transduction events; which leads to gene transcription and thus regulates cellular function. The Janus kinases (JAK) are a family of intracellular tyrosine kinases and associated with the signaling process of multiple cytokines [11,12▪]. The JAK plays a critical role in innate immunity, adaptive immunity and hematopoiesis [11,12▪,13,14].

THE JANUS KINASE/SIGNAL TRANSDUCER AND ACTIVATOR OF TRANSCRIPTION PATHWAY

The Janus Kinase family is composed of four members: JAK1, JAK2, JAK3 and TYK2 [11,12▪]. The JAK associates with the intracellular domain of receptor subunits of the class I and class II receptor superfamily. The STAT family has seven members STAT 1, 2, 3, 4, 5, 5a and 6 [13,14]. The STAT comprises an important class of molecules that transmit signals from type I and II cytokine receptors to the nucleus. The STAT resides in the cytosol prior to activation [11,12▪,13,14].

The JAK-STAT signaling is initiated by interaction of a cytokine and its specific receptor on the surface of the target cell. The cytoplasmic portion of the receptor undergoes conformational changes, which leads to phosphorylation (activation) of the JAK associated-receptor (Fig. 1). Phosphorylation of the receptor in turn initiates recruitment of the STAT via its SH2 domains, which leads to phosphorylation and dimerization of the STAT proteins. The phosphorylated STAT homodimers/heterodimers migrate to the cell nucleus; bind to specific DNA binding sites and thus regulate gene transcription (Fig. 1). Cytokines that bind type I and type II receptors include interleukins, interferons, interferon-like cytokines, colony-stimulating factors, hormones and growth factors (Fig. 2) [15].

JANUS KINASE/SIGNAL TRANSDUCER AND ACTIVATOR OF TRANSCRIPTION PATHWAY IN THE PATHOGENESIS OF SPONDYLOARTHRITIS

JAK-STAT pathway represents a group of several intracellular molecules with a key role in signal pathways activated by growth factors and cytokines. Cytokines are major drivers of autoimmunity, and biologic agents targeting cytokines have revolutionized the treatment of immune-mediated diseases. Because of the cross talks between the JAK-STAT pathway and cytokine system it is believed that the JAK-STAT signaling cascade plays a critical role in an immune mediated inflammatory reaction. Currently, only very few studies have been reported to understand the molecular mechanisms of JAK-STAT pathway in the inflammatory proliferative cascades of spondyloarthritis (SpA)-related conditions. There is a major research effort to understand the regulatory role of the JAK-STAT pathway in the pathogenesis of SpA.

Janus kinase-3 (JAK3) is mainly expressed in the immune cells. Tofacitinib, a small organic molecule has been developed targeted against JAK3 for the treatment of autoimmune arthritis [16]. The efficacy of tofacitinib has been attributed to its regulatory role on T cells [16,17]. More recently, it has become clear that tofacitinib targets JAK1 and JAK2 with IC50 values in the same order of magnitude as that of JAK3 [18]. JAK1 and JAK2 are expressed in nonimmune cells including the synovial cells of joints. This has expanded the possible cellular targets for JAK inhibitors and has opened a new field to determine the pathologic role of the JAK-STAT pathway on other nonimmune cellular components of the inflammatory-proliferative cascades of autoimmune diseases

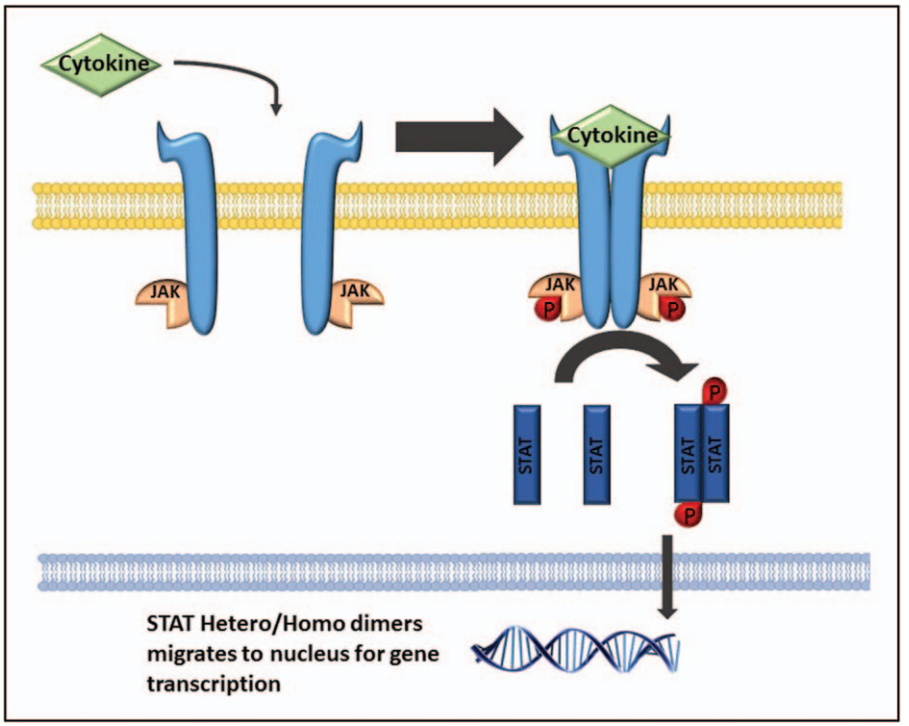

FIGURE 1. Cytokine-induced JAK/STAT signaling pathway. A specific cytokine binds to the extracellular domain of its receptor which leads to conformational changes to its intracellular domain and phosphorylation of the JAK proteins. Phosphorylation of the intracellular domain of a receptor in turn initiates recruitment of the STATs via their SH2 domains and induces phosphorylation of the STAT proteins. The activated STAT homo/hetero migrates to the nucleus to induce gene transcription which in turn impacts multiple biological cellular functions as mentioned in the Figure 2.

such as keratinocytes in psoriasis and synovial cells (FLS) in rheumatoid arthritis (RA) and psoriatic arthritis (PsA) [19,20].

So far, very limited studies have been done to understand the regulatory role of JAK-STAT kinase on FLS biology. Early reports suggest that in PsA, explant tofacitinib can inhibit JAK1/JAK2, and thus inhibits FLS migration and secretion of the certain FLS chemokines [21▪▪].

In a recent study, JAK/STAT expression was determined in multiple inflammatory skin conditions including in the psoriasis plaques [22]. In the epidermal layer, JAK1 and JAK3 were overexpressed in psoriasis and in an in-vitro psoriasis model, it was observed that tofacitinib inhibited phosphorylated (p)JAK3 and pJAK1 expression in psoriatic keratinocytes.

Aberrant activation of interleukin 23 (IL-23)/IL-17 cytokine axis is a dominant disease in SpA such as in PsA and ankylosing spondyloarthritis (AS) [8,9▪]. JAK2 is recruited to IL-23 receptor, so it is expected that JAK/STAT-mediated signaling system is important in the pathogenesis of PsA and AS. We hypothesized that in SpA, JAK/STAT signaling system regulates the Th17 cells and that tofacitinib which inhibits JAK-2 likely targets the Th17 cells by inhibiting the IL-23-induced JAK/STAT signaling system. To substantiate our hypothesis, we carried out experiments with the following aims: we evaluated the expression of JAK-STAT signaling proteins in sorted activated $CD3^+$ T cells collected from blood and synovial fluid of PsA patients; further to elucidate the functional significance of JAK-STAT signaling, we examined whether the activation and proliferation of the memory T cells and the Th17 cells are regulated by the kinases of the JAK-STAT pathway [23▪▪].

We observed that in PsA, activated $CD3^+$ T cells in the presence of IL-23 induced activation of JAK2 and STAT3. Further, we noticed tofacitinib markedly inhibited phosphorylation of JAK2 and STAT3; and also tofacitinib inhibited IL-23-induced proliferation of the IL-17^+effector memory T cells in PsA. These critical observations provide new insight in the understandings of the pathogenesis of PsA and other types of SpA: that generation of the pathologic IL-17^+ activated memory T cells and their proliferation are regulated by the JAK-STAT signaling system; a plausible mechanism of action of tofacitinib is likely to be inhibition of the IL-23/IL-17 cytokine axis by inhibiting the IL-23-induced JAK-STAT signaling system [23▪▪].

Polymorphisms of JAK-STAT kinases could be another mode of mechanism for underlying cause

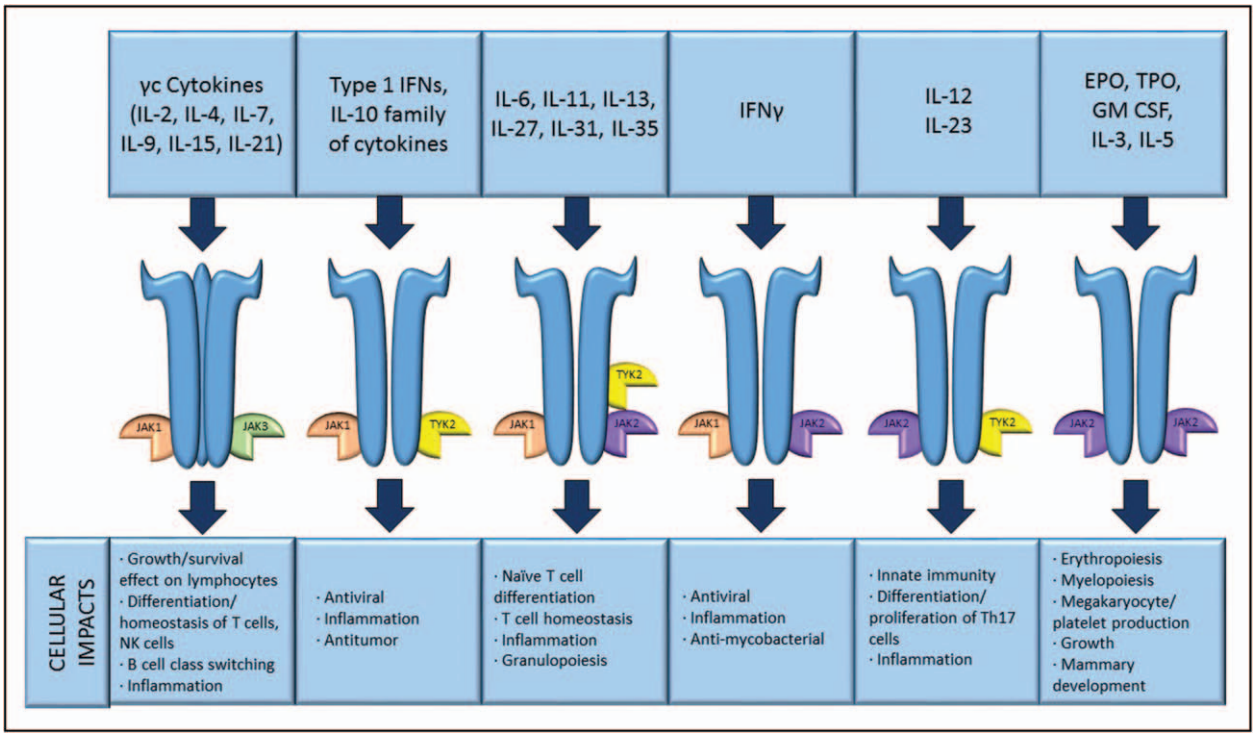

FIGURE 2. Impact of JAK-STAT signaling on cellular function and its relevance to spondyloarthritis. Cytokines that bind type I and type II receptors include interleukins, interferons, interferon-like cytokines, colony-stimulating factors, hormones and growth factors as mentioned here. Cytokine/growth factor binding signaling consists of specific JAK and STAT combinations and that leads to array of distinct transcriptions of specific genes and which is capable of impacting multiple functions of various cells including the immune cells [15]. As mentioned here, IL-2, IL-6, IL-9, IL-12 and IL-23 can influence T-cell differentiation, proliferation and expression of specific cytokines including IL-17 which are relevant for the pathogenesis of spondyloarthritis.

of SpA conditions. JAK2 polymorphisms have been implicated to be associated with ankylosing spondylitis (AS) [24]. Nucleotide polymorphisms in the JAK-STAT pathway have also been studied in Chron's disease. It has been reported that the two single-nucleotide polymorphism (SNPs) in STAT3 (rs744166 or rs3816769) and one in JAK2 (rs10758669) significantly differ in frequency between Chron's disease cases and controls [25]. The two STAT3 SNPs influence the risk of colonic Crohn's disease, whereas the JAK2 SNP is associated with ileocolonic disease, and increases the risk of developing ileal disease complicated by stricturing.

JANUS KINASE/SIGNAL TRANSDUCER AND ACTIVATOR OF TRANSCRIPTION INHIBITORS: NOVEL THERAPY FOR SPONDYLOARTHRITIS

The concepts for development of JAK inhibitors have come from several key observations. First, inhibition of JAK function would result significant immunosuppression as JAK-mediated signaling system is associated with multiple cytokines which are important for immune-mediated inflammatory reaction (Fig. 2). Further, JAK3 is restricted to the immune cells and it is of interest that both JAK3-deficient animals and human patients carrying inactive alleles display a phenotype that is restricted to the immune system [26]. These observations made the foundation to design inhibitors against JAK3 as immunosuppressive agents, which resulted in the development of tofacitinib (CP-690,550). Ruxolitinib (INCB018424, Jakafi, Incyte) is the first JAK inhibitor approved by Food and Drug Administration (FDA) in November 2011, and it is a potent inhibitor of both JAK1 and JAK2 for the treatment of polycythaemia vera and myelofibrosis [27].

Efficacy and safety of oral dosing with tofacitinib have been demonstrated in phase 2 and 3 studies of RA, and tofacitinib, 5 mg twice daily (BID), received FDA approval in 2012 for this indication. Recently, tofacitinib has been investigated also for the treatment of patients with moderate-to-severe chronic plaque psoriasis. Efficacy and safety of oral dosing with tofacitinib in individuals with plaque psoriasis have been demonstrated in phase 2 studies and are currently being investigated in phase 3 registration studies [28,29]. A phase II study of tofacitinib in chronic plaque psoriasis patients has

demonstrated that the PASI 75 response rates at week 12 were significantly higher compared with the placebo [28]. Also, tofacitinib was effective in reducing the severity of psoriasis, as demonstrated by improvements on physician and patient-reported outcomes in individuals with plaque psoriasis. A recent data (phase II) also suggest that baricitinib an oral Janus kinase (JAK) 1/JAK2 inhibitor is effective in psoriasis [30▪▪].

These promising results in RA and psoriasis have generated significant interest to develop JAK-STAT inhibitors as an option for the treatment of PsA and AS. So far, the most impressive report is from van der Heijde *et al.* [31▪▪]. In this randomized placebo control phase II trial (NCT01786668), they have investigated the therapeutic efficacy of tofacitinib on adult patients with active AS. Patients received twice daily either placebo ($n = 51$) or one of three dosages of tofacitinib for 12 weeks: 2 mg ($n = 52$), 5 mg ($n = 52$) or 10 mg ($n = 52$). The primary efficacy endpoint was ASAS20 response rate (Assessment of Spondyloarthritis International Society 20% improvement) at week 12. Secondary endpoints were disease activity, patient-reported outcomes and MRI Spondyloarthritis Research Consortium of Canada (SPARCC) scores.

The results showed that patients taking tofacitinib 5 and 10 mg twice daily had better clinical efficacy compared with the placebo in reducing clinical signs/symptoms and objective endpoints of active AS including the improvement in MRI SPARCC scores. More specifically, it was observed that 5-mg tofacitinib had an actual ASAS20 response rate of 80.8% compared with 41.2% for placebo ($P < 0.001$). Although numerically the 2-mg (51.9%) and 10-mg (55.8%) tofacitinib groups also had a higher response, it was not significantly higher response rate than the placebo group. All tofacitinib groups had ASAS40, Bath AS disease activity index 50% (BASDAI50) response rates and change in Ankylosing Spondylitis Disease Activity Score (ASDAS) of similar magnitude, and were significant compared with the placebo. In a recent abstract, Maksymowych *et al.* [32] have also reported that treatment with tofacitinib is associated with clinically meaningful reductions in axial MRI inflammation in patients with AS. Minimum clinically important differences (MCIDs) for SpondyloArthritis Research Consortium of Canada (SPARCC) MRI Sacro-Iliac joint and spine scores (SIJ and spine) are at least 2.5 and at least 5, respectively [32]. Here, the authors have observed that proportion of patients achieving MCID in SIJ or spine was approximately three times higher in pooled tofacitinib group vs. placebo ($P < 0.05$ for SIJ and $P < 0.01$ for spine).

In a recent report, Mease *et al.* [33] have observed the efficacy and safety of tofacitinib in PsA. This was a randomized, multicenter, double-blind, placebo and active-controlled phase 3 study, against adalimumab. Patients with PsA were randomized 2 : 2:2 : 1:1 to tofacitinib 5 mg twice daily ($n = 107$), tofacitinib 10 mg twice daily ($n = 104$), adalimumab 40 mg subcutaneous injection/every 2 weeks ($n = 106$) or placebo; and at 3 months, placebo patients were rerandomized, patients who started with placebo advanced to tofacitinib 5 mg ($n = 52$) or 10 mg ($n = 53$) twice daily. This was a 12-month study and the primary endpoints were: ACR20 response at 3 months and Health Assessment Questionnaire Disability Index (HAQ-DI) change at 3 months.

At baseline, demographic and disease characteristics were similar in the study and the control groups. Tofacitinib was superior to placebo at 3 months both in ACR20 and HAQ-DI response rates. As compared to the placebo, HAQ-DI responses were statistically significant for all three active dosing arms. ACR20 response at 3 months: 50% in the tofacitinib (5 mg BID group), 61% in the tofacitinib (10 mg BID group) and 52% in the adalimumab group, compared with 33% in the placebo-treated patients. ACR20 responses were not only maintained, but they also got better in 12 months: 68, 70 and 60%, respectively, in the three active treatment arms. Adverse event rates were similar between all treatment arms including the placebo arm at month 12. The common adverse events were over 12 months, which were upper respiratory tract infection, nasopharyngitis and headache.

CONCLUSION

The emergence of small molecule-targeted therapies represents a new phase in targeted therapy owing to the ability of these agents to simultaneously block multiple signaling pathways. Tofacitinib is the first targeted small molecule to be approved by FDA for the use in rheumatologic diseases and is likely to be followed by a number of other Jakinhibitors (Jakinibs). It has been reported that the safety profile of tofacitinib in general appeared similar to that of biologic disease-modifying antirheumatic drugs, which includes risks of infections and abnormalities of the liver function test; in addition, a close follow up is required for neutropenia, lymphopenia, hyperlipidemia and serum creatinine levels [34–36]. An increased risk of herpes zoster has been reported in patients with tofacitinib compared with placebo [36].

JAK inhibitors have brought another paradigm shift in respect to the first-line therapy for autoimmune diseases. In the coming 10 years, a new chapter is going to unfold about indications of JAK inhibitors in multiple autoimmune and inflammatory diseases.

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Conflicts of interest

None.

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Axial spondyloarthritis classification criteria: the debate continues

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Purpose of review
The Assessment of Spondyloarthritis International Society (ASAS) axial spondyloarthritis (axSpA) classification criteria marked a major step forward in SpA research, distinguishing axial from peripheral disease, and allowing earlier identification through MRI. This facilitated all aspects of research including epidemiology, therapeutics and patient outcomes.

Recent findings
The ASAS axSpA classification criteria have been applied broadly in research, and were validated in a recent meta-analysis of international studies. Concerns arose because of clinical differences between the clinical and imaging arms, which imply different risk for radiographic progression, and perform differently in validation studies. Low specificity of the MRI finding of sacroiliac joint bone marrow edema may lead to misclassification in populations with low axSpA prevalence. We suggest methodology to improve upon the criteria, including rigorous assessment of potential candidate criteria sets, discrete choice experiments to allow consideration of feature weights, and validation. Separately, assessment of structural and inflammatory MRI abnormalities should be performed to refine the MRI definition of sacroiliitis.

Summary
The debate regarding the validation and modification of the ASAS axSpA classification criteria should lead to international efforts to build upon the gains made by these criteria, to further refine the axSpA population definitions for research and ultimately improve patient outcomes.

Keywords
classification, outcomes research, spondyloarthritis

INTRODUCTION

Spondyloarthritis (SpA) is a family of related diseases affecting the axial and peripheral skeleton. Ankylosing spondylitis, the prototypic form of SpA, is commonly diagnosed in the presence of definitive sacroiliitis on conventional x-rays. The modified New York Classification Criteria (mNYCC) for ankylosing spondylitis, which rely on radiographic changes and have been commonly used in research, were developed in 1984. The radiographic changes of sacroiliitis, however, are estimated to take 6–10 years to develop following symptom onset [1]. Moreover, although the degree of 'radiographic sacroiliitis' as seen on the plain x-rays is essential to classify a patient according to mNYCC, the reliability of this grading is poor, and training makes little impact on improving the reproducibility [2]. In the decades, because the mNYCC development, with increasing availability and utilization of MRI, it was recognized that MRI features of sacroiliitis preceded radiographic changes, allowing earlier identification of patients who would go on to develop ankylosing spondylitis. In 2003, the Food and Drug Administration (FDA) approval of tumor necrosis factor inhibitors (TNFi) for the treatment of ankylosing spondylitis indicated a paradigm shift in the management of ankylosing spondylitis. Around the same time, the dramatic efficacy of TNFi and other biologic therapies in treating rheumatoid arthritis had led to efforts to treat the disease early and aggressively. Rheumatologists wondered if treating ankylosing spondylitis early would improve patient outcomes, but diagnosing ankylosing spondylitis early and reliably was the main hurdle.

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KEY POINTS

- The Assessment of Spondyloarthritis International Society (ASAS) 2009 axial spondyloarthritis (axSpA) classification criteria have been a breakthrough in the rheumatology community, distinguishing axial from peripheral disease SpA, and allowing earlier identification of axSpA though use of MRI.
- Following the broad implementation of the ASAS axSpA criteria, concerns have arisen regarding important clinical differences and specificities between the clinical and the imaging arms of the axSpA criteria, which have prognostic implications for radiographic progression.
- The specificity of the 'positive MRI definition' considering bone marrow edema alone without structural changes is another cause for concern in populations where axSpA prevalence is lower than that in the original ASAS cohort, and in which misclassification would be more common.
- Opportunities to improve upon the ASAS axSpA criteria include reconciling heterogeneity between the clinical and imaging arms, to incorporating weighting of axSpA features, and refining the MRI definition of sacroiliitis.

DEVELOPMENT OF THE ASSESSMENT OF SPONDYLOARTHRITIS INTERNATIONAL SOCIETY CLASSIFICATION CRITERIA

In 2009, the Assessment of SpondyloArthritis International Society (ASAS) published new criteria for classification of axial spondyloarthritis (axSpA). [3,4] These criteria were developed beginning with expert review of paper cases of chronic back pain of unknown origin, whose detailed clinical information was duplicated both with and without information of SI joint MRI results (inflammation present versus absent) for a total of 142 cases. Candidate criteria sets were developed using clinical reasoning and considering combinations of any, up to 2, or up to 3 extra-spinal SpA manifestations. Two criteria sets were selected for further testing by their maximal sensitivity and specificity. ASAS members then contributed chronic back pain patients (onset <45 years) to a cohort study comprising 649 patients. In 40% of this sample, the candidate sets were further developed using various definitions of inflammatory back pain, and subsequently validated in the remaining 60% sample (Fig. 1).

In addition to the goal of classifying persons with axSpA who had imaging findings of sacroiliitis, either on x-ray or MRI, the 2009 ASAS criteria also allow classification of those with solely clinical features of SpA. Thus, the ASAS axSpA criteria may be fulfilled by patients with chronic back pain (≥3 months) with onset prior to age 45 years who have either: X-ray changes meeting the mNYCC or MRI findings of active sacroiliitis and one other clinical feature of SpA ('imaging arm') or HLA-B27 positivity in combination with at least two other clinical features of ('clinical arm'; Fig. 1). In 2011, ASAS also published criteria for peripheral SpA, which aided in differentiating axSpA as a distinct entity from peripheral SpA for further research [5].

To be applied in patients with chronic back pain (more than 3 months) starting before the age of 45	
IMAGING ARM	**CLINICAL ARM**
Sacroiliitis* plus ≥1 SpA feature	HLA-B27 positivity plus ≥ 2 SpA features**
SpA features: • Inflammatory back pain • Arthritis • Enthesitis • Dactylitis • Uveitis • Psoriasis • Crohn's/colitis • Good response to NSAIDs • Family history of SpA • HLA-B27 positivity • Elevated CRP	

FIGURE 1. ASAS classification criteria for axial spondyloarthritis. Modified from [3,4].

THE POSITIVE IMPACT OF THE ASSESSMENT OF SPONDYLOARTHRITIS INTERNATIONAL SOCIETY CLASSIFICATION CRITERIA

The ASAS axSpA classification criteria have been a huge step forward in our understanding of the spectrum of SpA, and have been widely adopted by the international rheumatology community [6]. The notion of dividing 'spondyloarthritis' in to axSpA and peripheral SpA as distinct phenotypes, and then dividing axSpA further in to ankylosing spondylitis and nonradiographic axSpA (nr-axSpA) has revolutionized our thinking of these conditions. The introduction of two new concepts, axSpA and nr-axSpA, has allowed identification of patients early in the course of their disease, before they can be classified as ankylosing spondylitis. The ability to identify patients who axSpA who lack radiographic changes (nr-axSpA) has led to a clearer understanding of the natural history and risk factors for axSpA, and greater appreciation for the burden of axSpA worldwide [7]. In addition, the use of MRI to identify patients with axSpA earlier in the disease course, prior to development of radiographic changes, has led to identification of more homogeneous

populations for inclusion in research studies. These developments have led to advanced research into the possibility of prevention of disease progression, particularly through the development and testing of new medications in early stages of the disease.

PERFORMANCE OF THE ASSESSMENT OF SPONDYLOARTHRITIS INTERNATIONAL SOCIETY AXIAL SPONDYLOARTHRITIS CRITERIA

To assess performance of the axSpA criteria, ASAS previously established an international 25-center cohort study, which included 649 patients seeking evaluation for back pain with onset less than 45 years. Axial SpA was diagnosed in 60% of these patients. Estimates of the performance of these criteria vary according to the specific population assessed. When compared to the older ESSG and Amor criteria at the time of the original study, sensitivity of the ASAS axSpA criteria were similar, and specificity was greater (84 vs. 65–78%) [3]. Subsequently, a long-term follow-up study assessed the predictive validity of the axSpA criteria by reassessing the diagnosis of patients in the original ASAS axSpA criteria development cohort. Mean follow up was 4.4 years (range 1.9–6.8) for the 394 participants from the original cohort, and the gold standard against which ASAS axSpA criteria were compared was the rheumatologist's diagnosis (not necessarily the same clinician). The imaging and clinical arms of the axSpA criteria were considered both separately and in combination with resulting positive predictive values ranging from 86 to 96% [8].

The ProSpA study assessed the performance of the ASAS criteria in a population of U.S. adults age 18 or older with chronic back pain with onset prior to age 45 [9]. With direct application of the ASAS criteria, 47% were classified as axSpA. The overall specificity of the ASAS criteria was 79%, somewhat lower than reported in more 'selected' referral populations, which was thought to be related to a relatively lower prevalence of males and HLA-B27 positive individuals in the ProSpA study than in previous studies.

A recent meta-analysis assessed the performance of the ASAS axSpA classification criteria in seven observational cohorts comprising nearly 5000 patients, including the U.S. ProSpA study [10▪]. Individual studies reported overall specificities ranging from 62 to 95%, with the pooled specificity of 87%. Specificities for the imaging arm (±clinical arm) ranged from 74 to 99% and for the clinical arm (±imaging arm) ranged from 71 to 97% for the individual studies. The pooled specificity was maintained across groups that fulfilled the imaging or clinical arms, irrespective of fulfilment of the other arm (range: 87–97%). Taken together, studies on the performance of the ASAS axial SpA criteria demonstrate overall good specificity, which is critical to identification of the intended population for study.

CONCERNS REGARDING THE ASSESSMENT OF SPONDYLOARTHRITIS INTERNATIONAL SOCIETY AXIAL SPONDYLOARTHRITIS CLASSIFICATION CRITERIA

Despite the good performance of these criteria as noted above, there is variability in how the criteria perform across different populations – especially in unselected chronic low back pain populations where the pretest probability of axSpA is low – and within other subgroups.

In October 2013, the FDA rejected the application by two TNFi (certolizumab and adalimumab) for the treatment of nr-axSpA. Among many other reasons, the FDA's concern about the specificity of the ASAS axSpA classification criteria when erroneously used for diagnostic purposes. Although four TNFi have been approved in the European Union to treat nr-axSpA, none have garnered FDA's approval in the United States. These issues continue to be debated, and we highlight the concerns raised about these criteria below, related to subgroups identified by the criteria, the issues around specificity of the MRI sacroiliitis definition, and the lack of weights given to SpA features.

Lack of homogeneity between the clinical and imaging arms of the Assessment of Spondyloarthritis International Society criteria

Studies indicate that important differences exist in the clinical characteristics of patients fulfilling the clinical and imaging arms, and their prognosis regarding disease progression. The clinical arm, which spans the spectrum of those who duly fulfill the imaging requirements all the way to those with normal imaging, has reduced specificity relative to the imaging arm (83 vs. 97%, respectively) [11]. Studies showed that subjects fulfilling the clinical arm were less likely to be male (42 vs. 59%, $P < 0.05$) and had lower mean C-reactive protein (CRP; 5.2 vs. 11.6, $P < 0.05$), two factors associated with lower radiographic progression to axial spondyloarthritis [12,13]. HLA-B27 positivity is 100% in the clinical arm (by definition), and lower in the imaging arm [12,13]. The proportion of subjects with nr-axSpA fulfilling each of the arms is not consistently

reported, but would be important to consider in future work.

Clinicians' reliance on MRI results and reduced MRI specificity in typical chronic back pain populations

MRI is the imaging modality of choice for axSpA, and has allowed identification of early disease where x-ray changes are minimal or absent. Both structural and inflammatory abnormalities may be present in/around the SI joints in axSpA. The current ASAS definition of MRI sacroiliitis is a single bone marrow edema lesion in the SI joint on two consecutive slices, or more than one bone marrow edema lesions on a single slice [14,15]. However, concern exists regarding this definition, as degenerative changes in the SI joints can also lead to similar bone marrow edema lesions, and they can be found in normal healthy individuals too [16]. The clinicians' reliance on MRI results influenced the ASAS criteria development process, in that expert diagnosis changed in 21% of paper cases when MRI results were added [3]. This influence of MRI results was also demonstrated in the ProSpA study, in which the majority of patients diagnosed with axSpA fulfilled the imaging arm, whereas those not diagnosed with axSpA more commonly fulfilled the clinical arm [9]. In addition, the reported high specificity of the imaging arm (97%) warrants closer consideration in populations different than the ASAS cohort, which had an axSpA prevalence of 60% [4]. The expected estimate for axSpA prevalence among unselected young adults with chronic back pain would be 5% [17], and in this setting the misclassification of patients as axSpA would outweigh the correct classification [18▪]. Indeed, this is suggested by a study in young adults with chronic low back pain onset prior to age 45, in which MRI 'sacroiliitis' was present in 21%, but expected to be much less common [19]. Taken together, these findings illustrate a need to re-evaluate the role of MRI features in classification of axSpA, and the definition of 'positive MRI'.

Inability to weigh clinical features

Although the ASAS criteria require at least one or two clinical features of SpA (the imaging and clinical arms, respectively), each of the clinical features carries the same weight in the current ASAS criteria. For example, an HLA-B27 positive patient with inflammatory back pain and elevated CRP has a positive likelihood ratio (LR+) product of 70, whereas a HLA-B27 positive patient with sacroiliitis on MRI and acute uveitis has an LR+ product of 1314. Current criteria do not distinguish the relatively greater risk of SpA conferred by some features [20]. In addition, the ASAS criteria do not have a mechanism to address correlation between features (e.g. HLA-B27 positivity and positive family history of SpA). Classification criteria for gout and systemic sclerosis have both used methodology to incorporate weighting of disease features, which could be used in classifying axSpA, as outlined later.

POTENTIAL METHODOLOGY FOR IMPROVING THE SPECIFICITY OF THE AXIAL SPONDYLOARTHRITIS CLASSIFICATION CRITERIA

Various processes can be used for improving the specificity of the existing criteria. Here we describe a method similar to those used in development of classification criteria for rheumatoid arthritis, gout and systemic sclerosis [21–25].

Item generation and reduction

A list of candidate items that differentiate axSpA from mimicking conditions could be generated from literature review, and patient/expert opinion. The resulting extensive list of candidate items would be reduced through a Delphi exercise and/or nominal group technique and then be tested for their discriminatory capacity for axSpA in a sample from existing North American as well as registries from the rest of the world and cohorts that contain both axSpA and mimicking conditions.

Consensus process to identify factors that impact the probability of axial spondyloarthritis

Rheumatologists with a special interest in axSpA would be asked to contribute paper cases of patients for whom axSpA was in the differential diagnosis. An international axSpA expert panel would review the results of the item generation/reduction process, then rank-order each case from the lowest to highest probability of having axSpA. The item generation/reduction process and paper cases will form the basis for in-depth discussion to identify key features that positively or negatively impact the probability of axSpA and to develop potential classification criteria sets.

Item weighting

Item weighting may be performed through discrete-choice experiments, a process that has been used in development of rheumatoid arthritis, systemic sclerosis, and gout classification criteria [21–25].

Paper cases from SpA experts internationally would be purposively sampled to reflect the spectrum of probability that each case could be classified as having axSpA (i.e. early versus established, and radiographic vs. nonradiographic disease). Standard software would be used to develop paired case scenarios that differ in two attributes. The case pairs would be presented to an international panel of axSpA experts, who will select the case from the pair that he/she believes has a higher probability of being classified as having axSpA. Through iterative pairwise choices, the software will assign relative weights to each case attribute.

Defining a threshold for classifying axial spondyloarthritis

The expert panel would consider candidate criteria sets (some incorporating item weighting) relative to the gold-standard axSpA definition of expert opinion. For each criteria set, a cutoff score would be calculated to maximize the sum of specificity and sensitivity. The expert panel will then participate in a threshold identification exercise, which will assess experts' willingness to enroll paper cases into a study (e.g. a phase III trial for a new biologic agent for axSpA with unclear efficacy and safety).

Validation of the final criteria

Using data from existing axSpA registries and cohorts (remainder of the split-sample reserved for this purpose), the sensitivity and specificity of the revised axSpA classification criteria will be assessed. In subsequent studies, performance of the revised criteria will be compared with that of the original ASAS criteria, as well as the ESSG and Amor criteria, and assessed in other populations such as unspecified chronic back pain.

MRI features in axial spondyloarthritis

To further establish the role of specific MRI features that differentiate inflammatory arthritis involving the SI joints from mechanical or other causes of back pain, MRIs will need to be compared among patients presenting with back pain, and whose diagnosis is subsequently established though other clinical/laboratory assessments. This may be conducted in existing cohorts, if such imaging is available, or a new cohort may be assembled in order to address this question.

CONCLUSION

The 2009 ASAS SpA classification criteria marked an important step forward in our understanding of the spectrum of SpA, and our ability to define the clinical spectrum of peripheral and axSpA for studies of novel therapies and patient outcomes. These criteria have succeeded in changing our vocabulary, has expanded our ability to treat axial spondyloarthritis patients early and have been instrumental in garnering European regulatory authority approval for four TNFi to treat nr-axSpA. Nonetheless, opportunities exist to improve these criteria; to reconcile the heterogeneity that exists in populations classified by the clinical and imaging arms, to determine weighting of axSpA features, and to define and refine definitions of MRI-associated sacroiliitis. Herein, we have outlined the arguments on both side of the debate, and also one of the many possible methodologies to improve specificity of the classification criteria. ASAS classification criteria have been a major breakthrough in the field of spondyloarthritis with important implications for research and patient care. A healthy debate about the pros and cons of the existing criteria leading to further modifications can only improve patient care.

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Conflicts of interest

A.D.: Past-Chair, Spondyloarthritis Research & Treatment Network (SPARTAN); M.D.: None.

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Infections in rheumatoid arthritis

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Purpose of review
The purpose of this review is to provide an update concerning recent advances in the evidence- based study of serious infections in patients with rheumatoid arthritis (RA) treated with biological drugs or conventional disease-modifying antirheumatic drugs (DMARDs), concentrating on studies published in the last 18 months.

Recent findings
New studies have further strengthened existing evidence relating the use of biological drugs to serious infections. The risk does not seem to be any different with short-term or long-term use. There is still a lack of conclusive studies identifying biomarkers, but it is plausible that the drugs have direct effects on cytokines and cell activity and then serious infections.

Summary
The frequent infections of patients with RA may be due to the disease itself (altered immunological function, disability, immobility, joint surgery), extra-articular manifestations or DMARDs, immunosuppressants and steroids. The use of biological drugs lead to the development of serious infections including tuberculosis. Patients should be informed of their increased risk, and physicians need to be aware of these complications and how to treat them.

Keywords
anti-tumour necrosis factor drugs, fungal and viral infections, infections, newer biological drugs, orthopaedic surgery, perioperative infections

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic and progressive inflammatory condition that is associated with increased mortality and comorbidities such as cardiovascular disease, malignancies and infections [1–3]. The frequent infections of patients with RA may be due to the disease itself (altered immunological function, disability, immobility and/or joint surgery), extra-articular manifestations or disease-modifying antirheumatic drugs (DMARDs), immunosuppressants and steroids) [3–5]. After controlling for potential confounders, one population-based study found that, in comparison with age and sex-matched controls, an inception cohort of 609 patients showed a 70% increase in confirmed infections and an 85% increase in hospitalizations due to infections, particularly infections of the bones, joints, skin, soft tissue and the respiratory tract [4]. Infections are also partially responsible for the increased mortality associated with RA, particularly genitourinary and bronchopulmonary infections [6].

DISEASE-MODIFYING ANTI-RHEUMATIC DRUGS

Conventional DMARDs can increase the risk of infections, including tuberculosis (TB) [7], and low-dose methotrexate (MTX) seems to inhibit T cell activation and granulocyte function.

Bacterial, viral and fungal infections

Van der Veen *et al.* [8] compared the frequency of bacterial infections between patients with RA treated with MTX and those treated with other DMARDs (including hydroxycloroquine, sulphasalazine, gold, penicillamine and azathioprine) or who had never received a DMARD. The overall rate of infections (particularly skin and upper respiratory tract infections) and the use of antibiotics were slightly higher in the MTX-treated group, but there was no increase in serious infections leading to drug withdrawal. Furthermore, MTX-treated patients

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KEY POINTS

- Anti-TNF drugs are associated with an increased risk of TB and other serious infections.
- Abatacept, rituximab and tocilizumab are mainly associated with forms of pneumonia and pyogenic bacterial infections.
- Tofacitinib increases the risk of herpes zoster infection.
- Anti-TNF drugs increase the risk of peri-operative infections after orthopaedic surgery.

with long-lasting RA show an increased rate of herpes zoster infection compared with patients with non-inflammatory musculoskeletal disorders or these treated with other DMARDs [9]. A retrospective, longitudinal study of a population-based RA cohort in British Columbia [10] showed that the use of DMARDs without corticosteroids was associated with a small bur statistically significant decrease in the risk of mild infection of unclear clinical significance [adjusted rate ratio 0.90, 95% confidence interval (95% CI) 0.88–0.93] in comparison with untreated individuals, and no increase in the risk of serious infections (adjusted rate ratio 0.92, 95% CI 0.85–1.0), whereas the use of corticosteroids increased the risk of both, possibly because controlling RA-related inflammation counterbalanced the potential immunosuppressive effects of DMARDs. Bernatsky *et al.* [11] found that the risk of hospitalization due to infection seems to be highest in patients treated with cyclophosphamide (rate ratio 3.26, 95% CI 2.28–4.67) or systemic glucocorticoid agents (rate ratio 2.56, 95% CI 2.29–2.85); azathioprine was associated with a moderately higher risk (rate ratio 1.52, 95% CI 1.18–1.97). Furthermore, there was a suggestion that MTX may be associated with an increased risk of pneumonia (rate ratio 1.16, 95% CI 1.02–1.33), whereas antimalarial drugs such as hydroxychloroquine and chloroquine did not seem to be associated with an increased risk of any infection.

Opportunistic infections mainly presenting as pneumonia with focal or diffuse infiltrates are potential complications of low-dose MTX therapy, and can occur even when leukocyte counts are normal. However, although there are many case reports of MTX-related infection, the concomitant use of corticosteroid therapy may have been a predisposing factor [12]. Jenks *et al.* [13] investigated the frequency of infections in RA patients treated with leflunomide alone or in combination, and found that the overall infection rate was 3.3/100 patient-years, but higher in patients with severe disease treated with combined MTX and corticosteroids. Wolfe *et al.* [14] found that the use of leflunomide (but not sulphasalazine or MTX) was associated with an increased risk of pneumonia.

Septic arthritis and perioperative joint infections

In a randomized controlled trial (RCT) in which MTX was continued or discontinued before elective orthopaedic surgery, and the results were compared with those observed in patients who had never received MTX, significantly fewer patients who continued MTX experienced surgical complications and infections within 1 year of surgery (2%) than those who discontinued MTX (15%) or had never received it (10.5%); they also experienced no disease flares, whereas 8% of the patients who discontinued MTX were observed. The presence of any of the analysed chronic diseases (diabetes, bronchiectasis, etc.) increased the risk of complications, as did treatment with penicillamine, indomethacin, cyclosporin, hydroxychloroquine, chloroquine and/or prednisolone, but not treatment with any dose of MTX regardless of whether it was continued or discontinued before surgery [15].

The United Kingdom General Practice Research Database (GPRD used to evaluate the risk of developing septic arthritis) (excluding infected joint replacements) has shown that the incidence of septic arthritis is 12.9 times higher in individuals with RA than in those without [16], and higher in those treated with penicillamine [adjusted incident rate ratios (IRRs) 2.51, 95% CI 1.29–4.89; $P = 0.004$], sulfasalazine (adjusted IRR 1.74, 95% CI 1.04–2.91; $P = 0.03$) and prednisolone (adjusted IRR 2.94, 95% CI 1.93–4.46; $P < 0.001$) than in those receiving other DMARDs, including MTX, or not receiving any DMARD. The increased risk was attributed to both the disease process and the use of DMARDs [16].

Given these data, the evidence-based conclusion is that MTX can be safely continued in patients undergoing elective orthopaedic surgery [17].

BIOLOGICAL DRUGS

Ten biological therapies are currently licensed to induce disease control and/or remission and improve of the quality of life of patients with RA, but there are still concerns regarding the risk of serious adverse events [18], as a number of studies have shown that their use can lead to the development of serious infections requiring hospitalization and/or the administration of intravenous antibiotics, or even death [19▪▪].

ANTITUMOUR NECROSIS FACTOR DRGUS

Tuberculosis

TB (mainly caused by the reactivation of latent tuberculous foci as a result of a destabilised balance between host immunity and pathogen virulence) [20] is the opportunistic infection that is most frequently associated with antitumour necrosis factor (TNF) drugs, and highly likely to lead to widespread, complicated extra-pulmonary infection [21,22].

A recent meta-analysis of RCTs and long-term extension studies of RA patients found 31 cases of TB occurring during anti-TNF treatment: an odds ratio (OR) of 1.92 (95% CI 0.91–4.03; $P = 0.085$). The incidence was higher in those treated with mAbs (OR 307.71, 95% CI 184.79–454.93) than in those treated with etanercept (ETN) (67.58, 95% CI 12.1–163.94), and higher in areas in which TB is more frequent [23]. RCTs of certolizumab pegol and golimumab have also shown significantly higher rates of TB than those observed with earlier anti-TNF drugs, but these were carried out in countries with higher background population rates [24–26].

All candidates for treatment with anti-TNF drugs should therefore be screened for TB, and it is strongly recommended that those with latent TB start TB treatment before starting anti-TNF drugs [27], particularly in endemic areas. The diagnosis of latent TB is mainly based on the patient's medical history and the findings of a physical examination, a tuberculin skin test (TST) or interferon-gamma release assay (IGRA), and chest radiography. The main disadvantages of TSTs (the need for training in interpreting the results, the time required for the reaction and the effect of Koch bacillus vaccination on the findings) [28] have been partially overcome by the use of IGRAs, although there are only limited data concerning patients recently exposed to TB, children aged less than 5 years and immunocompromised individuals (including patients with rheumatic diseases). Patients who are TST or IGRA positive should undergo chest radiography to exclude active TB and, if negative, begin treatment for latent TB infection 1 month before the start of anti-TNF therapy and continue it for 6–9 months; if positive, anti-TNF drugs should be discontinued immediately, but whether or not to resume anti-TNF therapy after TB treatment is completed, it is controversial [19▪▪].

Effective screening and prophylaxis have decreased the risk of TB [29▪].

Bacterial infections

Registries have greatly improved our understanding of the risks associated with anti-TNF drugs because they contain data relating to thousands of patients with 'real world' disabilities and comorbidities, as well as those who would be considered ineligible for RCTs [30–34]. They have consistently reported a slightly increased risk of severe infections (particularly lower respiratory tract, skin and soft tissue infections) during the first 6 months of treatment in older patients, those with highly active disease and those taking monoclonal antibodies other than ETN or concomitant corticosteroids [30–35].

Dixon *et al.* [30] found that there is a four-fold increased risk of skin and soft tissue infections in anti-TNF treated patients, which suggests that TNF plays a more physiological role in host defences of the skin and soft tissues. They also found a time-dependent decrease in risk that is attributable to high-risk patients discontinuing anti-TNF treatment because of death, inefficacy or side effects, patients lost to follow-up and improvements in functional status and lower corticosteroid doses [33]. A Cochrane review of anti-TNF drugs used for different indications found that severe infections were more likely in patients treated with infliximab (INF) and certolizumab than with control treatments (OR 1.41, 95% CI 0.75–2.62, and OR 4.75, 95% CI 1.52–18.5) [36▪▪]. Early studies of INF, adalimumab (ADA) and ETN did not find any differences in infection rates [30–32], but more recent studies have found an increased relative risk of infection with INF [33,34]. The Gruppo Italiano Studio Early Arthritis (GISEA) registry showed that there was a significant difference in the risk ($P < 0.0001$), and multivariate models confirmed that the use of steroids ($P < 0.046$), concomitant DMARD treatment ($P = 0.004$), advanced age at the start of anti-TNF treatment ($P < 0.0001$) and the use of interferon ($P < 0.0001$) or ADA ($P = 0.023$) rather than ETN were statistically significant predictors of infection [34]. It has also been found that exposure to more than one anti-TNF drug during therapy leads to a two-fold risk of developing a severe infection [5].

A British Society for Rheumatology Biologics Register (BSRBR) study [37] has shown that recommending patients to avoid high-risk foods when starting anti-TNF drugs may reduce the reportedly increased risk of *Listeria* infection due to foods made using unpasteurised milk, or *Salmonella* infection due to undercooked eggs or meat [4].

A recent meta-analysis has confirmed that anti-TNF drugs increase the occurrence of severe infections in comparison with conventional DMARDs (rate ratio = 1.48, 95% CI 1.18–1.85), but no significant difference was found between ETN and mAbs (rate ratio = 0.55, 95% CI 0.22–1.35) [38▪▪]

An analysis of 15 132 patients with RA exposed to ADA in clinical trials found that the most

frequently reported adverse events were severe infections, including pneumonia (0.7 E/100 person-years), cellulitis (0.3 E/100 person-years) and bacterial arthritis and sepsis (both 0.2 E/100 person-years). The frequency of the remaining SIs was 0.1 E/100 person-years or less [39].

Fungal infections

As cryptococcosis, histoplasmosis and coccidioidomycosis have all been associated with anti-TNF drugs in endemic areas [40], anti-TNF treatment should be started cautiously in patients living in or visiting such regions. Patients receiving anti-TNF drugs may also be at an increased risk of developing *Pneumocystis jiroveci* and *Nocardia* infection [40–42].

Fungal infections are extremely rare after anti-TNF drug treatment, and there is no clear indication that any one agent predisposes patients to them [19▪▪]. However, a recent study from Taiwan showed that 20 (0.22%) of 9132 patients with RA were newly diagnosed with cryptococcal infection after the identification of RA. All of these patients had been receiving corticosteroid treatment for some time (3.9 ± 3.3 years) before infection, and the risk of developing cryptococcal infection was higher among those with chronic kidney disease who were receiving the monoclonal anti-TNF antibody (ADA) [43].

A recent analysis of 15 132 RA patients exposed to ADA in clinical trials reported 40 opportunistic infections in 35 patients (excluding oral candidiasis, herpes zoster and TB), a rate of 0.2 E/100 person-years. The most frequently reported were oesophageal candidiasis (<0.1 E/100 person-years) and coccidiomycosis, cytomegalovirus infection and mycobacterium avium complex infection (<0.1 E/100 person-years) [39]. Patients should therefore be told about the risk before starting anti-TNF therapy and, if a patient develops a fever, fungal infections should be considered. In the case of histoplasmosis and cryptococcus, patients should be advised to avoid exploring caves or cleaning bird roosts. In areas endemic for coccidioides such as South-west USA, patients should have their *Coccidiodes immitus* titres checked before starting anti-TNF drugs and, if positive, empirical flucanozole prophylaxis can be considered [42].

Septic arthritis and perioperative joint infections

Despite the widespread use of the new biological drugs, patients with RA continue to undergo arthroplasty to restore lost function and relieve the pain caused by damaged joints [44▪], and are at a risk of developing superficial wound and prosthetic joint infections (PJIs), which may occur early after surgery and be attributed to bacteria entering the surgical site, or later in the case of blood-borne infections [45]. The risk can be reduced by administering prophylactic systemic antibiotics within 1 hour of incision, ensuring a laminar air flow in the operating room, and using of antibiotic-laden prosthesis fixation cement, but the very presence of an orthopaedic implant increases the possibility that even a small number of bacteria form a biofilm that adheres to the prosthetic material and rapidly form microcolonies [46]. This makes the diagnosis and treatment of infection more difficult because bacterial aggregation and formation of a polysaccharide matrix make the bacteria inaccessible to normal host defences [47]. Cytokines such as tumour necrosis factor-alpha (TNFα) play an important role in initial host defences, and this may explain the somewhat increased risk of PJI observed in patients receiving anti-TNF drugs [44▪].

A study using the pooled data of 3681 patients recently exposed to anti-TNF and 4310 with no recent exposure has shown that the risk of infection associated with elective orthopaedic surgery is significantly higher in the former (OR 2.47, 95% CI 1.66–3.68; $P < 0.0001$) [48▪▪], thus indicating that the risk of both superficial and deep infection may be 2–4% higher in patients treated with biological agents at the time of surgery [47].

Moreover, the BSRBR has shown that patients with RA receiving anti-TNF are twice as likely to develop septic arthritis as those treated with nonbiological DMARDs and, as this could affect the healing of a surgical wound [49,50], some guidelines suggest discontinuing biological treatment 1 week before surgery. RA flares upon discontinuing treatment are more likely in patients with established disease than in those with early disease, and so TNF blockers need to be resumed promptly after surgery in order to avoid this risk [44▪]. The almost universal policy of discontinuing anti-TNF drugs is therefore based on the principle of caution and expert opinion.

A recent meta-analysis of 12 studies evaluating postoperative infection risk in patients treated with anti-TNF drugs has confirmed that the risk is doubled (rate ratio = 1.81, 95% CI 1.31–2.50), although the discontinuation of treatment did not alter the risk significantly: rate ratio = 0.69 (95% CI 0.39–1.21) [51].

Herpes zoster infection

The German RABBIT registry has confirmed the clinical trial finding of frequent herpes zoster infection, a neurocutaneous disease that is characterized by a painful vesicular dermatomal rash due to the reactivation of varicella zoster virus (VZV) [31,52]. A

recent meta-analysis of seven registries found that the pooled risk ratio for herpes zoster was 1.61 (95% CI 1.16–2.23; $P = 0.004$), and that severe herpes zoster occurred in 4.9–20.9% of the patients treated with anti-TNF drugs as against 2–5.5% of those treated with conventional DMARDs [30]. The same meta-analysis revealed a significantly increased risk of herpes zoster in up to 61% of patients with systemic inflammatory diseases, thus raising the question as to whether systematic prophylactic treatment should be given to those with a known history of herpes zoster, and whether previously unaffected patients should be vaccinated [53]. The Centers for Disease Control and Prevention (CDC) in the USA has recommended that all adults aged more than 60 years be vaccinated against shingles regardless of previous exposure [54]; however, the Zostavax vaccine is a live therapy and should be used cautiously in immunosuppressed individuals and, although low-dose corticosteroids or MTX are not contraindications, the vaccine should not be administered to individuals undergoing established anti-TNF treatment [54].

Hepatitis B infections

Hepatitis B virus (HBV) infection is a major public health concern in many countries, as approximately one-third of the world's population has serological evidence of past or present infection, and 350–400 million people (1.25 million in the USA) are chronic HBV surface antigen (HBsAg) carriers. The virus is responsible for chronic hepatitis, cirrhosis and hepatocellular carcinoma, and is associated with more than 600 000 deaths every year [55].

The reactivation of HBV has been attributed to a relative lack of TNF or a decreased T cell activation and interferon production, and a number of reports indicate that INF may be associated with reactivation [56], although the entity of the risk has not been established. HBV reactivation is related to serological status before starting anti-TNF drugs, and is greater in HbsAg-positive than in anti-HBc positive patients [57]. A recent systematic review and meta-analysis of 10 studies found that the prevalence of HBV reactivation was 3.9% among patients treated with ETN, and 4.6% among those treated with ADA; furthermore, pooled prevalence among patients not receiving any antiviral prophylaxis was 4.0% [58]. The rate of HBV reactivation is relatively low in anti-TNF treated patients with rheumatic conditions, but screening is recommended: antiviral prophylaxis and early treatment with nucleoside/nucleotide analogues should be given to those with overt chronic HBV infection, and lamivudine prophylaxis to active and inactive HBV carriers [59]. Occult anti-HBc positive, HbsAg-negative carriers requiring anti-TNF treatment do not need prophylaxis, but a close observation is advised (an HBsAg test every 3 months) in order to be able to identify HBV reactivation and start antiviral therapy as soon as possible [59]. Prophylaxis should be started at least 1 month before biological treatment, and resumed (together virological monitoring) for at least 6 months after its discontinuation.

Hepatitis C infection

The estimated global prevalence of HCV infection is 2.2%, corresponding to about 130 million HCV-positive individuals worldwide; it is low in North European and North American countries, and higher in Japan, China, Italy and other Mediterranean countries [60].

Not a lot is known about the use of anti-TNF drugs and chronic hepatitis C virus (HCV) infections, but all patients should be screened for HCV before starting anti-TNF treatment [60]. Preliminary data suggest that the drugs are well tolerated [61], and Zein [62] has proposed that the combination of pegylated interferon and ETN (the most widely studied anti-TNF drug) should be used to treat HCV infection. Although well tolerated, anti-TNF drugs should be administered together with antiviral therapy, particularly in the case of patients with associated hepatitis B infection.

NEWER BIOLOGICAL AGENTS

The use of abatacept, rituximab and tocilizumab is associated with a high incidence of severe infections, most of which are forms of pneumonia or pyogenic bacterial infections, but invasive aspergillosis and TB have sometimes been reported [19▪▪].

Tuberculosis

The risk of TB is unclear: no cases in RCTs of rituximab and tocilizumab [19▪▪], two unconfirmed cases in RCTs of abatacecpt [63,64] and seven cases in RCTs of tofacitinib [65]. The European League Against Rheumatism (EULAR) consensus statement notes that there are insufficient data to recommend mandatory screening for TB before treatment with rituximab, but recommends rituximab as the first-line biological drug if TB chemoprophylaxis is contraindicated and for patients from endemic regions [66].

Bacterial, fungal and viral infections

A meta-analysis of the tocilizumab trials carried out up to 2009 found that the increased risk of severe infections in comparison with controls was nearly

significant (hazard ratio 1.78, 95% CI 0.98–3.23) in patients receiving a dose of 8 mg/kg in combination with MTX [67]. Similarly, a meta-analysis of abatacept, rituximab and anakinra found a nonsignificant trend towards an increased risk of severe infections at the higher doses of rituximab (1 g vs. 500 mg) and abatacept (10 vs. 2 mg/kg) [68]. A recent Bayesian network meta-analysis of 106 RCTs has also found that the risk of severe infections is higher at standard or high doses (OR 1.31 and 1.90, respectively), but not at low doses (OR 0.93; 95% CI 0.65–1.33), as well as in trials lasting 6–12 months, when biological agents were used in combination with conventional DMARDs, in patients with established RA, in studies carried out before 2004 and in patients previously treated with conventional DMARDs or anti-TNF drugs [36▪▪].

The French Society of Rheumatologist's ORA Register has reported that 103 of the 1017 patients treated with abatacecpt were very elderly (>75 years), 215 elderly (65–74 years), 406 middle-aged (50–64 years) and 293 very young (<50 years), and that increased age was associated with a higher rate of discontinuation because of adverse events, especially severe infections [69].

The risk of progressive multifocal leukoencephalopathy associated with rituximab has received considerable attention since the FDA issued a black-box warning after two cases were reported in lupus patients but, although case reports suggest that the risk in rituximab-treated patients with RA may be increased, the absolute risk is extremely low [36▪▪]. The rates of herpes zoster infection are not systematically reported in RCTs and observational studies of the newer biological agents [19▪▪], but are significantly increased with tofacitinib [70]. Finally, Curtis *et al.* [71▪] showed that the rate of herpes zoster associated with tofacitinib was approximately double than that observed in patients using biological agents.

Septic arthritis and perioperative joint infections

Data from the Autoimmunity and Rituximab Registry of 133 patients who underwent 140 operations within 12 months of a rituximab infusion show that, although 7.4% of the 95 patients who underwent orthopaedic procedures developed a complication (most frequently infection), there was no association with the timing of the rituximab dose [72]. This suggests that no special dosing arrangements are necessary for rituximab-treated patients scheduled for elective orthopaedic surgery.

There are no data suggesting that tocilizumab is associated with perioperative risk. However, the drug acts by decreasing the hepatic production of C-reactive protein (CRP) and other acute-phase reactants [73], and this may complicate the early diagnosis of an infection. Clinicians should suspect infection in such patients.

There are not perioperative management guidelines for abatacept or tofacitinic [19▪▪], but abatacecpt should be stopped 14 days prior to surgery, and tofacitinib 1 week before.

Hepatitis B virus and hepatitis C virus infection

HBV reactivation has been observed in rituximab-treated RA patients carrying HBsAg and in those with resolved HBV infection, but the discontinuation of immunosuppressive treatment and antiviral therapy allows the infection to be controlled within a few months. Consequently, prophylaxis with lamivudine is only recommended for rituximab-treated patients with onco-hematological diseases, and HBsAg/HBV DNA levels should be carefully monitored in all of the other cases [74]. In line with this, Varisco *et al.* [75] have shown that the administration of rituximab and DMARDs to patients with RA with resolved HBV leads to negligible HBV reactivation, thus confirming that universal anti-HBV prophylaxis is not necessary.

There are few published data concerning the use of abatacept and tocilizumab in HBV patients, but the findings of a retrospective observational study by Padovan *et al.* [76] have shown that abatacept is well tolerated in patients with RA with concomitant HBV infection even without antiviral prophylaxis.

Rituximab has been widely used to treat lymphomas and HCV-related mixed cryoglobulinemia, but little is known about the use of anti-CD20 therapy in the treatment of patients with RA with HCV infection [77,78], or about the use of tocilizumab and abatacept [79,80].

CONCLUSION

Anti-TNF drugs are associated with an increased risk of TB and other severe infections, particularly infections of the bones, joints, skin, soft tissue and the respiratory tract; abatacept, rituximab and tocilizumab are mainly associated with forms of pneumonia and pyogenic bacterial infections; and tofacitinib increases the risk of herpes zoster infection. Despite the widespread use of the new biological drugs, patients with RA continue to undergo arthroplasty to restore lost function and relieve the pain caused by damaged joints, and this increases the risk of perioperative infections. This is particularly true in the case of patients treated with biological and

nonbiological DMARDs, although it should be remembered that age, comorbidities, the use of corticosteroids and functional status are also predisposing factors. Patients with RA should therefore be informed of the increased risk of infection, and physicians should monitor them carefully in order to detect infections as early as possible

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Conflicts of interest

The authors declare that they have no competing interests.

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Human papilloma virus and lupus: the virus, the vaccine and the disease

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Purpose of review
Systemic lupus erythematosus (SLE) is a well known, widespread autoimmune disease, involving multiple organ systems, with a multifaceted, widely unmapped etiopathogenesis. Recently, a new aspect of morbidity has been described among SLE patients: infection with human papilloma virus (HPV). We set out to review data regarding the intricate relationship between the two and attempt to determine whether HPV may pose as a contributing factor to the development of SLE.

Recent findings
We relate to epidemiological, molecular and clinical data. We have found evidence in all these fields suggesting HPV to be involved in the pathogenesis of SLE: increased prevalence of HPV infection among SLE patients; vast molecular homology between viral peptides and human proteins associated with SLE; several reports of SLE development post-HPV vaccination. Our findings suggest a possible involvement of HPV infection in the induction of SLE, via a mechanism of immune cross-reaction due to molecular homology.

Summary
We review clinical, epidemiological and molecular data suggesting involvement of HPV infection in the pathogenesis of SLE. We suggest that these findings may justify the development of new HPV vaccines containing viral peptides that bear no homology to the human proteome, in order to avoid possible adverse immune cross-reactivity.

Keywords
autoimmunity, cross-reactivity, human papilloma virus, molecular homology, systemic lupus erythematosus

INTRODUCTION

Systemic lupus erythematosus (SLE) has been long considered as the prototype of autoimmune diseases. It is a chronic inflammatory condition characterized by numerous immunological and clinical manifestations. SLE involves a variety of target organs – the kidneys, skin, joints, blood vessel walls, mucous membranes and nervous system – and is associated with great morbidity and mortality [1,2]. The distinct pathogenesis of the disease is yet to be unravelled; however, in recent years, a new aspect has risen in the research of the disease: infection with the human papilloma viruses (HPVs).

HPV is a group of viruses belonging to the papillomavirus family, a family of double-stranded circular DNA viruses with an ability to infect epithelial cells of the skin as well as oral and genital mucosa. More than 150 HPV types have been isolated and fully sequenced. Infection with HPV is considered the most prevalent sexually transmitted disease worldwide. Moreover, persistent infection with at least 15 different strands of the virus was found to be strongly associated with squamous cell carcinoma and adenocarcinoma of the cervix [1,3].

As of date, three HPV vaccines (HPVv) are administered in common practice: the bivalent Cervarix (aimed against serotypes 16 and 18), the quadrivalent Gardasil (aimed against serotypes 6, 11, 16 and 18) and the recently introduced 9-valent vaccine (aimed against serotypes 6, 11, 16, 18, 31, 33, 45, 52 and 58) [4]. The vaccines use different adjuvants, and both have been studied for efficacy

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KEY POINTS

- HPV infection is significantly more prevalent among SLE patients, regardless of use of immunosuppressive drugs.
- There is wide evidence of various infectious agents, such as EBV, being involved in the induction of SLE, possibly due to molecular homology leading to an immune cross-reaction.
- We have found a significant overlap between HPV proteins and human proteins associated with SLE, suggesting a possible immune cross-reaction post-HPV infection or vaccination may trigger disease onset in prone individuals.
- We suggest the use of unique peptide-based vaccines in order to eliminate the risk of cross-reaction.

and safety. Both were found to be effective, providing a long-lasting protection against HPV infection and premalignant lesions [5,6].

Herein, we intend to review current data regarding the intricate relationship between HPV infection and SLE induction.

HUMAN PAPILLOMA VIRUS AS AN INFECTIOUS CAUSE FOR SYSTEMIC LUPUS ERYTHEMATOSUS

It has long been ascertained that certain infectious agents may cause the development of autoimmunity, and specifically, SLE has been associated with Epstein–Barr virus (EBV), cytomegalovirus (CMV), human endogenous retroviruses (HERVs) and several other infectious agents [7,8]. Recently, a possible causality has been suggested between HPV and SLE [9]. The suggested mechanism behind this association between HPV and SLE is that of immune cross-reactivity.

HYPOTHESIS OF IMMUNE CROSS-REACTIVITY

A ground breaking publication in the 1960s gave birth to the theory that antigens of infectious agents bearing similarity to host molecules may initiate a cross-reactive immune response, leading to the development of autoimmunity [10]. Following this initial publication, the theory of molecular homology and its role in the development of certain autoimmune diseases have been widely explored [11–14].

In order to assess whether HPV may be an instigating factor in the propagation of SLE, via immune cross-reactivity, several aspects have been explored: first, a review of epidemiological data was conducted to ascertain a connection between HPV carriage and SLE and produce the *epidemiological level of evidence*. Second, a common denominator was demonstrated between HPV elements and human elements involved in SLE; this may be viewed as the *molecular level of evidence*. Finally, clinical reports were scanned for cases of SLE induction post-HPV infection or vaccination, which may be viewed as the *clinical level of evidence*.

EPIDEMIOLOGICAL EVIDENCE

Several studies examining the prevalence of HPV infection among patients with SLE yielded interesting results, suggesting a higher prevalence of HPV infection among SLE patients. One of these studies demonstrated a threefold increase in HPV prevalence among SLE patients as compared with controls, which was associated with the use of immunosuppressive drugs. However, when comparing SLE patients with mild or no use of immunosuppressive drugs to controls, higher rates of HPV infection were found in the SLE patients despite the fact that they had a significantly lower number of classical risk factors; SLE patients displayed a higher age at sexual debut and a lower number of lifetime sexual partners [15]. In a similar study conducted a few years later, the risk for genital infection with HPV was higher among 88 women with SLE than 70 healthy controls, with an odds ratio of 7.2 [95% confidence interval (95% CI), 2.9–17.8; $P = 0.0001$]. This association was found following adjustment for factors such as early sexual activity and number of sexual partners. In other words, SLE patients were found to have increased odds to carry HPV infection regardless of their sexual activity status. Furthermore, in this study, the use of immunosuppressive drugs was not associated with a higher prevalence of HPV infection [16]. Furthermore, a meta-analysis recently published, reviewing 27 articles, found increased prevalence of cervical dysplasia and cancer associated with HPV infection among SLE patients [17▪▪]. These findings raise the question: which event is the preceding one? Are women with SLE at a higher risk for HPV infection, or is HPV infection the primary event, inducing development of SLE in prone individuals? Further evidence lead us to suggest that there might be truth in the latter speculation.

MOLECULAR EVIDENCE

We have recently analysed peptide sharing between human proteins that, when altered, are associated with SLE, and L1 proteins of four HPV strains: 6, 11,

16 and 18 [9]. In light of the publication of a new 9-valent HPV vaccine [18], we have expanded our analysis to include all nine strains. We used the peptide platform common to HPV L1s strains 31, 33, 45, 52 and 58, and human proteins related to lupus (Table 1) as a tool to analyse the molecular connections between HPV infection and SLE disease [19–50,51▪▪,52–66,67▪▪,68–90].

Table 1 summarizes that two main groups, that is complement proteins and natural killer (NK) cell receptors (see text highlighted in bold in Table 1), stand out in the viral versus human peptide overlap and directly relate to SLE disease. More in detail:

(1) Seven complement proteins (listed in Table 1) participate to a complex, multiple peptide overlap with HPV L1s from the tested strains. That is, a wide array of pentapeptides disseminated throughout complement proteins might be targeted by cross-reactions triggered by anti-HPV immune responses. Such cross-reactivity might lead to hypocomplementaemia, thus representing a direct link between HPV infection and related lupus. In fact, hypocomplementaemia is a well known feature of SLE disease and the measurement of complement levels and functional activity in serum is commonly used as a marker of disease activity in SLE [28,91,92].

(2) Table 1 also summarizes the concrete possibility that HPV infection can trigger immune cross-reactions against NK cell receptors. Actually, immune responses following HPV infection could hit 10 NK receptors (listed in Table 1) that repeatedly share seven pentapeptides with HPV L1 from the tested strains for a total of 25 multiple occurrences.

In practice, this peptide commonality may directly connect HPV infection to SLE. In fact, inhibition of NK cell activity characterizes patients with SLE [93–96], and a significant decrease in $CD16^+$ or $CD56^+$ NK cells was observed at the time of diagnosis of paediatric SLE [97]. Moreover and of crucial importance in the still unclear SLE pathogenesis, it has to be underlined that NK cells are a powerful defense against viral and microbial pathogens [98]. Consequently, cross-reactions that inactivate/destroy the NK cells will lead to further recurrent infections.

NK cells are also important in the central nervous system (CNS) homeostasis and autoimmunity [99]. It has been reported that NK cells resident in the CNS suppress CNS autoimmune disease [100]. CD56 is a cluster differentiation antigen of NK cells also known as neural cell adhesion molecule 1 precursor (NCAM1). As summarized in Table 1, NCAM1 shares the pentapeptide SEATV with L1s. Then, a first observation is that cross-reactions with NCAM1 might further increment the destruction of NK cells.

Moreover, NCAM1 is also involved in the regulation of higher cognitive functions [101] and, when altered, underlies memory disorders and learning deficits [102]. In the adult nervous system, NCAM1 occurs in structures wherein neurogenesis does persist such as hippocampus [103], hypothalamus [104] and trigeminal ganglion and brainstem [105]. Functional disturbances in these neuro-anatomical areas by HPV-induced immune cross-reactions with NCAM1 might lead to neuropsychiatric disorders [106], as well as to a wide symptomatology that possibly includes obstructive sleep apnoea [107]; fatigue, tiredness and lack of energy, which are accompanying symptoms in obstructive sleep apnoea [108]; sleepiness, narcolepsy and idiopathic hypersomnia, depression and pain [109,110].

This clinical scenario is of enormous relevance in the context of the present review given that the entire set of symptoms describe above characterizes lupus. Indeed, fatigue, fibromyalgia, impaired health status, pain, anxiety, depression, obstructive sleep apnoea and sleep disturbance are catalogued as constitutional common aspects of SLE [111–115].

(3) Finally, although the high level of viral versus human peptide overlap illustrated in Table 1 prevents a detailed match-by-match discussion, nonetheless, it is noteworthy to highlight that numerous canonical SLE autoantigens share peptide sequences with HPV proteins. Examples are lupus La autoantigen [53], methyl-CpG-binding protein 2 [57,58], proteins P0 and P1 [76,77], Sm protein B/B′ and Sm protein D [79,80], *inter alia*, are well known antigens that are involved in various forms of SLE diseases. Obviously, immune HPV-triggered cross-reactions against such autoantigens might lead to or accelerate lupus disease [17▪▪].

CLINICAL EVIDENCE

Searching for clinical evidence for SLE development post-HPV infection may prove somewhat challenging as the exact onset of infection with HPV is unnoticed as a rule. For this reason, we chose to examine clinical reports regarding the development of SLE post-HPV vaccination, as it simulates infection with HPV while offering a more accurate time table.

Table 1. Pentapeptide sharing between HPV L1s from strain 31, 33, 45, 52 and 58, and human proteins that, when altered, may relate to systemic lupus erythematosus syndromes

Peptide[a,b]	HPV strain[c]	SLE-associated protein involved in the peptide sharing[d]	Disease involvement[e]	Ref[e]
DILED	33	2B1D. MHC class II antigen DRB1∗13 (DR-13)	2B1D has a protective role in SLE	[19,20]
IKNPT	33	5NT3A. Cytosolic 5′-nucleotidase 3A. 7-methyl-guanosine nucleotidase	Possibly associates with anaemia that patients with SLE develop throughout the course of the disease	[21,22]
STQNP	45	BANK1. B-cell scaffold protein with ankyrin repeats.	SLE	[23]
LTPPP	33, 52, 58	BLK. Tyrosine-protein kinase Blk.	Disseminated lupus erythematosus	[24]
AGSAR FLLQA SRLLA QAGLQ	31 31, 33, 52 33, 58 52	CO4A. Complement C4-A.	Complement component 4A deficiency. A rare defect of the complement classical pathway mainly associated with systemic lupus with/out glomerulonephritis	[25–28]
AGSAR FLLQA AATAV QAGLQ SRLLA	31 31, 33, 52 45 52 33, 58	CO4B. Complement C4-B.	Complement component 4B deficiency. A rare defect of the complement classical pathway mainly associated with systemic lupus with/out glomerulonephritis.	[25–28]
LQDTK	31, 45	CO2. Complement C2	Complement component 2 deficiency mainly associated with SLE	[29]
PLLNK LLNKF RAPST	31, 33, 52 31, 52 58	CO3. Complement C3	Complement component 3 deficiency. Patients may develop pyogenic infections, arthralgia and vasculitic rashes, lupus-like syndrome and glomerulonephritis.	[30]
SGNPG	52	C1QA. Complement C1q subcomponent subunit A	Deficiency of C1QA leads to severe immune complex disease with features of SLE and glomerulonephritis.	[31]
LKNSV SGNTA	31 52, 58	CR1. Complement receptor type 1. C3b/C4b receptor. CD antigen CD35.	Deficiency of CR1: renal involvement in SLE	[32–34]
GSIVT	58	CR2. Complement receptor type 2. EBV receptor. CD21.	SLE9	[35]

Table 1 (*Continued*)

Peptide[a,b]	HPV strain[c]	SLE-associated protein involved in the peptide sharing[d]	Disease involvement[e]	Ref[e]
TSSGN	52	CTLA4. Cytotoxic T-lymphocyte protein 4. CD152.	SLE	[36,37]
RKKTK	31	DNSL3. Deoxyribonuclease γ. Liver and spleen DNase.	SLE16	[38]
FKDYV	31	ETS1. Protein C-ets-1 (p54)	SLE	[39]
SDAQI	31	IFIT3. Interferon-induced protein with tetratricopeptide repeats 3. Retinoic acid-induced gene G protein. RIG-G.	SLE	[40]
AGGPG GSLED LQAGL	31 31 33, 52	IRAK1. Interleukin-1 receptor-associated kinase 1.	Paediatric SLE.	[41]
SGSII	45	ITAM. Integrin alpha-M.	SLE6.	[42,43]
PAQPG	58	KI2LA. Killer cell immunoglobulin-like receptor 2DL5A.	Receptor on natural killer (NK) cells. Inhibits the activity of NK cells thus preventing cell lysis. Disturbance between activating and inhibitory killer cell IgG-like receptors may be one of the key factors underlying the pathogenesis of SLE.	[44–50,51▪▪]
LFFFL	33, 52, 58	KI2LB. Killer cell immunoglobulin-like receptor 2DL5B		
SKVVS	31, 33, 52, 58	KI2L1. Killer cell immunoglobulin-like receptor 2DL1		
SKVVS	31, 33, 52, 58	KI2L2. Killer cell immunoglobulin-like receptor 2DL2		
LFFFL	33, 52, 58	KI3L1. Killer cell immunoglobulin-like receptor 3DL1		
SKVVS AVPKV	31, 33, 52, 58 45	KI3L2. Killer cell immunoglobulin-like receptor 3DL2		
CEVPL	45	KLRG1. Killer cell lectin-like receptor subfamily G member 1.		
ACVGL	31, 33, 58	KI3S1. Killer cell immunoglobulin-like receptor 3DS1		
PAQPG	58	KI2S5. Killer cell immunoglobulin-like receptor 2DS5		

Table 1 (*Continued*)

Peptide[a,b]	HPV strain[c]	SLE-associated protein involved in the peptide sharing[d]	Disease involvement[e]	Ref[e]
GDCPP	31, 45, 52	KPCD (isoform 2). Protein kinase C δ type.	SLE	[52]
AQPGS	58	LA. Lupus La autoantigen. Sjoegren syndrome type B antigen. SS-B.	SLE	[53]
TPSGS SGTTA GTTAS	31, 33, 52, 58 33 33	LARP6. La-related protein 6. Acheron. Lupus antigen expressed in neurons and muscles.	SLE	[54]
VFRVR PKVSA	31, 33, 58 45	LTK. Leukocyte tyrosine kinase receptor. Protein tyrosine kinase 1.	SLE	[55]
ASTST	45	MAGB2. Melanoma-associated antigen B2	SLE	[56]
KGSGT GSGTT KKVKK SSVCK	33 33 33, 58 52	MECP2. Methyl-CpG-binding protein 2	Susceptibility to lupus	[57,58]
SEATV	31, 33, 52, 58	NCAM1. Neural cell adhesion molecule 1 precursor. CD antigen CD56.	Constitutional features of SLE	[28]
SKVVS APTST	31, 33, 52, 58 33	NLRP1. NACHT, LRR and PYD domains-containing protein 1. Death effector filament-forming ced-4-like.	Association of vitiligo with several diseases including SLE	[59]
LLTVG FGLTP	31, 45, 52 33, 52, 58	NMD3A. Glutamate receptor ionotropic, NMDA 3A (GluN3A) (N-methyl-D-aspartate receptor subtype 3A)	Neuropsychiatric lupus	[60–70]
LLTVG SAPTT	31, 45, 52 58	NMD3B. Glutamate receptor ionotropic, NMDA 3B (GluN3B) (N-methyl-D-aspartate receptor subtype 3B)		
ETSNR	58	NMDE1. Glutamate receptor ionotropic, NMDA 2A (GluN2A) (Glutamate [NMDA] receptor subunit ε -1) (N-methyl D-aspartate receptor subtype 2A)		
KRPAS	52	NMDE2. Glutamate receptor ionotropic, NMDA 2B (GluN2B) (Glutamate [NMDA] receptor subunit ε-2) (N-methyl D-aspartate receptor subtype 2B)		

Table 1 (*Continued*)

Peptide[a,b]	HPV strain[c]	SLE-associated protein involved in the peptide sharing[d]	Disease involvement[e]	Ref[e]
SASLQ	33, 58	NMDE3. Glutamate receptor ionotropic, NMDA 2C (GluN2C) Glutamate [NMDA] receptor subunit ε -3. N-methyl D-aspartate receptor subtype 2C.		
AGGPG AATAV TTRAP	31 45 58	NMDE4. Glutamate receptor ionotropic, NMDA 2D (GluN2D) (Glutamate [NMDA] receptor subunit ε -4) (N-methyl D-aspartate receptor subtype 2D)		
LQLIN	52	NMDZ1. Glutamate receptor ionotropic, NMDA 1 (GluN1) (Glutamate [NMDA] receptor subunit ζ-1)		
TETGN	33	PK3CG. Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit γ isoform. Ser/Thr protein kinase.	SLE	[71]
PEKQD NPYFS	45 58	PTN22. Tyr-protein phosphatase nonreceptor type 22 Hematopoietic cell protein-tyr phosphatase 70Z-PEP.	SLE and diabetes mellitus, insulin dependent (IDDM)	[72–74]
NPKKI KAKPK	31 33	PXK. PX domain-containing protein kinase-like protein (Modulator of Na, K-ATPase) (MONaKA)	SLE	[75]
IYNPE	45	RLA0. 60S acidic ribosomal protein P0	SLE	[76,77]
AGVNV	52	RLA1. 60S acidic ribosomal protein P1	SLE	[76,77]
PSASL	33, 52, 58	RNH2B. Ribonuclease H2 subunit B. Aicardi-Goutieres syndrome 2 protein. AGS2.	SLE	[78]
AGGPG	31	RSMB. Small nuclear ribonucleoprotein-associated proteins B and B′ (snRNP-B) (Sm protein B/B′)	SLE	[79,80]
AGGPG	31	RSMN. Small nuclear ribonucleoprotein-associated protein N (snRNP-N) (Sm protein D) (Sm-D) (Sm-N)	SLE	[79,80]

Table 1 (*Continued*)

Peptide[a,b]	HPV strain[c]	SLE-associated protein involved in the peptide sharing[d]	Disease involvement[e]	Ref[e]
NAKKL KKKKV KKKVK	33 52 52	SSRP1. FACT complex subunit SSRP1. Facilitates chromatin transcription complex 80-kDa subunit.	SLE	[81]
TVQSS	52	STAT4. Signal transducer and activator of transcription 4	SLE11	[82]
SGLQY	31, 33, 52, 58	TNAP3. Tumour necrosis factor α-induced protein 3.	Disseminated lupus erythematosus	[83]
LPPPS	45	TNIP1. TNFAIP3-interacting protein 1. A20-binding inhibitor of NFκB activation 1.	SLE	[84]
VPPPP	45	TREX1. Three-prime repair exonuclease 1. DNase III	SLE	[85]
EVPLD	45	TRNK1. TPR and ankyrin repeat-containing protein 1. Lupus brain antigen 1 homolog.	Psychotic bipolar disorder. Neuropsychiatric lupus	[86]

HPV, human papilloma virus; SLE, systemic lupus erythematosus.
[a]Shared pentapeptides are given in one letter code.
[b]Pentapeptide matches were used as probes, as a pentapeptide is a minimal immune-biological determinant [87]. Matching analyses were conducted as already described in detail [88]. In brief, L1s protein primary sequences were dissected into pentapeptides offset by one residue each other (i.e. MSVWR, SVWRP, VWRPS and so forth). Next, each L1 pentapeptide was used to search the SLE antigen library for occurrence(s) of the same pentapeptide.
[c]HPV L1 proteins refer to strains: 31 (P17388, VL1_HPV31); 33 (P06416, VL1_HPV33); 45 (P36741,VL1_HPV45); 52 (Q05138, VL1_HPV52); and 58 (P26535; VL1_HPV58). Further details at http://www.uniprot.org/.
[d]SLE-related proteins were retrieved from UniProt protein resource using the keyword 'lupus'. Proteins described in the scientific-clinical literature and involved in neuropsychiatric lupus such NRCAM1 [28], and NMDARs [60–65,67▪▪,68–70,89,90] were also analysed for a total of 129 human proteins. The 129 SLE-related proteins are described by UniProtKB entries and listed in Supplemental Table 1.
[e]Further references at http://www.ncbi.nlm.nih.gov/omim/; http://www.uniprot.org/.

As mentioned, both commonly used HPV vaccines are considered to have a decent safety profile; however, in the past several years, reports of diverse postvaccination autoimmune conditions have been accumulating [116▪▪]. Among those were several reports of postural orthostatic tachycardia syndrome (POTS), a disease suspected to be of an autoimmune origin, developing up to 2 months postvaccination [117,118]; two case reports of spontaneous pancreatitis developing up to 1 week postvaccination (while other common causes were excluded) [119,120]; several reports of primary ovarian failure developing postvaccination, with the presence of antiovarian and anti-TPO antibodies in two of the cases [121,122], as well as some 2000 cases of probable postvaccination autoimmune syndrome induced by adjuvants (ASIA) collected from the American vaccine adverse event reporting system (VAERS) [123].

When examining evidence of the development of SLE following the administration of HPVv, several interesting publications are worth mentioning: In 2012 and 2013, two case series were published reviewing a total of nine women ages 13–58 years who developed SLE symptomatology days to weeks after receiving the vaccine. Interestingly, all of the women had either a personal or a familial history of autoimmunity [124,125]. These cases are joined by a more recent case report published in 2016 describing a 15-year-old female who developed SLE following the second dose of Cervarix [126]. Furthermore, a recent case–control assessment of VAERS conducted with the purpose of examining autoimmune adverse events in patients receiving HPVv as compared with other vaccines found an odds ratio of 7.626 (95% CI 3.385–19.366) for developing SLE in individuals immunized with HPVv [127▪].

It should be noted that a study conducted in 2013, assessing the safety of Gardasil in 27 young females with SLE, found no increase in disease activity scores and concluded the vaccine to be well tolerated among young SLE patients [128]. However, this study, apart from its relatively small cohort, did not examine naive individuals vaccinated and therefore is not suitable to properly assess a possible role of HPVv in SLE development. To date, we have no knowledge of a large randomized controlled trial able to supply concrete data on the incidence of SLE among vaccinated individuals as compared with controls. Nonetheless, the described case series as well as the VAERS analysis seem to elude to a possible connection between HPVv and SLE development in prone individuals, justifying further research.

ATTENUATING FACTORS IN THE RELATIONSHIP OF HUMAN PAPILLOMA VIRUS AND SYSTEMIC LUPUS ERYTHEMATOSUS: THE MOSAIC OF AUTOIMMUNITY

In an attempt to explain this relationship between HPV and SLE, we must address the additional factors involved in the complex mosaic of autoimmunity [129]. Clearly, autoimmunity does not develop in most individuals receiving HPVv, and the infectious trigger represents merely one piece of a complex puzzle, alongside multiple variables, both 'innate' (genetic background, hormonal balance) and 'acquired' (environmental effects such as nutrition, lifestyle, climate, exposure to triggers, etc.), which together serve as the platform for the development of autoimmunity. In this context, the history of autoimmunity found in almost all case reports of SLE post-HPVv is extremely relevant, as it suggests a genetic predisposition for autoimmunity. One well known example of such a genetic susceptibility is human leukocyte antigen (HLA) class II allele DRB1, different serotypes of which were shown to be associated with SLE [130,131]. Indeed, identifying traits of genetic susceptibility holds great promise, as it implies the possibility to determine who will most likely develop autoimmunity upon exposure to certain triggers.

UNIQUE PEPTIDE VACCINES: A POSSIBLE SOLUTION

In light of the mentioned body of evidence, it seems that current HPV vaccines may hold a significant risk for developing autoimmune phenomena in specific individuals. However, there is clear benefit in administering these vaccines in terms of cancer prevention. Therefore, the question arises: is there a way to eliminate the risk of HPV vaccines while maintaining the benefits? A novel suggestion to this end lies in a recent publication [132▪▪] suggesting a change be made in the pathogenic content of these vaccines; while the current vaccines are composed of HPV proteins bearing significant similarity to human proteins, it is possible to select viral proteins that are unique and bear no similarity to the human proteome. Altering the content of the vaccine in this manner may guarantee effective immune response against viral elements that will prevent infection, while avoiding the potential cross-reactivity that may lead to the development of autoimmunity.

CONCLUSION

SLE is a complex autoimmune disease with a convoluted, mostly undeciphered etiopathogenesis. However, there is a vast body of evidence supporting the theory that certain infectious agents may be involved in the induction of this disease. Recently, several publications have implicated infection with HPV to be highly associated with SLE in the epidemiological level. Furthermore, evidence are accumulating of the development of autoimmune phenomena post-HPV vaccination. These findings raise the hypothesis of HPV infection posing as a trigger for SLE development in prone individuals. A significant possible mechanism for this process is of molecular homology, or shared peptides between HPV and human proteins, leading to an immune cross-reaction that may result in autoimmune disease. We have demonstrated herein that L1 proteins of HPV possess vast peptide homology to human proteins associated with SLE, thus supporting the possibility of an immune cross-reaction. We believe that this described mechanism may serve as one possible aetiological factor in the development of SLE, which is clearly complex and multifactorial. Of course, there is still much to be illustrated in the intricate processes leading to the development of SLE; however, in light of these circumstantial evidence implicating HPV as a cofactor, we suggest the introduction of HPV vaccines based on unique peptides strands bearing no homology to the human proteome, thus reducing the risk of a possible cross-reaction.

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Conflicts of interest

Y.S. appears as a medical consultant in vaccine compensation court, USA.

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Cryoglobulinemia vasculitis: how to handle

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Purpose of review
More than 50% of hepatitis C virus (HCV) infected patients produce a mixed cryoglobulin and two-third of them will develop a symptomatic cryoglobulinemia vasculitis (CryoVas). In the present review, we aim at summarizing the most recent advances in diagnosis and treatment of HCV-CryoVas.

Recent findings
The treatment of HCV-CryoVas has much changed during the last months. The recent emergence of new direct-acting (DAA) interferon (IFN)-free antivirals, enabling high cure rates with a very good safety profile now permit to cure most patients with HCV-CryoVas. Multidisciplinary consensus recommends to consider IFN-free DAAs as first-line treatment for HCV-CryoVas patients. Immunosuppressive treatments (i.e. rituximab, glucocorticosteroids, cyclophosphamide and plasmapheresis) remain an interesting therapeutic approach, in severe form of HCV-CryoVas, failure or contradiction to antiviral treatments.

Summary
The great efficacy of DAA on HCV-CryoVas represents a major advance in clinical practice, as these new antivirals provide for the first time a well tolerated and definite treatment of such complication for most patients.

Keywords
cryoglobulinemia, direct-acting antivirals, hepatitis c virus, treatment, vasculitis

INTRODUCTION

Cryoglobulinemia is defined by the presence of circulating immunoglobulins that precipitate at cold temperature and dissolve with rewarming. Cryoglobulinemia is categorized by immunochemical analysis into three types [1]. Type I cryoglobulins are monoclonal immunoglobulins. Type II cryoglobulins consist of a monoclonal immunoglobulin with a rheumatoid factor activity associated with polyclonal IgG, whereas type III cryoglobulins comprised polyclonal IgG and IgM with rheumatoid factor activity. Type II and III are often referred to as mixed cryoglobulinemia.

The cause of cryoglobulinemia depends on the immunochemical determination. In type I cryoglobulinemia vasculitis, it is mandatory to look for the presence of an underlying B-cell lymphoproliferative disorder, mainly Waldenström macroglobulinemia, multiple myeloma or monoclonal gammopathy of unknown significance. The main cause of mixed cryoglobulins (type II and type III) is chronic hepatitis C virus (HCV) infection, representing 70–90% of mixed cryoglobulins. Of note, conversely, the presence of a mixed cryoglobulin is identified in about 50% of HCV-infected patients, although only 10–15% of them have a symptomatic cryoglobulinemia vasculitis (CryoVas) [2,3]. Type II cryoglobulinemia composed of monoclonal IgM kappa is by far the most frequent in HCV-CryoVas patients. In case of persistent mixed cryoglobulin despite HCV clearance, a B-cell lymphoma should searched [4]. For rare cases of mixed cryoglobulins not associated with HCV infection, the main causes include other chronic infectious diseases, B cell malignancies and autoimmune diseases (mainly Sjögren syndrome and systemic lupus).

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KEY POINTS

- DAA IFN-free antivirals lead to high cure rates with a very good safety profile in patients with HCV-cryoglobulinemia vasculitis.
- IFN-free DAAs should be considered as first line for treatment of HCV-cryoglobulinemia vasculitis patients.
- Immunosuppressive treatments (i.e. rituximab, glucocorticosteroids, cyclophosphamide and plasmapheresis) remain an interesting therapeutic approach, in severe form of HCV-cryoglobulinemia vasculitis, failure or contradiction to antiviral treatments.

HOW TO DIAGNOSE HEPATITIS C VIRUS RELATED MIXED CRYOGLOBULINEMIA VASCULITIS?

Main clinical features

The disease expression is variable, ranging from mild clinical symptoms (fatigue, purpura, arthralgia) to fulminant life-threatening complications (glomerulonephritis, widespread vasculitis) [2,5,6]. Mixed cryoglobulinemia lesions in HCV-infected patients are often related to small vessel vasculitis induced by immune complex deposits.

Fatigue is the main symptom, noted in 80–90% of patients. The main cutaneous sign is a palpable purpura (70 to 90%), which begins at the lower limbs and may extend to abdominal area, less frequently to the trunk and upper limbs. Cutaneous ulcers and cold-associated symptoms (Raynaud's phenomenon, acrocyanosis) are less frequent.

Arthralgia (40–60%) usually involves large joints and are bilateral and symmetric. Arthralgia involves more frequently fingers, knee, ankles and back. Frank arthritis is reported in less than 10% of patients without articular deformation or destruction. Sicca symptoms of either the mouth or eyes have been reported in 10–30% of HCV-infected patients. Although sicca symptoms are very frequent in HCV-infected patients, a characterized Sjögren's syndrome defined by the presence of anti-SSA or anti-SSB antibodies and a typical salivary gland histology are uncommon.

Neurologic manifestations (50–70%) are variable, ranging from pure sensory polyneuropathy to mononeuritis multiplex. The most frequently described form is a distal sensory or sensory-motor polyneuropathy. Polyneuropathy usually presents with painful, asymmetric paresthesia, which later becomes symmetric. Motor deficit is inconstant, mainly affects the lower limbs and often appears a few years after sensory symptoms. Central nervous system involvement is infrequent (<10%) and may manifest as stroke, epilepsy or cognitive impairment.

Renal manifestations (20–40%) usually present as a proteinuria with microscopic haematuria and sometimes a variable degree of renal insufficiency. Histological analysis most often reveals an acute or chronic type-I membranoproliferative glomerulonephritis with subendothelial deposits.

Other severe manifestations are rare (<5%). Digestive involvement manifests as abdominal pains and gastrointestinal bleeding secondary to mesenteric vasculitis. Cardiac involvement is associated with significant mortality and includes mitral valvular damage, coronary vasculitis complicated by myocardial infarction, pericarditis or congestive cardiac failure. Lungs are rarely involved. However, some patients may experience interstitial lung fibrosis, pleural effusions or pulmonary intra-alveolar haemorrhages.

Mixed cryoglobulin and other biological surrogate markers

In order to confirm the diagnosis, the presence of cryoglobulinemia is investigated in the serum. Cryoglobulinemia is confirmed by the detection of protein that precipitates in the patient's serum maintained at 4°C during at least 7 days, and dissolved when heated at 37°C. In the most expert centre, patients are considered to have a significant cryoglobulin level when more than 0.05 g/l on two determinations [5,7]. To avoid false-negative results due to immunoglobulin cold precipitation, blood sampling for cryoglobulin detection should be carried immediately after blood is drawn using a thermostable device (37°C). Serum should be kept warm and tests should be carried out at 37°C. Cryoglobulin detection should be repeated if first tests are negative, although clinical features are suggestive of CryoVas.

Other laboratory surrogate markers, easier to detect than cryoglobulins, may provide indirect evidence of the presence of cryoglobulinemia. Specific but inconsistent complement abnormalities are observed, such as decreased early components (C1q, C2, C4) and CH50, with normal C3 level. The diagnosis of CryoVas is usually based on the association of clinical vasculitis symptoms, a cryoglobulinemia and a decreased C4 serum level. Rheumatoid factor activity is also often found in patients with a mixed cryoglobulinemia, in contrast to type 1 cryoglobulins. Electrophoresis and immunoelectrophoresis reveal either a polyclonal hypergammaglobulinemia or a monoclonal component. A recent analysis of HCV-infected patients with

asymptomatic circulating cryoglobulin found increased levels of rheumatoid factor-IgG and free light chain in cryoglobulins-antinuclear antibody positive patients, suggesting that these test could be used to identify a state of 'silent autoimmune condition' before the transition to a frank disease in asymptomatic HCV patients [8].

In clinical daily practice

To summarize, the presence of purpura, weakness, polyneuropathy and renal involvement associated with decreased C4 serum level, the presence of mixed cryoglobulinemia and a positive rheumatoid factor represent the main clinical and biological signs of Cryovas. If HCV infection is not already diagnosed, searching for HCV is mandatory.

After HCV-CryoVas diagnosis, patients should be investigated for [9▪] other vasculitis involvements, including arthritis, neuropathy (electromyogram alterations), glomerulonephritis (increased proteinuria, increased serum creatinine and glomerulonephritis at renal biopsy); B-cell lymphoproliferation (corticosteroids/positron emission tomography scan, nodal or bone marrow biopsy); other HCV extrahepatic complications, including diabetes, dyslipidemia, cardiovascular events, thyroiditis; and liver complications such as liver fibrosis (Fibrotest and Fibroscan) and the presence of hepatocellular carcinoma (liver ultrasound and serum level of α foeto-protein).

PROGNOSIS

In a cohort of 151 HCV-associated mixed cryoglobulin (MC) vasculitis, the 1-year, 3-year, 5-year and 10-year survival rates were 96, 86, 75 and 63%, respectively. Baseline factors associated with a poor prognosis were the presence of severe liver fibrosis (hazard ratio 5.31), central nervous system involvement (hazard ratio 2.74), kidney involvement (hazard ratio 1.91) and heart involvement (hazard ratio 4.2) [9▪,10]. The Five-Factors Score (FFS), a vasculitis scoring system based on five clinical items (proteinuria >1 g/day, serum creatinine >140 μmol/l, cardiomyopathy, severe gastrointestinal involvement and central nervous system involvement) with the presence of each being accorded one point, was significantly associated with outcome. In multivariate analysis, severe fibrosis (hazard ratio 10.8) and the FFS (hazard ratio 2.49) were significantly associated with a poor prognosis [10]. Among patients without severe fibrosis, the FFS was a good predictor of outcome, whereas among those with severe fibrosis, the severity of vasculitis had no prognostic value.

The most common causes of death in HCV-CryoVas are infection, end-stage liver disease, cardiovascular disease and more rarely vasculitis [i.e. renal involvement with end-stage renal and central nervous system (CNS) involvement] and lymphoma/neoplasia [11,12].

HOW TO TREAT HEPATITIS C VIRUS RELATED MIXED CRYOGLOBULINEMIA VASCULITIS?

HCV-CryoVas manifestations improve or disappear when a sustained clearance of HCV is achieved [i.e. sustained virologic response (SVR)]. During the decade 2002–2012, antiviral therapy with Pegylated interferon (PegIFN) and ribavirin for 12 months led to SVR in 50–60% of HCV-CryoVas patients (17,18). Patients who relapsed for HCV infection after responding to antiviral therapy usually relapsed for the vasculitis with the return of viremia (19). The use of triple HCV therapy combining PegIFN, ribavirin and a direct-acting antiviral (DAA) (NS3/4A protease inhibitor, i.e. boceprevir or telaprevir) led to improved SVR rates (65–70%) in HCV-CryoVas patients with genotype 1 infection [13,14]. However, such combination should be given for a long period (48 weeks) and serious adverse events occurred in up to 47% of patients [13].

Other second-generation DAAs are now approved. The NS3/4A inhibitor simeprevir and NS5B inhibitor sofosbuvir allow shortened courses of IFN-free therapy, which are associated with high (>95%) SVR rates and relatively few toxicities. In the first prospective, open-label trial, including 24 HCV-CryoVas patients (50% genotype 1, 50% cirrhosis) treated with sofosbuvir and ribavirin, a clinical complete remission was achieved in 87.5% and SVR in 74% of patients at week 12 after the end of treatment [15▪▪]. The cryoglobulin level decreased from 0.35 to 0.15 g/l. Seven patients also received Rituximab. Antiviral therapy discontinuation was required in two (8%). In a retrospective case series, including 12 HCV patients (50% cirrhosis, 67% genotype 1, seven patients with kidney involvement) treated with sofosbuvir and simeprevir (67%) or ribavirin (33%), the rate of SVR was 83% at 12 weeks after the end of treatment [16▪▪]. Four patients received Rituximab concomitant with DAA therapy. Median cryoglobulin levels decreased from 1.5 to 0.5%; cryoglobulins levels disappeared in four out of nine patients. Two patients had serious adverse events. Gragnani *et al.* [17▪▪] have recently reported the results of a cohort of 44 consecutive patients with HCV-CryoVas [genotypes 1 ($n=23$), 2 ($n=13$), 3 ($n=5$) and 4 ($n=3$)]. Patients were treated with

sofosbuvir-based treatments [associated with ribavirin alone ($n = 18$), or simeprevir ($n = 12$), ledipasvir ($n = 10$) or daclatasvir ($n = 4$) and ribavirin ($n = 9$)]. Two patients with severe vasculitis received reduced dose of rituximab. All patients had negative HCV viremia at week 12 and at week 24 posttreatment, at which time all had a clinical response of vasculitis. The mean Birmingham Vasculitis Activity Score decreased from 5.41 at baseline to 2.35 at week 4 on treatment, then to 1.39 at SVR12 and 1.27 at SVR24. The mean cryocrit value fell from 7.2 to 1.8% from baseline to SVR24. Only mild adverse events occurred in 59% of patients, except for one patient with ribavirin-related anaemia requiring blood transfusion. In a nationwide Italian study, Kondili *et al.* [18] reported the disappearance or improvement of more than 50% of CryoVas symptoms in 31 out of 37 (84%) of patients after DAA. Finally, a Canadian group described 11 patients with HCV-CryoVas who received IFN-free DAA combinations (56 years old, 61% women, 57% cirrhotics) [19]. A full or partial clinical response of CryoVas was obtained in 91% and a complete or partial immunological response in 81%. A full or partial renal response was noted in 80%. A serious adverse event was reported in only 12%.

Despite the evidence of the positive impact of effective antivirals on HCV-CryoVas symptoms, immunosuppression still remains a major treatment option. In case of severe CryoVas manifestations (severe renal impairment, skin necrosis, gut or CNS involvement) or in patients with failure or contraindication to antivirals, Rituximab has shown a better efficacy than conventional immunosuppressive treatments (i.e. glucocorticoids, azathioprine, cyclophosphamide or plasmapheresis) or placebo [20,21]. Addition of rituximab to Peg-IFN and ribavirin led to a shorter time to clinical remission, better renal response rate and higher rates of cryoglobulin clearance [22,23].

International guidelines [24] recommend to treat HCV-infected patients with severe extrahepatic manifestations such as CryoVas. More recently, multidisciplinary consensus and evidence-based recommendations on the management of HCV-extrahepatic manifestations have been proposed [25]. They recommend to consider IFN-free DAAs as first-line treatment for HCV-CryoVas patients who do not need urgent/life-threatening measures. As the degree of clinical improvement depends on the reversibility of the HCV-induced damage, early viral eradication is recommended. The choice of IFN-free DAA combination should follow general criteria for the treatment of HCV infection, accurately taking into account CryoVas complications (i.e. renal impairment). Both IFN and RBV-free DAA combinations should be preferred in patients with kidney disease, ischemic tissue lesions (i.e. skin ulcers, ischemic heart disease) and anaemia (i.e. lymphoproliferative disease). Accurate evaluation of the kidney damage is absolutely mandatory for the choice of DAA treatment and follow-up schedule [26].

In case of HCV-CryoVas needing urgent/life-threatening measures, the combination of IFN-free DAA and nonetiologic therapy can be allowed. The choice of nonetiologic therapy should always take into account the severity of vasculitis, the degree of HCV-related liver damage and, in case of DAAs coadministration, the possible drug–drug interactions. Nonetiologic therapy includes glucocorticoids, rituximab, cyclophosphamide and plasmapheresis. Such therapies should be also useful in less severe CryoVas cases when patients present persistent vasculitis manifestations despite antiviral treatment or have contraindication to antivirals. The persistence of immunological/laboratory abnormalities alone (i.e. cryoglobulinemia) after successful antiviral therapy in the absence of clinical manifestations does not justify therapy. The presence of active CryoVas manifestations despite a SVR should lead to search for the presence of B-cell lymphoma.

CONCLUSION

The treatment of HCV-associated MC vasculitis has much changed during the last months. The recent emergence of new direct-acting IFN-free antivirals, enabling high cure rates with a good safety profile, should permit to cure most patients with HCV-CryoVas. Immunosuppressive treatments remain an interesting therapeutic approach, in rare cases of severe HCV-CryoVas, failure or contradiction of antiviral treatments.

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Conflicts of interest

P.C. has received consultancies, honoraria, advisory board, speakers' fees from Abbvie, Astra Zeneca, Bayer, Boehringer Ingelheim, Gilead, Glaxo Smith Kline, Janssen, Merck Sharp Dohme, Pfizer, Roche, Servier and Vifor. P.C. is an inventor of a patent application owned by his academic institution and licensed to ILTOO pharma, a biotechnology company developing low-dose IL-2 in autoimmune diseases, which holds shares. C.C.

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Silicone breast implants and autoimmune rheumatic diseases: myth or reality

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Purpose of review
In the present review, recent findings regarding silicone breast implants (SBIs) complicated by rheumatic autoimmune diseases are described.

Recent findings
Despite changes in the principal constituents of the silicone implants during the past 50 years, silicone remained an adjuvant that may 'bleed' and subsequently may be a chronic stimulus to the immune system resulting in similar clinical manifestations as 50 years ago. Silicones are spread throughout the body and can be detected in tissues and the central nervous system. Autoimmune/inflammatory syndrome by adjuvants (ASIA), allergies, autoimmune diseases, immune deficiencies and lymphomas occur in patients with SBIs. There is a need for adequately adjusted epidemiological studies to ascertain the frequency of these diseases. Explantation of the breast implants, however, should be advised to patients with complaints, as 60–80% of patients show an amelioration of the signs and symptoms after explantation.

Summary
SBIs are associated in a proportion of patients with complaints such as fatigue, cognitive impairment, arthralgias, myalgias, pyrexia, dry eyes and dry mouth. Silicones can migrate from the implant through the body and can induce a chronic inflammatory process. Explantation of SBI results in the majority of patients in an amelioration of the symptoms.

Keywords
anaplastic large cell lymphoma, autoimmune/inflammatory syndrome by adjuvants, explantation, immune deficiency, silicone breast implants

INTRODUCTION

The first silicone breast implants (SBIs) were performed by Cronin and Gerow in 1962 [1]. Silicone gel was wrapped in an impermeable silicone envelope developed by Dow Corning. The SBI implantation procedure was considered a success, and since then, millions of women received SBI either as a cosmetic procedure or because of postmastectomy reconstruction. Soon thereafter, local and distant complications of the SBI procedure were reported and the first case reports were published with women developing arthralgias and fatigue and sometimes an autoimmune disease [2–5]. Over the next 50 years, hundreds of patients are reported with similar symptoms and signs [6▪▪]. Both patients and doctors suspect that these complaints are caused by the implants. Indeed, removal of the SBI results in an amelioration of symptoms in 60–80% of the patients [7▪▪].

During recent years, we have seen over 200 patients with clinical signs and symptoms of this so-called silicone-incompatibility syndrome. In the current review, we describe signs and symptoms, and discuss potential pathophysiological mechanisms and disease management.

SYMPTOMS AND SIGNS

Typically, patients develop chronic fatigue and are already tired when they wake up, whereas the fatigue is not alleviated by rest. Patients have a substantial reduction in the ability to engage levels of occupational, educational, social and/or personal

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KEY POINTS

- Silicone breast implants are associated in a proportion of patients with complaints such as fatigue, cognitive impairment, arthralgias, myalgias, pyrexia, dry eyes and dry mouth.
- Silicones can migrate throughout the body and can be detected in tissues and the central nervous system.
- Migrated silicones induce a chronic inflammatory process.
- Probably due to chronic inflammation autoimmune/inflammory syndrome induced by adjuvants (ASIA), allergies, autoimmune diseases, immune deficiencies and lymphomas occur in patients with silicone breast implants.
- Explantation of the breast implants should be advised to patients with complaints, as 60–80% of patients show an amelioration of the signs and symptoms after explantation.

activities as before the illness started. Sleep disturbances such as problems falling asleep and/or staying asleep are often present. In addition, most patients report postexertional malaise. Probably related to these symptoms are the symptoms of cognitive impairment resulting in memory deficits ('Alzheimer-light'), absent-mindedness, word-finding difficulties and difficulty paying attention.

Another early symptom is the occurrence of arthralgias or arthritis that is present in more than 90% of the patients. Most patients fulfil the 2016 criteria for fibromyalgia (see Table 1) [8]. Most (70–80%) patients also suffer from morning stiffness that sometimes may last more than an hour. Patients, however, may also present with a symmetric polyarthritis compatible with a diagnosis of rheumatoid arthritis [9,10▪▪].

In addition, up to 90% of the patients have myalgias and/or muscle weakness. Weakness can be severe and may render the patient to be bedridden. In one study, an electromyography (EMG) was performed in 93 patients. The EMG was

Table 1. Fibromyalgia 2016 criteria

Criteria
A patient satisfies modified 2016 fibromyalgia criteria if the following 3 conditions are met:
(1) Widespread pain index (WPI) ≥7 and symptom severity scale (SSS) score ≥5 OR WPI of 4–6 and SSS score ≥9
(2) Generalized pain, defined as pain in at least four of five regions, must be present. Jaw, chest and abdominal pain are not included in generalized pain definition.
(3) Symptoms must have been present for at least 3 months.
(4) A diagnosis of fibromyalgia is valid irrespective of other diagnoses. A diagnosis of fibromyalgia does not exclude the presence of other clinically important illnesses.
Notes
(1) WPI: note the number of areas in which the patient has had pain over the last week. In how many areas has the patient had pain? Score will be between 0 and 19.
(2) Symptom severity scale (SSS) score
Fatigue
Waking unrefreshed
Cognitive symptoms
For the each of the 3 symptoms above, indicate the level of severity over the past week using the following scale:
0 = No problem
1 = Slight or mild problems, generally mild or intermittent
2 = Moderate, considerable problems, often present and/or at a moderate level
3 = Severe: pervasive, continuous, life-disturbing problems
The symptom severity scale (SSS) score is the sum of the severity scores of the three symptoms (fatigue, waking unrefreshed and cognitive symptoms) (0–9) and the sum (0–3) of the number of the following symptoms the patient has been bothered by that occurred during the previous 6 months:
(1) Headaches (0–1)
(2) Pain or cramps in lower abdomen (0–1)
(3) Depression (0–1)
The final symptom severity score (SSS) is between 0 and 12.

Adapted from [8].

abnormal in 53% of the patients [11]. Most often, a 'myopathic' pattern was found in these patients [11].

Furthermore, two-third of the patients report pyrexia, whereas night sweats are common. Some patients additionally have strongly elevated ferritin levels and fulfil the diagnostic criteria for (silicone-induced) Still's disease [12▪].

Importantly, 75% of patients have dry eyes and/or a dry mouth. Symptoms of the dry eyes are often severe and may result in blurred vision and/or a keratitis sicca if left untreated. Sjogren syndrome A/Sjogren syndrome B (SSA/SSB) antibodies are only present in a minority of patients [5], whereas salivary gland biopsies disclose mononuclear cell infiltrates different from what can be found in Sjogren's syndrome [13,14].

Furthermore, 30–50% of the patients develop new-onset Raynaud's phenomenon sometimes with nailfold abnormalities as demonstrated by capillaroscopy suggestive of systemic sclerosis.

Another important manifestation that is present in 30–40% of patients is the occurrence of ischemic cerebral disease or a multiple sclerosis-like syndrome [5,11]. Anticardiolipin antibodies and/or lupus anticoagulant are detected in only a minority of the patients. As patients without these antibodies lack traditional risk factors for a cerebro-vascular accident, a diagnosis of seronegative anti-phospholipid syndrome is often considered [15,16].

Allergies are reported in 50–80% of the patients [17]. In most patients, these allergies are preexistent. In many cases, however, the patient report that allergic complaints had disappeared before the SBI operation and returned thereafter. Allergic complaints include sneezing, itching of the nose and eyes, red eyes, rhinorrhea, nasal congestion and postnasal drip. Furthermore, asthmatic patients may suffer from cough, wheeze and shortness of breath. Food allergies also occur and about 10–20% of the patients develop new-onset urticaria and/or quincke's oedema. A remarkable frequent finding (about 50% of patients) is metal-allergy with nickel-induced dermatitis. Furthermore, some patients present with episodic symptoms suggesting a diagnosis of mast cell activation syndrome [18,19]. Finally, some patients present with a multiple chemical sensitivity syndrome [20]. Dyspnoea in SBI patients can be a result of severe asthma, pulmonary nodules, interstitial lung disease and/or pulmonary silicone embolism [21–23]. Furthermore, 20–40% of patients suffer from severe and/or recurrent (upper respiratory tract) infections.

Breast pain, tenderness and burning sensations are occasionally present. In addition, changes in breast shape, breast asymmetry, firmness of the breasts and breast enlargement may be noticed. Lymph nodes (axillary, cervical and inguinal) are often enlarged and tender (70–80% of patients).

Cardiovascular complaints include signs of orthostatic intolerance such as dizziness, disturbed balance, irregular heartbeat and sometimes chest pain. A mitral valve prolapse and/or joint hypermobility is found in about half of the patients [24].

Twenty to forty percent of patients suffer from gastrointestinal symptoms such as abdominal pain with changes in bowel movement patterns such as found in irritable bowel syndrome. Swallowing difficulties and/or dysphagia are in most cases related to the sicca complaints.

A substantial amount of patients (10–20%) have interstitial cystitis. The skin may be painful and burning sensations ('pins and needles') suggest that (atypical) small fibre neuropathy is present [25]. A prominent livedo reticularis can be found in about 20–30% of patients, whereas mild livedo reticularis is present in another 30–40% of patients. Occasionally, tender subcutaneous nodules can be observed in the arms, legs, abdominal wall and/or elsewhere in the body. Histologically, these nodules demonstrate granulomatous inflammation (i.e. migratory silicone granulomas) [22,26]. Finally, 20–40% of patients have ill-defined skin rashes, unexplained (sometimes severe) pruritus and/or alopecia.

Laboratory findings are often nonspecific. Generally, C-reactive protein levels are normal. Angiotensin-converting enzyme and soluble interleukin-2 receptor levels are, however, in up to 50% of patients elevated. Antinuclear antibodies are present in 20% of patients, whereas various other antibodies such as SSA/SSB, anti-dsDNA, anti-Scl-70, anticardiolipin, anti-cyclic citrullinated peptide antibodies, IgM-rheumatoid factor, antineutrophil cytoplasmic antibodies and/or cryoglobulins may be found [5,6▪▪]. Furthermore, antipolymer antibodies have been described, but their diagnostic value is at present uncertain [27]. Vitamin D insufficiency and/or deficiency is a frequent finding and 20–50% of patients have decreased levels of IgG and/or IgG subclasses [5,6▪▪].

AUTOIMMUNE/INFLAMMATORY SYNDROME INDUCED BY ADJUVANTS, AUTOIMMUNE DISEASES AND ANAPLASTIC LARGE T-CELL LYMPHOMA

The symptoms described above received during the last 50 years several different names: human adjuvant disease, siliconosis, silicone incompatibility syndrome and – more recently – autoimmune/inflammatory syndrome induced by adjuvants (ASIA) [6▪▪,28]; Table 2. Others, however, state that

Table 2. Criteria for the diagnosis of autoimmune/inflammatory syndrome induced by adjuvants

Major criteria
Exposure to an external stimulus (infection, vaccine, silicone, adjuvant) prior to clinical manifestations
The appearance of 'typical' clinical manifestations
Myalgia, myositis or muscle weakness
Arthralgia and/or arthritis
Chronic fatigue, un-refreshing sleep or sleep disturbances
Neurological manifestations (especially associated with demyelination)
Cognitive impairment, memory loss
Pyrexia, dry mouth
Removal of inciting agent induces improvement
Typical biopsy of involved organs
Minor criteria
The appearance of autoantibodies or antibodies directed at the suspected adjuvant
Other clinical manifestations (i.e. irritable bowel syndrome)
Specific HLA (i.e. HLA DRB1, HLA DQB1)
Evolvement of an autoimmune disease (i.e. multiple sclerosis, systemic sclerosis)
Patients are considered to have ASIA when either two major or one major and two minor criteria are present

HLA, human leukocyte antigen.
Adapted from [28].

these patients do not suffer from a separate disease, but are merely suffering from idiopathic chronic fatigue syndrome/mylagic encephalomyelitis (CFS/ME), fibromyalgia or mass somatization [29–31].

We hypothesize that as a consequence of the immune activation, ASIA, allergies, autoantibodies, autoimmune diseases, IgG and/or IgG subclass deficiencies and finally lymphomas may develop.

ASIA was firstly described by Shoenfeld and Agmon-Levin in 2011. This syndrome assembles a spectrum of immune-mediated diseases triggered by adjuvants in persons who are genetically predisposed to it [28]. Potential triggers are silicones, injection of mineral oil or other foreign substances and/or vaccines.

In 2013, we reported 32 patients with ASIA due to silicone incompatibility syndrome [5]. Median time between start of complaints and time of breast implant was 10 years (2–24 years). Fifty-three percent of the ASIA patients had an established systemic autoimmune disease, 22% of patients had an organ-specific autoimmune disease and 47% of patients a humoral immunodeficiency (either hypogammaglobulinemia or a IgG subclass deficiency). Subsequently, many patients with self-reported symptoms were evaluated in the Netherlands [6▪▪,17]. From these, about 95% fulfilled the criteria for ASIA (Table 2). These patients all had fatigue and/or cognitive symptoms, arthralgias and/or myalgias, and sicca complaints and/or pyrexia. Seventy to eighty percent of these ASIA patients had cosmetic breast augmentation, whereas 20–30% of these patients had breast reconstruction after mastectomy for breast cancer. More than 99% of the patients were women, the remaining being (transgender) males.

At present, there are no epidemiologic studies performed to calculate the risk of ASIA in SBI patients. In the Netherlands, more than 4700 women with SBI and health issues registered themselves at a Dutch foundation for women with illness due to breast implants. Unfortunately, it is not known how many Dutch women have SBI. Importantly, however, since April 2015, data about all new patients with SBI are being collected, independently and prospectively, in the Dutch Breast Implant Registry. Clearly, more epidemiological studies on the association between ASIA and SBI are needed.

Many patients also fulfil the criteria for CFS/ME [32], fibromyalgia [9], sarcoidosis [5,33] and/or undifferentiated connective tissue disease. Furthermore, a substantial number of patients have well defined systemic autoimmune diseases such as Sjogren syndrome, antiphospholipid syndrome, rheumatoid arthritis, systemic sclerosis, systemic lupus erythematosus, eosinophilic granulomatosis with polyangiitis and different other forms of vasculitis [5,6▪▪,21].

Epidemiologic evidence for an increased occurrence of these autoimmune diseases is, however, sparse [10▪▪]. In a recent meta-analysis, increased risks for rheumatoid arthritis and Sjögren syndrome were found. Importantly, the systematic review concluded that studies still do not provide conclusive evidence regarding safety of SBI. Further investigations are required to determine whether increased occurrences exist between silicone gel implants and autoimmune diseases [10▪▪].

SBI patients, however, clearly have an increased risk to develop lymphomas [34,35▪,36▪▪]. Especially, the risk to develop an anaplastic large T-cell lymphoma (ALCL) of the breast negative for anaplastic lymphoma kinase-1 (ALK-1) but positive for CD30 is strongly increased (odds ratio of 18.2).

PATHOPHYSIOLOGY OF SILICONE BREAST IMPLANTS RELATED DISEASE(S)

In the late 1940s and in the 1950s, silicones were directly injected in the breast for augmentation purposes. Injected silicones, however, did not remain at the injection site and spread through the body and induced a foreign body reaction

resulting in granulomatous inflammation [37]. Furthermore, autoimmune/inflammatory phenomena may occur.

Silicone-gel can migrate outside the outer shell after SBI rupture. Migration through an intact shell has also been demonstrated (so-called 'gel bleed'). Recently, silicone material was found in multiple organs, nervous tissue and the brain in a patient at autopsy [38▪▪].

The association between SBI and ASIA may result in the following scenario [39–41]: Silicon-containing particles are captured by macrophages, resulting in entrapment within lysosomes. Subsequently, inflammasomes are activated, resulting in the production of cytokines such as interleukin-1β. Also, reactive oxygen species (ROS) and reactive nitrogen species are produced. Subsequently, apoptosis of macrophages occurs resulting in the release of silicon-containing particles that can be taken up once again by other macrophages. Exposure to silicon-containing particles also leads to a massive production of interleukin-17 resulting in an influx of neutrophils that are activated and produce ROS and release enzymes such as myeloperoxidase. In addition, silicon-containing particles are transported to the regional lymph nodes, resulting in a pronounced adjuvant effect.

In animal models, it has been shown that SBI induces an adjuvant effect [42–44] and increase the susceptibility to and/or exacerbate autoimmune diseases [45–47]. In nonsusceptible animals, however, autoimmunity could not be induced [45].

Which women susceptible are for development of SBI-related disease is at present unknown. However, several factors have been postulated [48]. Firstly, patients who are known to have (a history of) allergy and/or an established autoimmune disease are at risk. Furthermore, those who have a familial predisposition for autoimmune disease are also prone to develop symptoms after SBI. It is important to realize that not only immunogenetic (i.e. human leukocyte antigen) factors play a role in the development of SBI-induced ASIA but probably also environmental factors such as smoking and obesity [48,49,50▪].

Finally, in women with SBI, it is found that the capsule around these SBIs contain inflammatory cells that are predominantly Th1/Th17 cells, whereas regulatory T cells in the capsules are defective in suppressing these intracapsular T cells [51]. These findings suggest that the Th17/Treg balance is disturbed that may result in the development of inflammatory/autoimmune diseases [52]. Importantly, many patients with ASIA due to SBI have a humoral immune-deficiency [5] and a vitamin D deficiency [53▪▪]. These two factors also increase the risk to develop an autoimmune disease in susceptible patients [5,53▪▪]. Furthermore, the chronic inflammation by the SBI in the capsule may result in progression from polyclonal lymphocyte stimulation to monoclonal lymphocyte stimulation, which in turn will result in lymphoma formation such as ALCL [35▪].

DISEASE MANAGEMENT

Unfortunately, there are no randomized clinical trials performed on the management of women with SBI-related diseases. Also, there are no (inter)-national guidelines formulated. However, on the basis of our personal experience, some therapeutic considerations should be considered.

Firstly, vitamin D deficiency and/or insufficiency should be corrected. As vitamin D may act as a regulatory agent of the immune system [53▪▪,54,55], we prescribe vitamin D supplementation to our patients [55,56]. Secondly, triggers of immune activation should be avoided and/or treated. The patient should try to quit smoking. Furthermore, antiallergic medication should be prescribed to patients with allergic rhinosinusitis, whereas bacterial (respiratory) infections should be treated with antibiotics, especially when IgG levels and/or IgG subclasses are deficient [57]. Furthermore, for eye symptoms, preservative-free tear supplements should be prescribed.

There is ample evidence that explantation of the SBI is an important first step in the management of women with SBI-related disorders [7▪▪,17]. In our recent review, we found that 469 of 622 reported patients (75%) improved after explantation. The shorter the period is that the SBI were in place, the better the amelioration of systemic symptoms and signs following removal [58]. In patients who had already developed an established autoimmune disease, only 16% improved without additional immunosuppressive therapy [7▪▪].

Unfortunately, several women still suffer from ASIA after explantation possibly because silicones are present throughout the body [38▪▪]. There are no medications that can cure ASIA, but therapy can help reduce symptoms. Suggested medications include minocycline or doxycycline [59,60,61▪], hydroxychloroquine or corticosteroids to dampen inflammation. In addition, medication may be prescribed for symptoms due to central sensitization [62▪▪], gastrointestinal involvement [63] and/or cardiovascular involvement [64]. Finally, as in patients with fibromyalgia, a combination of drug, cognitive behavioural and exercise treatment should be considered [65,66]. Also, some patients need psychiatric consultation [67].

CONCLUSION

SBIs are associated in a proportion of patients with complaints such as fatigue, cognitive impairment, arthralgias, myalgias, pyrexia, dry eyes and dry mouth. During the last few years, the concept that these symptoms are due to an adjuvant effect of migrated silicones has been further worked-out. Due to either SBI rupture or gel-bleed, silicones can migrate through the body into tissues and the central nervous system. Furthermore, these silicones can induce a chronic inflammatory process that may ultimately result in (an increase of) allergies, autoimmune diseases, immune deficiency and/or lymphomas. Explantation of SBI results in the majority of patients in an amelioration of the symptoms. There is an urgent need to start adequately adjusted epidemiological studies and creative post-marketing surveillance to obtain better evidence which percentage of patients does develop ASIA, immune deficiency, autoimmune diseases and/or ALCL.

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Conflicts of interest

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In this study, 100 patients with ASIA due to silicone implant incompatibility syndrome diagnosed in 2014 were compared with 100 historical patients with adjuvant breast disease diagnosed between 1985 and 1992. Despite changes in the principal constituents of the silicone implants during the past 50 years, similar clinical manifestations were observed in the 2014 cohort, the 1985–1992 cohort and 18 other large cohorts of patients that were reviewed. It is concluded that silicone-related disease has not changed during the last 30 years.

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In this manuscript, a critical review of the existing literature reflecting the results of explantation of SBIs in patients with silicone-related complaints and/or autoimmune diseases was performed. Explantation of the silicone breast improved silicone-related complaints in 75% of the patients. In patients with autoimmune diseases, however, improvement was only infrequently observed without additional therapy with immunosuppressive therapy, that is in 16% of the patients. The effect of explantation did not influence autoantibody testing such as ANA.

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Breast implant associated anaplastic large cell lymphoma (ALCL) is a rare T-cell lymphoma arising around breast implants. Public awareness has increased following a safety communication warning of the association of breast implant associated ALCL by the U.S. Food and Drug Administration in 2011. Difficulty with determining an accurate assessment of risk, including diagnosis or standardized treatment regimen has led surgeons to commonly omit preoperative discussion of this rare and frequently misunderstood cancer. A model of breast implant associated ALCL informed consent implementation and healthcare provider education are reviewed with 1-year process follow-up at a tertiary cancer centre. Breast implant associated ALCL should be included during preoperative counselling on the risks of breast implantation when obtaining informed consent. Education of healthcare professionals and provision of patient-focused materials ensures effectiveness of the informed consent process.

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An autopsy was performed in a 56-year-old woman who had been exposed to gel bleed from her SBIs for 17 years. Paraffin samples were stained with hematoxylin and eosin as well as with Modified Oil O Red. Tissues embedded in plastic were sectioned and prepared for light microscope using toluïdin blue staining for transmission electron, microscopy and energy-dispersive X-ray microanalysis to measure elemental Silicon (Si). Two types of silicone material were found in multiple tissue and brain samples of this patient. The first is a droplet-like form. EDX measurements demonstrated that the droplets are composed of elemental Si. The second is a plaque-like form; these structures are composed of elemental Si and Ti (Titanium). It is concluded that Si migration had occurred throughout the whole body.

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The development of autoimmunity and/or autoimmune diseases is multifactorial. Vitamin D is one of the factors that might play a role. It is postulated that both the presence of adjuvants and insufficient levels of vitamin D may result in the development of autoimmunity in patients with ASIA in relation to SBI. In this study, it was found that the risk to develop autoantibodies was significantly increased in vitamin D deficient and/or insufficient patients (relative risk 3.14). Whether vitamin D supplementation results in a decrease of autoimmunity needs to be studied prospectively.

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The most common cause of surgical readmission after SBI remains infection. Six causative organisms are principally involved: *Staphylococcus epidermidis* and *S. aureus*, Escherichia, Pseudomonas, Propionibacterium and Corynebacterium. Empiric antibiotics should be vancomycin (with the possible inclusion of gentamicin). Minor infections should be treated with tetracycline or doxycycline as a second-line agent.

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Undifferentiated connective tissue disease, fibromyalgia and the environmental factors

Laura Andreoli and Angela Tincani

Purpose of review
The aim of this study was to discuss the role of environmental factors in the induction and perpetuation of autoimmunity, with particular focus on undifferentiated connective tissue disease (UCTD) and fibromyalgia. These two entities may share undefined clinical and laboratory features and recognize environmental exposures as triggering factors. From this particular point of view, both UCTD and fibromyalgia may resemble the picture of the 'Autoimmune/Inflammatory Syndrome Induced by Adjuvants' (ASIA).

Recent findings
A case–control study on environmental exposures showed that patients with UCTD were significantly more exposed to several adjuvants (vaccines, metal implants, proximity to metal factories and foundries) than age and sex-matched healthy controls. UCTD exposed to major ASIA triggers (vaccines, silicone) displayed typical features of ASIA (general weakness, chronic fatigue, irritable bowel syndrome) in the context of a predisposing genetic background (familiarity for autoimmunity).

Summary
The induction and perpetuation of autoimmunity is a complex process that requires the interaction between the individual genetic background and the environment. Environmental factors are gaining increasing attention since the description of ASIA, a syndrome that includes symptoms typically seen in patients with fibromyalgia and UCTD. A recent case–control study focusing on environmental exposures suggested that nearly half of patients with UCTD may fall within the ASIA spectrum.

Keywords
adjuvants, autoimmune/inflammatory syndrome induced by adjuvants, autoimmunity, fibromyalgia, undifferentiated connective tissue disease

INTRODUCTION

Several conditions in the field of autoimmunity are characterized by nonspecific signs and symptoms that cannot be included in any well defined diagnostic category, such as chronic fatigue, myalgia, muscle weakness, arthralgia or arthritis. The term 'undifferentiated' used to describe all these conditions not only reflects an undefined clinical picture but also a poor knowledge of the underlying etiopathogenic mechanisms.

Undifferentiated connective tissue disease (UCTD) is a term that encompasses a broad spectrum of conditions characterized by signs, symptoms and laboratory features that are suggestive of systemic autoimmune diseases (SADs). However, the picture cannot be clearly classified into a definite SAD according to the international classification criteria for each disease. Such a kaleidoscope of clinical presentations poses the question whether the UCTD can be considered as a distinct entity or may be early forms of definite SAD. Given this open discussion, the classification criteria for UCTD are still a work in progress [1].

Among the manifestations that can be observed in UCTD patients, fibromyalgia is one of the most common clinical pictures. The term 'FM' itself refers to a 'syndrome' characterized by widespread pain, fatigue and other functional symptoms of poorly understood pathogenesis [2,3▪]. Recent findings suggested a link between fibromyalgia and the immune system through the involvement of cytokines and chemokines in the pathogenic mechanisms [4–6], similarly to what has been described in UCTD patients [7].

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KEY POINTS

- Environmental factors play a crucial role in the induction and perpetuation of autoimmunity.
- Undifferentiated connective tissue disease (UCTD) and fibromyalgia may share clinical and laboratory features of the so-called ASIA (autoimmune/inflammatory syndrome induced by adjuvants).
- Nearly half of the patients with UCTD may fall within the ASIA spectrum according to a case–control study on environmental exposures.

Therefore, UCTD and fibromyalgia are both emerging conditions from an epidemiological point of view that still have many underlying disease mechanisms to be unravelled. Particularly, the interplay between genetic background and environmental factors needs to be elucidated. This article will review the current knowledge on the role of the environment in triggering and perpetuating pathogenic mechanisms in UCTD, fibromyalgia and related disorders.

THE BASIS OF AUTOIMMUNITY

Autoimmunity is a complex pathological phenomenon that can display into several different clinical presentations. However, it is possible to identify three pillars that underlie the induction and perpetuation of autoimmunity, whatever the clinical phenotype is. Autoimmune diseases, either organ-specific or systemic, arise from the interaction between a predisposing genetic background, an impaired immune regulation and triggering environmental factors [8▪▪].

The majority of autoimmune diseases recognize multiple genetic factors, while monogenic autoimmune diseases are rare. The major histocompatibility complex (MHC) holds several Human Leukocyte Antigens (HLA) genes that have been identified in early times as relevant predisposing factors for autoimmunity. Their strong predictive value has also been confirmed by genome-wide association studies (GWAS), which found other non-HLA genes to be involved in the determination of autoimmune diseases (e.g. Protein tyrosine phosphatase, non-receptor type 22, interferon regulatory factor 5, etc.) [9]. Besides genes, epigenetic mechanisms (acetylation, phosphorylation, methylation, etc.) play an important role in affecting the function of the immune system [10]. The breach of immunologic tolerance that preludes to autoimmunity derives from the impaired functioning of the innate and adaptive immune system. Potential mechanisms that underlie autoimmunity include molecular mimicry, epitope spreading, bystander activation, polyclonal activation of B and T cells, and autoinflammatory activation of innate immunity [8▪▪]. Being autoimmune disease not congenital, but rather developing in any decade of life, a crucial question has always been to understand what was the trigger for such a disease. Much attention has been devoted to environmental factors, as epidemiological studies, laboratory research and animal models have increasingly shown their role in the onset of autoimmunity [8▪▪]. Particularly, changes in lifestyle have led to the exposure of an increasing number of physical and chemical environmental agents, which can be considered as a putative reason for the increase in autoimmune diseases in the past decades.

ENVIRONMENTAL FACTORS TRIGGERING AUTOIMMUNITY

Recently, all the exogenous and endogenous environmental exposures have been denominated as ‘exposome’, which includes infectious and non-infectious agents that interact with our organism throughout life [11▪].

Infections

Microorganisms such as viruses, bacteria, fungi and parasites can induce or trigger an autoimmune disease, as shown by clinical and experimental studies [8▪▪]. Autoimmune diseases that have been reported to be triggered by viruses include rheumatoid arthritis, thyroid diseases, primary biliary cirrhosis, type I diabetes and autoimmune hepatitis [8▪▪]. Besides exogenous infectious agents, which can be collectively called as ‘infectome’, increasing interest has being raised by the ‘auto-infectome’, that is the minor part of the microbiome that includes the infectious agents inflicting self-damage and tissue destruction leading to the development of autoimmune disease [11▪].

Microbiome

The human microbiome is the genomic collection of the entire repertoire of human-associated microorganisms, the microbiota. The largest microbial community is found in the gut, where the day-to-day symbiosis is beneficial in activities, including digestion of nutrients, xenobiotic degradation, vitamin production and protection from pathogens [12]. At times, homeostasis is disturbed, and changes in microbial composition and diversity occur; these

shifts are termed dysbiosis. Dysbiosis, especially in the gut, has been linked in recent years with disease states, but a direct causal relationship cannot be determined in every case. Many factors could contribute to dysbiosis, including host-genetics (sex, HLA haplotypes), age (changes in microbiota due to ageing) and diet ('western diet' rich in fat and protein and widespread use of antibiotics have been associated with increasing incidence of autoimmune diseases) [13▪▪]. Complex interactions between genetics, environment and the microbiota shape the inflammatory status in the gut. Increases in pathobionts or decreases in anti-inflammatory commensals favour aberrant immune interactions with microbes, leading to dysbiosis and direct barrier damage. In genetically predisposed individuals, barrier damage is thought to instigate chronic inflammation [14]. Overall, the proposed model linking the microbiome and autoimmunity claims that genetic and environmental factors affect the immune function directly and indirectly through the microbiota [15▪▪]. Therefore, there is currently great interest in characterizing the microbiome associated with different autoimmune diseases with the purpose to manipulate it as a therapeutic tool [16].

Xenobiotics

The term 'xenobiotics' collects several physical and chemical factors that can stimulate autoreactive B and T cells and perpetuate autoimmunity [9].

Exposure to ultraviolet light induces apoptosis of keratinocytes and other dermal cells, thus releasing self-molecules and proinflammatory cytokines, triggering systemic inflammation. Such a pathogenic mechanism can be implicated in the emergence of connective tissue diseases, particularly systemic lupus erythematosus, although strong epidemiological data are lacking [17].

Cigarette smoking contains several substances that promote oxidative stress and the release of proinflammatory cytokines. There is evidence that smoke can be implicated in the pathogenesis of several autoimmune diseases by multiple mechanisms and can be responsible for a more severe course of the disease [18▪▪]. Fibromyalgia patients tend to report improvement upon smoking, but a recent study showed that smoking helps to cope with the disease, but does not ameliorate physical symptoms [19].

Chemical substances and heavy metal particles can act as disruptors of the immune system [8▪▪]. A striking example comes from the follow-up of the rescue/recovery workers at the World Trade Center after the terroristic attack in 2001. Debris and dust created by the collapse of the World Trade Center remained in the air for a long time, exposing the workers to an amalgam of glass fibres, silica, asbestos, polycyclic aromatic hydrocarbons, dioxin, furans and polychlorinated biphenyls. The firefighters and the policemen who worked in the site of the attack were found to have an increased incidence of autoimmune diseases [Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus (SLE), Systemic Sclerosis, primary Sjogren's syndrome (pSS), etc.] as compared with controls [20▪]. Metals were also claimed to be the initiators of nonspecific symptoms classified as CSF and FM in metal-sensitized patients [21]. Patients with definite autoimmune diseases (SLE, RA, pSS) [22] and with fibromyalgia [23] were also found to have an increased frequency of metal hypersensitivity, particularly nickel, gold and mercury that are present in dental restorative materials.

Other substances under the umbrella of 'xenobiotics' that can induce and perpetuate autoimmunity are alcohol, drugs, cosmetics, hydrocarbons [8▪▪] and tattoos [24].

Diet/Nutritional factors

Over the past years, multiple lines of evidence have supported a major role for specific dietary factors (including vitamin D, vitamin A, selenium, zinc, omega-3, fatty acids, probiotics and flavanols) in determining the immune responses involved in infections, allergies and autoimmune diseases [25].

Patients with systemic autoimmunity diseases often report to better manage their symptoms when following certain dietary restrictions or supplementations. Gluten sensitivity has been increasingly reported in autoimmune patients, including those with fibromyalgia [26] and UCTD [27]. Although it is premature to recommend any special dietary regimen in patients with autoimmune diseases, it is worth to mention that research is ongoing to evaluate the effects of dietary interventions on the immune system [28].

Among nutrients, vitamin D has certainly drawn much attention in the past decade as a hormone with several immunomodulatory properties [29▪]. Hypovitaminosis D is widespread in autoimmune diseases, suggesting its role in the induction and perpetuation of autoimmunity [29▪]. Low levels of vitamin D have also been described in fibromyalgia [30] and UCTD patients [31]. In the latter, vitamin D deficiency was shown to negatively impact on the immune system function [32], while supplementation with the active form of vitamin D can help to restore the balance between pro- and anti-inflammatory factors [32,33].

Table 1. Major and minor criteria suggested by Shoenfeld and Agmon-Levin in 2011 for the definition of the autoimmune/inflammatory syndrome induced by adjuvants

Major criteria
Exposure to an external stimuli (Infection, vaccine, silicone, adjuvant) prior to clinical manifestations
The appearance of 'typical' clinical manifestations
Myalgia, myositis or muscle weakness
Arthralgia and/or arthritis
Chronic fatigue, un-refreshing sleep or sleep disturbances
Neurological manifestations (especially associated with demyelination)
Cognitive impairment, memory loss
Pyrexia, dry mouth
Removal of inciting agent induces improvement
Typical biopsy of involved organs
Minor criteria
The appearance of autoantibodies or antibodies directed at the suspected adjuvant
Other clinical manifestations (i.e. irritable bowel syndrome)
Specific HLA (i.e. HLA DRB1, HLA DQB1)
Evolution towards an autoimmune disease (i.e. MS, SSc)

Adapted from Shoenfeld and Agmon-Levin in 2011 [34].

THE 'AUTOIMMUNE/INFLAMMATORY SYNDROME INDUCED BY ADJUVANTS'

In recent years, the definition of the autoimmune/inflammatory syndrome induced by adjuvants (ASIA) [34] has shifted the attention towards adjuvants as triggers of various pathological entities of autoimmune cause. Adjuvants are indeed substances that can enhance the immune response and that sometimes, in particular conditions, can induce themselves an immune response.

Several pathological entities have been included within the ASIA spectrum: postvaccination phenomena, macrophage-miofascitis syndrome, the 'Gulf War Syndrome' and the 'Sick Building Syndrome'. All these conditions share the common features of chronic fatigue syndrome and fibromyalgia, in terms of chronic pain syndrome driven by central hyperalgesia. In addition, signs of aberrant immune response can be found: fever, arthritis, myositis, demyelination and positive autoantibodies.

The classification criteria for ASIA (Table 1) include major features (onset of typical clinical manifestations after the exposure to an adjuvant such as chronic fatigue and myalgia; the clinical improvement after withdrawal of the trigger; compatible biopsy of the involved organs) and minor ones (autoantibodies against the triggering factor; irritable bowel syndrome; specific HLA; evolution towards a definite autoimmune disease) [34]. More recently, the addition of a mandatory criterion requiring temporal association and clinically relevant adjuvant dose has been suggested to allow better definition of what constitutes a diagnosis of ASIA [35].

According to the literature and to the Registry including more than 300 cases of ASIA [36▪▪], the main adjuvants involved in the onset of ASIA are silicone and vaccines.

Despite changes in the principal constituents of the silicone implants during the past 50 years, silicone remains an adjuvant that may 'bleed' and subsequently may be a chronic stimulus to the immune system resulting in typical clinical manifestations of ASIA [37]. Complaints are likely to disappear after prosthesis explantation, although patients who develop a full blown autoimmune disease are likely to require immunosuppressive treatment [38]. Chronic inflammation may result in monoclonal activation of the immune system in predisposed individuals, ultimately leading to lymphoma [39]. It would be important to identify individuals who are at increased risk of developing silicone-induced ASIA. Currently, individuals with previously diagnosed autoimmune disorders or with genetic preponderance for hyperactive immune system may not be considered as candidates for silicone implantation [40].

The association between vaccinations and autoimmune phenomena is rooted in the literature. Autoimmunity can emerge as either simple appearance of autoantibodies or as a full-blown autoimmune disease [41,42▪]. For instance, the onset of both fibromyalgia [43] and UCTD [44,45] has been described following hepatitis B vaccination. The fact that vaccines and adjuvants can trigger a pathogenic autoimmune response is corroborated by animal models. The use of animal models has enabled the study of the effects of application of adjuvants in a homogeneous population with certain genetic backgrounds [46]. However, the link between vaccinations and autoimmunity should not induce to change the current policy of vaccinations in the general population, but rather shall fuel the field of *vaccinomics* in order to identify novel customized, personalized approaches to evaluate the individual risk of developing an autoimmune condition. Autoimmunity is a complex and multifactorial phenomenon and emerges from a predisposing genetic background, being HLA-DRB1 a prototypical example [47]. It should be kept in mind to weigh the magnitude of autoimmune postvaccination phenomena against the number of vaccinated individuals who did not develop any autoimmune complication. As a whole, the benefit of vaccinations overweighs the risk of inducing autoimmune conditions in the general population.

Table 2. Features linking undifferentiated connective tissue disease and autoimmune/inflammatory syndrome induced by adjuvants in a case–control study on environmental exposures

(1) UCTD patients had more environmental exposures to adjuvants as compared to controls	UCTD were significantly more exposed to (1) tetanus vaccination; (2) HBV vaccination; (3) metal implants; (4) proximity to metal factories and foundries (home located less than 1 km). Cigarette smoking and allergies were more frequent in UCTD.
(2) Half of UCTD exposed to major ASIA triggers	Fifty-seven percent of patients with UCTD had been exposed to either vaccines containing adjuvants or silicone implants.
(3) UCTD exposed to major ASIA triggers displayed typical features of ASIA	As compared with nonexposed UCTD patients, those exposed to major ASIA triggers displayed more frequently general weakness, chronic fatigue, irritable bowel syndrome.
(4) UCTD exposed to major ASIA triggers had familiarity for autoimmunity	As compared with nonexposed UCTD patients, those exposed to major ASIA triggers had more frequently first-degree relatives with autoimmune diseases (56% vs. 33%).

ASIA, autoimmune/inflammatory syndrome induced by adjuvants; HBV, hepatitis B virus; UCTD, undifferentiated connective tissue disease.
Adapted from [48].

CAN UNDIFFERENTIATED CONNECTIVE TISSUE DISEASE FALL WITHIN THE AUTOIMMUNE/INFLAMMATORY SYNDROME INDUCED BY ADJUVANTS SPECTRUM?

Similarly to ASIA, UCTD is an autoimmune condition characterized by nonspecific signs and symptoms, alluding to the idea that the exposure to adjuvants can also be a trigger of UCTD.

To investigate the possible environmental triggers of UCTD, we recently performed a case–control study on the exposure to different adjuvants in patients with UCTD and in age and sex-matched controls [48]. Exposure to several adjuvants prior to UCTD onset (during the 10 years before diagnosis) was found to be significantly more frequent than healthy controls, suggesting that nearly half of UCTD patients in our cohort might fall within the spectrum of ASIA. Interestingly, patients exposed to major adjuvants displayed the typical features of ASIA, particularly fibromyalgia symptoms (Table 2).

CONCLUSION

The induction and perpetuation of autoimmunity is a complex process that requires the interaction between different factors, particularly the individual genetic background and the environment. Environmental factors are gaining increasing attention since the description of ASIA, a term that includes several entities that share clinical and laboratory features as a consequence of the exposure to adjuvants. Fibromyalgia symptoms are typically present in ASIA. The kaleidoscopic picture of UCTD may also resemble ASIA and, recently, a case–control study focusing on environmental exposures suggested that nearly half of patients with UCTD may fall within the ASIA spectrum.

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Conflicts of interest

None.

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Epigenetics of CD4$^+$ T cells in autoimmune diseases

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Purpose of review
Autoimmune disorders are a group of overactive symptoms because of abnormal immune responses. Progress of novel mechanisms for autoimmune diseases has been restrained by incomplete understanding of immune disturbance. Recent advances in autoimmune diseases have been well documented by epigenetic alterations (DNA methylation, histone modification, and microRNAs), which alter the transcription activity of genes that are involved in autoimmune responses.

Recent findings
Multiple environmental factors (trichloroethylene, breast milk, and vitamin C) initiate aberrant epigenetic modifications in CD4$^+$ T cells, leading to a list of transcriptional deregulations in several genes (Ifng, Cd70, Tnf, Dnmt3a, and Foxp3) that determine T-cell identity. In addition, epigenetics target regulatory genes (Tim-3, cereblon, protein kinase C theta, octamer transcription factor 1, basic leucine zipper transcription factor ATF-like, p70 kinase, and lactate dehydrogenase A) to influence T-cell activation, differentiation, and metabolism.

Summary
In this review, we decipher findings that identify how epigenetic regulates CD4$^+$ T-cell functions and the advancement of novel epigenetic mechanisms in systemic lupus erythematosus, rheumatoid arthritis, and multiple sclerosis. Further researches could be conducted to explore new clinical application of epigenetic regulation based on T cells in autoimmune diseases.

Keywords
autoimmune diseases, CD4$^+$ T cell, epigenetic modifications

INTRODUCTION

Epigenetic landscape has been deciphered specifically in order to help us further understand the exact role of this magic regulation of gene but not through altering gene sequence [1]. These modifications comprises a mechanistically alterations of gene structure around promoter regions, including the permissive or repressive regulation of the gene transcription. This is achieved mainly by the DNA methylation, histone posttranslational modifications, and some small microRNAs (miRNAs). DNA methylation is implicated to be a repressive regulation and is often mediated by de-novo DNA methyltransferase (DNMT) enzymes. Histones are some tiny basic proteins, in coordination with DNA, forming the chromatin structures in the cell nucleus [2] and with a certain modification at several different amino acid residues. More than a half of protein-coding genes of mammals are found to be encoded through thousands of miRNAs that corporately affect the gene expression. Aiming at the complementary sequences within 3′-untranslated region (3-UTR) of a transcript, miRNAs can repress translation of target gene, and/or reduce mRNA stability. Increasing evidence suggests that epigenetic reprogramming participates in T-cell responses, thus defines cell identity and function to environmental challenges [3–5] (Fig. 1).

ENVIRONMENT FACTORS INFLUENCE EPIGENETIC REGULATION IN CD4$^+$ T CELLS

Many environmental factors have been displayed as significant elements in autoimmune diseases. Interestingly, these environmental factors are suggested

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KEY POINTS

- Epigenetic modification is a bridge between internal chromatin to external environment to regulate gene transcription activity in T cells.
- Environmental factors through epigenetic mechanisms play varieties of roles to influence T-cell function and immune responses.
- Emerging evidences show the importance of epigenetic network and epigenomic analysis in T-cell activation, differentiation, and metabolism.
- Dysregulated T-cell reactions because of the aberrant epigenetic regulation lead to inflammatory responses in autoimmune diseases.

to be connected with epigenetic modifications to play a role.

Drinking water contained trichloroethylene (TCE) has been noticed as toxicity in many diseases, including cardiac defect in infants [6,7]. However, the exact hazardous role of TCE in other diseases is not well documented. Intriguingly, the mice exposed to TCE drinking water displayed a reduced DNA methylation level in their $CD4^+$ T cells, whereas an elevated methylation variance in certain genes, such as ifng, Cd70, Tnf, and Dnmt3a in first 22th weeks after TCE exposure. However, the phenomenon turned out to be negatively related with the previous observations starting from the 40th weeks, whereas the methylation level increased and ifng expression decreased [8▪].

Milk from breastfeeding is known to protect the infants to against from the allergy and atopy. But how the milk achieves its protective function in stabilizing immune system is hardly explored until recently. A study compared the children who are allergy to cow's milk with those normal controls, then set up a relationship between a lower TSDR demethylation with the allergic children, suggesting a direct role of Treg cell number with IgE-mediated

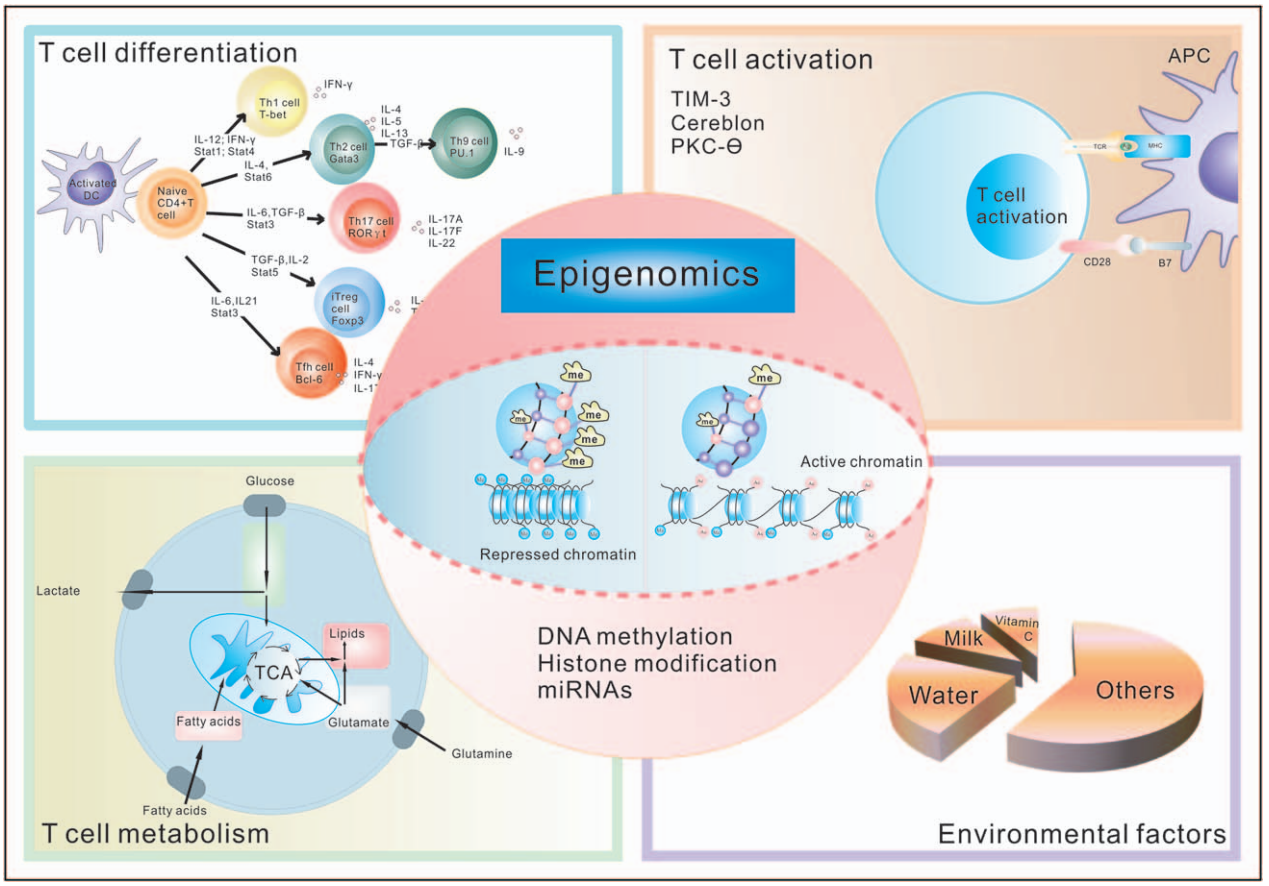

FIGURE 1. Environment factors initiate epigenetic regulations to influence T cell activation, differentiation, and metabolism. Epigenetic events, such as DNA methylation, histone modifications, and microRNAs (miRNAs) are tightly associated with T cell activation, differentiation, and metabolism. Environmental factors such as contaminated water, milk from breastfeeding and vitamin C are combined with epigenetic regulations to perform their function in T cells. The epigenetic switch can activate or repress lineage specific factors that determine the effector T-cell fate. Also, epigenetic marks are of great importance in T cells as there are many metabolic targets.

allergy [9]. In addition, studies have found that the milk-derived exosomal microRNAs can be linked to the reduced expression of methylation level in the FOXP3 promoter region, thus inducing the overexpression of Treg cell differentiation [10].

In a recent study, vitamin C has been recorded as a trigger in promoting TET enzyme family expression which mediates the 5hmC-induced DNA demethylation process. Vitamin C increases the activity of TET enzymes, thus achieving the stable expression of FOXP3 gene which guarantees the Treg cell function and efficacy [11].

EPIGENETIC MODIFICATIONS TARGETING REGULATORY GENES TO INFLUENCE T-CELL ACTIVATION, DIFFERENTIATION, AND METABOLISM

The differentiation process from naïve T cell to effector T cell is the expression variance of their target regulatory genes, such as key transcription factors or cytokine genes that determine the differentiation direction of specific T helper cell subsets.

T-cell immunoglobulin and mucin domain-containing protein 3 (TIM-3) is a gene that alternatively emerged in Th1 cell with the ability to suppress Th1 cell involved immunity. Importantly, a certain CpG island located in the TIM-3 promoter has been found under the DNA methylation regulation. Further, naïve T cell treated with methylation inhibitors presents an increase expression of TIM-3 upon in-vitro polarizing condition of several types of T helper cells [12].

Cereblon is an ubiquitin ligase complex that ubiquitinates many proteins, thus altering their functions. It is suggested that cereblon plays a role in T-cell activation by regulating potassium channels [13]. Cereblon restricts the T-cell activation process through balancing permissive and repressive epigenetic modifications such as H3K27me3 and H3K27ac, thus suppressing potassium flux and calcium-mediated signaling. Cereblon deficiency in $CD4^+$ T cell of experimental autoimmune encephalomyelitis (EAE) mice model is presented as exacerbated disease syndrome. The study also mentioned that less Th17 cells are detected in the absence of cereblon, and weakened T-cell activation [14▪▪].

Protein kinase C theta (PKC-θ) is involved in the process of T-cell activation by forming signaling pathway that results in T-cell transcriptional activities [15]. More recently, genome wide studies carried out that the role of PKC-θ in transcription activation is achieved by permissive histone modifications such as H3K4me and H3K27ac that recruit PKC-θ to stimulate human memory $CD4^+$ T cells [16]. Furthermore, these epigenetic marks also regulate PKC-θ signaling pathway to induce gene expression in human memory $CD4^+$ T cells, thus the transcriptional response produced by PKC-θ pathway regulated by epigenetic modifications again emphasizes the importance of epigenetics in T-cell activation and development.

Octamer transcription factor 1 (OCT-1) (Pou2f1) is a transcriptional factor that almost expressed in every organ and tissue and regulating gene expression in different cells such as $CD4^+$ T cells by recognizing an octamer DNA element or inducing chromosomal interactions [17,18]. OCT-1, coupled with GATA3, the major transcription factor of Th2 cell, are suggested to be associated with an epigenetic mark RHS5, which is a DNase I hypersensitive site (DHS) within the Th2 locus control region (LCR). The combination of OCT-1 and GATA3 can promote the transcription activity of Th2 cytokine gene interleukin (IL)4 expression through the regulation of epigenetic mark RHS5. Thus, OCT-1 and GATA3 alter Th2 cell differentiation via a epigenetic mechanisms [19].

Basic leucine zipper transcription factor ATF-like (BATF) is another transcription factor that is important for Th2 cell-mediated immune response [20] and Th17, Th9, and Tfh cell development. Evidence showed that in the absence of BATF, Th2, and Tfh cells cannot be produced because of the lack of BATF induced permissive epigenetic modifications. Similar to OCT-1, BATF is suggested to be recruited to the Rad50 hypersensitivity site RHS6 and RHS7 in the Th2 cell LCR [21].

p70 kinase (p70)(S6K1) gene in TORC1 pathway has been studied in determining protein expression and in Th1 and Th17 cell destiny. In p70(S6K1)-deficient mice, decreased expression of a set of Th17 cell-related genes has been displayed. Further experiments identified that histone H3 acetylation within the IL17A and F promotor region also presented a decreased pattern, which implies that less $IL17^+$ Th17 cells because the Rorγt has remained unchanged [22].

Aerobic glycolysis is an intriguing finding that most oncology cells are predominantly identified to produce energy when limited oxygen is available. A recent study has found that lactate dehydrogenase A (LDHA) can be produced by activated T cells as a result of aerobic glycolysis to facilitate the generation of interferon-γ (IFN-γ). This activity can be well performed without relying on its 3′-UTR, which is a potential mechanism involved in IFN-γ expression. Interestingly, increased level of histone acetylation and enhanced transcriptional activity of Ifng are retained by LDHA. However, conditional knockout of LDHA in T cells permits the mice to relieve

from immunopathology induced by overexpression of IFN-γ. Epigenetic mechanisms, combined with specific environmental conditions may somehow influence T-cell differentiation, further, T-cell responses. The promising finding will provide us with more alternative treatments when it comes to autoimmune diseases [23▪].

EPIGENETIC MODIFICATIONS AND AUTOIMMUNE DISEASES

Epigenetic reprogramming during the development of autoimmune diseases is now paid a great deal of attention from clinicians and researchers in epigenome area [24]. (Fig. 2)

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease, characterized by generating autoantibodies against cell nucleus, expressing altered cytokines, and forming immune-complex with multiple-organ dysfunctions [25]. Over the past year, a great body of studies has addressed the importance of the dysregulated T-cell response as a trigger in SLE [26].

Epigenetics is suggested to be associated with many environmental factors such as UV light, silica, infections, and cigarette smoke in SLE pathogenesis. High salt (sodium chloride, NaCl) is a very common aberrant physiological condition in creatures, MRL/lpr mice treated with high salty diet resulted in a severe lupus syndrome as compared with general MRL/lpr mice. Recently, a study has proved that high salt condition may play its detrimental role by inducing DNA demethylation that causes overproduction of a specific type of $CD4^+$ T helper cell (Tfh cell), which is identified to be related with the pathogenesis of SLE [27▪]. $CD4^+$ T cells transferred with oxidants or DNA methylation inhibitors into syngeneic mice has shown a group of lupus like syndromes such as increased serum anti-dsDNA antibody and glomerulonephritis. The results suggested that oxidants are negative regulator of DNA methylation in $CD4^+$ T cells and thus overexpressing genes such as CD40L and CD70 immune genes that were before silenced because of DNA methylation in both patients with SLE and lupus animal models [28▪].

Epigenome analysis of differential gene expression has been deciphered in lupus $CD4^+$ T cells. In East-Asian samples, researchers have identified a group of gene loci, specifically, GTF2IRD1-GTF2I, which are marked with different epigenetic changes in T and B cells [29▪▪]. In addition, genome-scale DNA methylation profiling of naïve $CD4^+$ T cells from different ethnicities has been examined, and a number of hypomethylated gene loci have been suggested from both African-American and European-American patients with lupus. Importantly, *cis*-regulatory variants abrogating CpG sites would thus partly explain the ethnicity difference in DNA

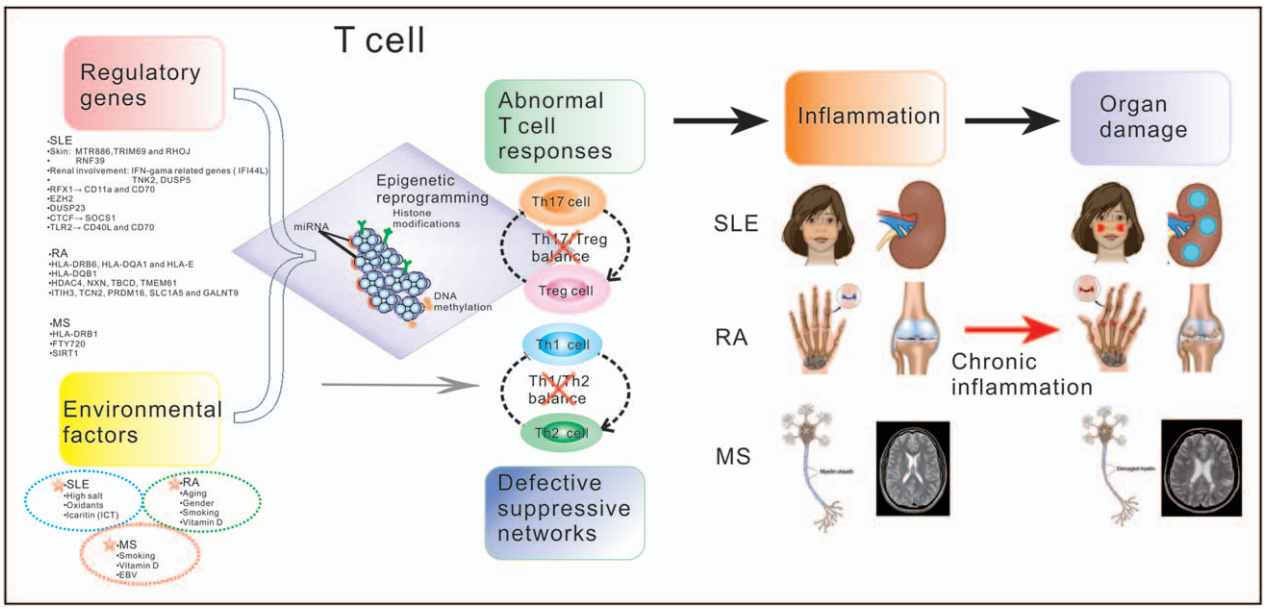

FIGURE 2. T-cell epigenetics in autoimmune diseases. The variance of regulatory genes state and the influence of environmental factors are triggers of SLE, rheumatoid arthritis, and multiple sclerosis. The results of the T-cell disturbance induced by a list of epigenetic modifications will initiate abnormal T-cell responses, thus generating inflammatory reactions that cause autoimmune diseases.

methylation [30▪]. Studies identified differential methylated CGs in naïve CD4$^+$ T cells from patients with or without renal involvement. TNK2 and DUSP5 have been found with a significantly reduced DNA methylation, and IFN-γ-related genes are suggested to be associated with renal involvement [31▪]. Zhao *et al.* [32▪▪] have proved that CpG methylation within IFN-γ regulated gene IFI44L promoter was significantly decreased than healthy control or other autoimmune diseases. DNA methylation regions (DMR) of naïve CD4$^+$ T cells from patients with SLE have been determined to calculate a relationship between DNA methylation variances and cutaneous presentations of lupus. Reduced methylation level of DMR included genes, such as MIR886, TRIM69, and RHOJ genes, and enhanced methylation level of RNF39 is indicated in lupus with skin involvement, such as malar or discoid rash [33].

Past few years have emerged an increasing number of epigenetic researches including a set of epigenetic-regulated genes [3]. Study has recently found that RFX1 is modified by polyubiquitination-mediated proteosomal degradation through STIP1 homology and U-box containing protein 1 (STUB1), which is elevated in SLE CD4$^+$ T cells. This study further explains the mechanisms that involved in RFX1 decreasing in SLE T cell, which implies that STUB1 promotes autoimmunity by some epigenetic regulations of RFX1 and may be explored as a potential therapeutic target in SLE [34]. Enhancer of zeste homolog 2 (EZH2) is an epigenetic regulator that can cause gene silencing by DNA methylation [35]. The recent study has found that fluctuation of EZH2 may be a significant regulator of lupus naïve CD4$^+$ T cells by maintaining Th2, Th17, and Tfh but Th1 cell responses [36]. Furthermore, microRNA-26a has been found to decrease with a glucose limitation by targeting EZH2. Meanwhile, a negative correlation has been noted in microRNA-26a expression level and lupus disease activity. Thus, EZH2 functions as an epigenetic modifier in regulating non-Th1 cell responses in lupus, and could be a therapeutic target in the future [37]. Dual specificity protein phosphatase 23 (DUSP23) is encode by the DUSP23 gene, level of which in CD4$^+$ T cells has recently been reported to be associated with DNMTs and MBDs enzymes that catalyze DNA methylation and three methylation-sensitive genes ITGAL, PRF1, and CD40L in patients with SLE. The study also proposed that the function of hypomethylation in regulating genes in CD4$^+$ T cells of patients with SLE can be counterbalanced by DUSP23, which increased DNMTs expression that induced the DNA methylation level [38]. The study of 5-hmC indicated that the level of DNA hydroxymethylation is differentially expressed in CD4$^+$ T cells of patients with SLE, and a transcription factor CTCF can regulate the DNA hydroxymethylation to induce the a increased expression of suppressor of cytokine signaling-1 (SOCS1), which contributes to SLE pathogenesis. Thus, from the genome wide study of lupus CD4$^+$ T cells we can draw the conclusion that not only DNA hypomethylation but also the DNA hydroxymethylation lead to the diseases pathogenesis [39,40]. Toll-like receptor 2 (TLR2) has been mentioned in a variety of studies to decipher its role in immune responses and autoimmune and inflammatory diseases. In a recent study, TLR2 has been found with an elevated expression in many immune cells including CD4$^+$ T cells form patients with SLE. In-vitro experiments showed that CD4$^+$ T cells stimulated with TLR2 would promote the expression of CD40L and CD70 and a range of inflammatory cytokines because of increased expression of H3K4me3 and H4 acetylation coupled with decreased expression of H3K9me3 in the IL17A and IL-17F promoter region [41▪].

Several studies have begun to unravel the contributions of differentially expressed microRNAs in lupus CD4$^+$ T cells of lupus pathogenesis [42]. Indeed, the dysregulated microRNA are critical events involved in aberrant immune responses in SLE, some of them are known to result in CD4$^+$ T-cell hypomethylation in lupus. A recent study of MRL-lpr mice enables us to gain a new insight into the role of the combination of DNA methylation and microRNAs. After identifying a great number of dysregulated microRNAs in lupus-prone mice, the study further observed that most of the increased microRNAs are enriched in a genomic imprinted DLK1-Dio3 domain. The interesting finding is that the use of DNA methylation inhibitor in MRL-lpr mice will promote the production of microRNAs especially in DLK1-Dio3 domain [43▪].

Epigenetics treatment for SLE has the potential to expand in the coming years as many targeting genes can be epigenetically regulated. Icaritin (ICT) is a natural compound from epimedium extracts that is suggested to have a role in many diseases. Studies has found that ICT may be an essential regulator in autoimmune reactions and inflammatory responses because of its role in maintaining the balance between IL17A and FOXP3, the latter one promotes Treg cell function and thus suppressing the overreactive responses of CD4$^+$ T cells from SLE. Further, enhanced expression of histone methylation has been found with the ICT to keep stable expression of FOXP3$^+$ Treg cell. Together, we may participate that ICT would be a therapeutic drug for SLE [44].

Rheumatoid arthritis

Rheumatoid arthritis (RA) is one of the most common autoimmune diseases characterized by a destructive inflammation in multiple joints. Increasing evidence shows that epigenetic modifications would provide the molecular biomarkers or therapeutic targets for diagnosis and treatment in rheumatoid arthritis [45].

A great body of studies is absolutely required in this area, with a special emphasis on particular T-cell subsets, using more modern arrays with truly genome-wide coverage. DNA methylation profiling has been detected in early patients with rheumatoid arthritis as compared with normal controls. Nearly 2000 CpGs showed significant difference in early patients with rheumatoid arthritis with a specific low level of methylation [46▪]. Furthermore, studies have proved that the enzymes involved in methylation are decreased including DNA methyltrasnferase 1 (DNMT1), but the enzymes correlate with demethylation are increased, such as ten-eleven translocation 1 (TET1), TET2, and TET3. The study further found that patients with rheumatoid arthritis treated with methotrexate (MTX) function as reverting the expression level of those methylation-sensitive enzymes, thus revising the aberrant disease states [47]. Treg-specific demethylated region (TSDR) methylation profiles have been presented separately for males and females [48]. These may implicate potent possibilities to further decipher the sex differential. More recently, genome wide study of $CD4^+$ T-cell DNA methylation carried out in China showed that many methylation sensitive genes display differential expression level because of hypermethylation or hypomethylation status. Among those genes, human leukocyte antigen (HLA)-DRB6, HLA-DQA1, and HLA-E are hypomethylated, whereas HLA-DQB1 is hypermethylated in CpG islands but hypomethylated in CpG shelf region. Beyond HLA-related genes, the study also showed that specific high level of methylation in HDAC4, NXN, TBCD, and TMEM61 genes, and relative low level of methylation in ITIH3, TCN2, PRDM16, SLC1A5, and GALNT9 genes [49].

Decreased level of miR-146a and miR-155 in response to T-cell stimulation was found in Tregs of patients with rheumatoid arthritis. The reduced expression of miR-146a was found in patients in active stage, which was also correlated with joint inflammation. This was because of the enhanced activation of the immune regulator STAT1 and modified phenotype of Treg in rheumatoid arthritis [50].

Multiple sclerosis

Multiple sclerosis is a demyelinating, autoimmune disease of the central nervous system (CNS), accompanying with axonal loss inflammation during a neurodegenerative process. It is known as a multifactorial and multigenic disease. Environmental factors play essential roles in promoting inflammatory responses and demyelination–remyelination process in multiple sclerosis [51]. Environmental risk factors, such as smoking, vitamin D deficiency, and Epstein–Barr virus infection are suggested to be triggers involved in multiple sclerosis [52]. The interplay of genetic, epigenetic, and environmental factors are account for the diseases, while epigenetic modifications of $CD4^+$ T cells may contribute more to help explain the pathogenesis of multiple sclerosis [53].

DNA methylation is significant part among epigenetic modifications with increasing evidence of its important role in multiple sclerosis by regulating target gene expression [54,55]. The epigenetic changes at the HLA-DRB1 locus implied a participation of these molecules in multiple sclerosis pathogenesis the myelin epitopes was presented to T cells by class II HLA with generation an antimyelin immunity [56].

Fingolimod (FTY720) is currently used as an oral medicine to treat patients with multiple sclerosis, it is considered as a T-cell trafficker and activator in the treatment of the disease by the evidence that the patients treated with FTY720 displayed a significantly reduced $CD4^+$ T cells and less inflammatory factors were produced when T cells were activated by the FTY720. In this process, epigenetic modifications were observed as elevated H3K9me3 and H3K27me3 in the IFNG and GZMB promoter. These all together showed a novel mechanism of FTY720 treatment in MS, epigenetic modifications are thus suggested to play a significant role in multiple sclerosis $CD4^+$ T cell to help integrate the protective mechanism of FTY720 in treating multiple sclerosis [57]. SIRT1 is a histone deacetylator among epigenetic regulators that generate gene silencing, in a recent study SIRT1 has been found to increases activity of the major transcription factor of Th17 cells, RORγt, thus promoting Th17 cell production and function in the pathogenesis and development of multiple sclerosis. The role of SIRT1 is further supported by the evidence that conditional knockout of Sirt1 in T cells or administrating SIRT1 inhibitors would cause a reduction of Th17 cell number, thus playing a significant role in protecting EAE mouse model [58].

miR-223 expression was significantly upregulated in $CD4^+$ T cells during the relapsing phase of multiple sclerosis, accompanied with increased Th17 cells and decreased treg cells. miR-223 may be associated with disease activity of multiple sclerosis and inhibiting miR-223 is suggested to be an

efficient approach to limit multiple sclerosis progression [59]. miR-21 restricts the autocrine inhibitory effects of IL2 through the enhanced the tumor growth factor-β signaling pathway, therefore promoted Th17 differentiation and mediated multiple sclerosis [60].

CONCLUSION

The recognition of different epigenetic modifications may inspire explorations of more uncharacterized mechanisms. Emerging studies bring us more new insights about how environmental factors and epigenetic regulations are worked in CD4$^+$ T cell of certain autoimmune diseases [61]. Epigenetic tools highlight the importance of potential therapeutic application to target specific gene expression during the certain diseases progression [62], and we firmly believed that further researches will help form a crosstalk between the epigenome of T-cell development and new approaches to clinical therapies based on T cells.

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Conflicts of interest

There are no conflicts of interest.

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From microbiome to infectome in autoimmunity

Dimitrios P. Bogdanos and Lazaros I. Sakkas

Purpose of review
The current review discusses the *pros* and *cons* of the microbiome studies conducted in search of the association between microbiota and autoimmunity.

Recent findings
We focus on the role of infectome and autoinfectome as a bridge to link the findings of microbiome studies with those emerging from investigations of the role of specific viruses and antiviral responses as triggers of autoimmunity (through various mechanisms such as molecular mimicry). The 'usual suspects', such as herpetoviruses and *Escherichia coli*, are thoroughly discussed in light of the data emerged by the microbiome studies, using as examples specific autoimmune rheumatic diseases and inflammatory bowel diseases.

Summary
We conclude that the studies of the oral cavity, gastrointestinal, and urinary tract microbiome are informative but can only be useful if further explored from the infectome perspective. This means that the plethora of bacteria associated with autoimmune diseases from microbiome studies can be and must be tested experimentally. If certain bacteria are associated directly or indirectly with autoimmune diseases, specific immunological mechanisms must be identified.

Keywords
autoantibody, infection, microbe, mimicry, virus

INTRODUCTION

Infectious agents have been regarded as likely initiators of autoimmunity responsible for the development of most, if not all, autoimmune disorders, including autoimmune rheumatic diseases [1]. Work on monozygotic twins reporting low concordance rates for autoimmune diseases gave great support to the idea that 'autoimmune diseases are infectious until proven otherwise' [2▪] and that gene and sex are probably less important than that of the infectious environment we are exposed to throughout lifetime [3]. Data originated from epidemiological, microbiological, virological, and immunological studies in humans [4▪,5▪], as well as findings from experimental autoimmune diseases, gave great support to the hypothesis of a microbial origin of autoimmunity [6▪▪].

The developments in technology allowing multiplex testing of dozen or even hundreds of microbes in one go and the study of the microbiome in the gut, urinary tract, and oral cavity have given us the opportunity to investigate the role of microbes as a 'fishing expedition' rather than a 'hypothesis-driven' microbe-specific manner [7]. Studies on the microbiome and how interacts with (or is influenced by) organ systems, such as those investigating the gut (microbe)–brain axis, reveal a critical role for the microbiota (mainly that of gut) in orchestrating organ development and system behavior [8]. They also reveal the striking role of the immune system as the regulator of the complex microbial–host interactions [9▪,10▪]. For example, we now know that microbial metabolites of dietary tryptofan modulate astrocyte activity and central nervous system inflammation via the aryl hydrocarbon receptor in severe experimental autoimmune encephalomyelitis, the animal model of multiple sclerosis [11▪]. We also know that a single acute infection caused by *Yersinia pseudotuberculosis* can lead to what is considered a 'long-lived immunological scarring'; signals derived from the microbiota maintain

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KEY POINTS

- Microbiome studies reveal association of autoimmune diseases with commensal bacteria previously unnoticed which need further investigation.
- Infectome studies investigating one or few infectious triggers can provide important information, but they lack the wealth of data provided by the microbiome studies.
- Microbiome and infectome studies specifically designed to investigate the role of microbial-induced immune responses against self antigens are urgently needed.

inflammatory mesentery remodeling and may participate in tissue destruction in autoimmune diseases, such as celiac diseases and Crohn's disease (CrD) [12]. We now have expression profiles of genes and microbes in individuals with autoimmune diseases and their unaffected first-degree relatives, including unaffected monozygotic twins, to study autoimmunity [13].

Few years back, we introduced the concept of infectome and autoinfectome [14,15,16▪]. The conceptual problem that we brought in to the attention of investigators was a profound one. Is it enough to know the gut microbiome of a very early systemic sclerosis (SSc) patient or do we need to go back several years before the onset of clinical autoimmune disease to witness the emergence of autoimmunity, even in the form of autoantibody production [17]? In most cases, it is the immune response (cellular or humoral) against the microbe that is responsible for breaking the tolerance in susceptible individuals [16▪]. At present, and in contrast to infectome/autoinfectome investigations, we cannot get such information from the study of the microbiome. For example, insights into the complex interactions between the virus and host can be gained when serial measurements from peripheral blood mononuclear cells or tissues collected in a prospective manner are performed. Work on acute infections, especially those strongly linked with autoimmune diseases, such as Epstein–Barr virus (EBV), cytomegalovirus (CMV), and hepatitis C virus (HCV) may help us not only to understand how these infections resolve but also how they cause autoimmunity. Studies on serial liver biopsies from chimpanzees investigating the dynamics of resolution of acute HCV infection demonstrated the important role of the early transient upregulation of interferon-stimulated genes in animals with sharp decrease of viremia; similar results underlining the role of those genes have also been obtained in lethal infection of macaques with the 1918 influenza virus [18]. The dynamics of virus–host interactions could help us in the investigation of autoimmunity, as interferon-stimulated genes are closely linked with the induction of several autoimmune diseases, exemplified in Sjögren's syndrome (SjS) [19].

FROM MICROBIOME TO INFECTOME: THE CASE OF INFECTIOUS MONONUCLEOSIS

Dunmire *et al.* [20] studied the viral and immunologic dynamics during the lengthy incubation period of primary EBV infection and found that despite an oral transmission mode, viral genomes were not detected in the oral cavity in significant quantities until patients had been infected for 5–6 weeks, that is, 1 week before symptoms onset. Significantly, viral genomes, though at low levels, were detected in the blood approximately 3 weeks before symptomatology reaching the highest blood levels at the time of symptom onset and coinciding with or just after the increased viral detection in the oral cavity. B cells were the major reservoir of EBV in the oral cavity prior to the onset of infectious mononucleosis. This very first report of the hierarchy of events during the incubation period of natural EBV infection in humans has also provided valuable data that could link EBV with autoimmunity. For example, a two-fold decrease of regulatory T cells was only seen after symptoms onset. Also, an inverse correlation between Tregs during acute infection and disease severity was also found [20]. These findings resemble those reported in infected mice.

Of relevance, a recent longitudinal prospective birth cohort study of children followed until 10 years of age investigating the interaction between commensal microbiota and viral exposure to EBV and CMV has shown that early *Staphylococcus aureus* colonization of the gut decreased the time to CMV acquisition [21] that may fit with data demonstrating an increased risk of allergy in infants who were CMV-infected but EBV-naive. The impact of microbiota on viral infection is not new. Seminal early studies conducted 50 years ago have shown that germ-free mice exhibit enhance susceptibility to coxsackie A and influenza A, underlining the direct effect of gut microbiota. Defensins, specialized antimicrobial peptides produced by host's immune cells in response to microbiota, have the ability to inhibit adenovirus replication *in vitro* [22], whereas lipopolysaccharide, a component of Gram-negative bacteria, can enhance viral replication. The effect of microbiota in viral persistence is relevant to viral-induced autoimmune diseases.

Epstein–Barr virus and systemic lupus erythematosus

Systemic lupus erythematosus (SLE) patients have many autoantibodies most frequently directed against nuclear antigens, such as double stranded DNA (dsDNA), Smith, Ro antigen (Ro), and so on. EBV, a dsDNA virus, is usually acquired silently during childhood and is carried throughout life in memory B cells as an asymptomatic infection. However, this delicate balance can be disturbed, and EBV may infect other cells, such B cells, epithelial cells, T cells, fibroblasts, and so on.

SLE patients harbor activated EBV. Levels of IgM (reflecting acute activation), IgA (reflecting reactivation), and IgG antibody against early lytic EBV antigen, early antigen diffuse, were increased in SLE patients [23,24]. EBV latent membrane protein 1 (EBV-LMP1) and EBV-encoded RNA 1 (EBER1) were frequently detected in lupus nephritis (LN) kidney biopsies in adults [25▪]. Furthermore, EBV-LMP1 expression in LN kidney biopsies from children was positively correlated with classification of LN [26]. EBV-LMP2A mimics B cell antigen receptor signaling in murine germinal center B cells and causes anti-dsDNA and anticardiolipin autoantibodies and immune complex, SLE-like, and glomerulonephritis [27▪].

EBV can break immunological tolerance in SLE by molecular mimicry, as discussed elsewhere [1]. A dominant 60 kDa Ro (Ro60) epitope cross-reacts with a peptide from EBV nuclear antigen1 (EBNA1). Furthermore, animals immunized with the dominant Ro60 epitope or the cross-reactive EBNA1 epitope develop autoantibodies against Ro60 and other autoantigens, and lupus manifestations. Similarly, EBNA1 contains a region with homology to Smith-B, and rabbits or mice immunized with the EBNA1 fragment containing this region-induced autoantibody production and leukopenia.

Epstein–Barr virus and Sjogren's syndrome

SjS is characterized by epithelitis of exocrine glands, mostly salivary and lacrimal glands, and autoantibodies, mainly anti-Ro. There are infiltration minor salivary glands with B and T cells that many times take the form of ectopic lymphoid, follicle-like, structures (ELS). A sizable proportion of SjS patients develop monoclonal gammopathy that evolves into lymphoma. Because of this, EBV has been for years considered a likely initiator of the disease. Type I interferon signaling is detected in SjS, and dsRNA through Toll-like receptor 3 activates type I IFN signaling [28]. High levels of antibodies against EBV early antigen, indicative of lytic EBV infection, were detected in SjS. Latent EBV infection in B cells and lytic EBV infection in plasma cells were detected ELS of salivary glands from patients with SjS. Furthermore, perifollicular plasma cells producing anti-Ro52 antibodies were frequently infected with EBV [29▪], and ELS-containing SjS salivary glands transplanted onto severe combined immunodeficiency mice produced anti-Ro52 and anti-EBV antibodies [29▪].

Epstein–Barr virus and anticitrullinated peptide antibodies in rheumatoid arthritis

Anticitrullinated peptide antibodies (ACPAs) are key autoantibodies with high specificity for rheumatoid arthritis (RA), account for the RA association with the histocompatibility complex, class II, DR beta 1 shared epitope and considered important for the pathogenesis of the disease, including the relevance of the microbiome in their development [7,30▪]. ACPAs recognized various proteins that have been posttranslationally modified at the arginine residue into citrulline by peptidyl arginine deiminase: vimentin, α-enolase, filaggrin, fibrinogen, histone, and so on. ACPAs are detected up to 14 years before the onset of clinical RA and whereas in the preclinical phase of RA recognize a limited number of citrullinated antigens, their antigenic specificities increase near the clinical disease onset. ACPAs against viral citrullinated peptide (VCP) derived from EBNA1 (VCP1) and EBNA2 (VCP2) are also detected in RA patients [31], even years before clinical disease onset [32]. Furthermore, anti-VCP1 abs cross-react with filaggrin citrullinated peptides and citrullinated fibrinogen [31].

Although no inciting citrullinated antigen common to all RA patients has been so far identified, it is plausible that EBV may be an initiator of ACPAs. EBV latent and lytic infection antigens were detected in ELS-containing RA synovial membrane B cells and plasma cells and a large proportion of ACPA-producing plasma cells were infected with EBV [29▪].

Cytomegalovirus and systemic sclerosis

SSc is a complex disease characterized by microvasculopathy (with endothelial cell injury and obliterative changes), extensive extracellular matrix deposition, and many autoantibodies and occurs in individuals with impaired regulatory mechanisms [33▪]. Endothelial cell apoptosis is the earliest skin event detected in avian and human scleroderma, and this may be caused by molecular mimicry. The strongest data supporting an infectious agent as involved in SSc holds for human CMV. Human CMV is associated with increased risk of

graft-versus-host disease, a model for SSc, and microvasculopathy of graft rejection. The majority of SSc patients have antibodies against human CMV late protein UL94, and the UL94 epitope shares homology with NAG-2, a tetraspan novel antigen-2 present on endothelial cells. Anti-UL94 abs from SSc patients bind to endothelial cells and induce apoptosis [34▪]. NAG-2 is also expressed on dermal fibroblasts, and anti-UL94 abs binding to fibroblasts induces a profibrotic phenotype. Also, topoisomerase I amino acid 121–126, within the epitope recognized by anti-Topo I monoclonal antibodies from SSc patients and tight skin mice (a model for SSc), shares five sequential aminoacid homology with human CMV late protein UL70 [35]. Of interest, neither UL57 nor UL83 CMV proteins are targets of cross-reactive antibodies involving SSc-related autoantigens [36,37].

Murine CMV can cause microvasculopathy in immunocompromised animals with no functional IFNγ receptor, as murine CMV infection in IFNγR−/− after whole-body irradiation develop neointima formation with myofibroblast proliferation in small vessels. AIM2 inflammasome, a sensor of cytosolic bacterial and viral DNA [38], is activated in SSc skin fibroblasts and can contribute to collagen production, as inhibition of caspase abrogated collagen production [39].

From gut microbiome to infectome in inflammatory bowel diseases: lessons to learn from *E. coli*

Inflammatory bowel diseases (IBD) are autoimmune diseases of the gastrointestinal tract. Two main forms of IBD have been acknowledged with distinct clinical, endoscopic, histopathological, and immunological features, namely CrD and ulcerative colitis (UC). Several authors have noted an increased prevalence of the IBD, and in particular CrD, in Western countries or in developed and developing countries with a radical dietary shift from traditional patterns to a Western diet high in fat and sugar [40].

A notable feature of CrD, distinct from UC, is the presence at high titers of the so-called pancreatic autoantibodies mainly targeting glycoprotein 2 (GP2), a heavily glycosylated protein with N-linked carbohydrates, which accounts for approximately half of the zymogen granule membrane proteins in acinar cells. Our group has shown that anti-GP2 antibodies characterize CrD patients with more extensive disease, and these data have been confirmed by subsequent independent studies [41,42].

The suggested pathogenetic link between Western diet, adherent-invasive *Escherichia coli* (AIEC), and CrD's induction has started to unfold following the understanding of GP2's pathophysiological role [43]. Western diet promotes the emergence of *E. coli* associated with the ileal, cecal, and colonic mucosa [44]. Amongst the pathogenic groups of *E. coli*, the AIEC group is largely influenced by Western diet as dysbiotic microbiota acquired after consumption of high-fat/high-sugar diet favors colonization by AIEC. This finding gains pathogenic connotations as GP2 is not only a component of the pancreatic fluid, but also a receptor on microfold cells (M) of intestinal Peyer's patches, which are believed to represent the first site of inflammation during CrD development. Of direct relevance, GP2 is one, if not the only receptor, of type I piliated enterobacteria (such as AIEC and *Salmonella enterica*) which contain the adhensin FimH expressed on the outer membrane of the bacterium. *E. coli* uptake is absent in GP2-deficient mice.

CONCLUSION

Studies of microbiome in autoimmunity will provide the impetus for future studies investigating the role of specific commensal bacteria that have never been linked before with specific autoimmune disease. Infectome studies must take into account the data stemming from the studies of the microbiome, as such investigations may explain how immune responses against some exogenous agents, especially viruses are playing a role in breaking tolerance to key autoantigens.

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Conflicts of interest

There are no conflicts of interest.

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The gut microbiota: a possible factor influencing systemic lupus erythematosus

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Purpose of review
Systemic lupus erythematosus (SLE) is an autoimmune disease of unknown cause. In recent years, with the emergence of microbiome research, changes in the gut microbiota composition have been correlated with a variety of autoimmune disorders, and several mechanisms linking these together have been suggested, including the hygiene theory, immune system activation and hormonal effects. It has therefore been suggested that gut microbiota may play a role in SLE. In this review, we summarize recent findings on the SLE-related microbiota compositions in both humans and rodents. Evidence linking microbiome with SLE opens a new avenue in researching the cause of SLE as well as improved future treatments.

Recent findings
Although two studies found a lower Firmicutes/Bacteroidetes ratio in SLE patients vs. controls, there were inconsistencies regarding significant differences in the abundance of specific genera or species. Studies of mouse disease models have shown some correlations between microbial compositions and disease states, also indicating differences between males and females.

Summary
Current data support an association between microbiota composition and SLE. Further research is needed to fully unravel this connection, potentially shedding light on mechanisms in SLE development and on the female bias of the disease, improving diagnosis and treatment.

Keywords
autoimmunity, bacteria, microbiota, systemic lupus erythematosus

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease affecting multiple tissues, and causing renal disease, joint pain, muscle pain, fever, fatigue, poor circulation, loss of appetite, inflammation and other symptoms. One of the unique features of SLE is the generation of self-antigen/antibody complexes including antinuclear antibodies, which promote inflammation. The age-range at diagnosis is 15–45 years, although the disease can appear at earlier or later ages. Unfortunately, treatment of lupus remains challenging. The most commonly used treatments are similar to those used in other autoimmune diseases, mainly corticosteroids and other immunosuppressants. Other treatments include NSAIDs, hydroxychloroquine (best known as an antimalarial treatment) and methotrexate. These are all aimed at modulating the immune system.

Although the cause of SLE remains unclear, it is thought to involve hormonal, environmental [e.g. drug exposure and ultraviolet (UV)-light] and genetic causes. However, in recent years, the gut microbiota has been suggested as another important factor. The gut microbial communities were shown to play important roles in health and disease. A healthy gut microbiota is essential for host metabolism, education and development of the immune system, hormone secretion and digestion [1▪]. Dysbiosis, a shift in the microbial composition, has been correlated with a large number of disease states, including autoimmune disorders such as inflammatory bowel disease (IBD), type 1 diabetes (T1D), multiple sclerosis (MS) and rheumatoid arthritis (RA) [1▪]. Although dysbiosis is associated with disease, it is not always clear whether it is an actual cause of disease development, or rather a symptom of the disease. In some cases, faecal transplants to

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KEY POINTS

- Gut microbial composition is altered in SLE vs. healthy controls.
- Mouse lupus models exhibit an altered microbiome vs. controls, with differences between males and females.
- Additional research is needed to link the specific immune, hormonal and microbiome changes that occur in lupus.

germ-free animals can be used to prove that the microbiota transfers disease phenotypes, such as in the cases of inflammation and weight gain. The gut microbiota is highly influenced by diet, environmental exposures, use of antibiotics and probiotics. Therefore, a better understanding of the desired microbial populations or the precise alterations related to disease may yield enhanced treatments based on probiotics or diet.

We believe that unravelling the microbial compositions, and the potential roles of these microorganisms, in autoimmune diseases in general and SLE in particular, may shed light on the cause and disease progression, and may even lead to diagnostic biomarkers. However, few studies to date have characterized the microbiota compositions in SLE. Here, we summarize these initial studies in patients and in animal models, and describe possible connections between SLE and microbiota composition.

THE MICROBIOTA COMPOSITION IN SYSTEMIC LUPUS ERYTHEMATOSUS

To date, the cause of lupus, the connection between various risk factors and potential pathways explaining cause are all unclear. It is therefore not surprising that in recent years, there have been attempts to decipher the microbial profiles correlated with SLE, as these may lead to a better understanding of the disease.

Several recent studies have characterized gut microbiota dysbiosis in SLE patients in remission vs. healthy controls. In the first study, which included a Spanish population consisting of 20 females per group, a lower Firmicutes/Bacteroidetes ratio was observed in the SLE group, as well as a reduction in abundance of some families in the Firmicutes phylum [2]. Such alterations have been shown for other disease states such as type 2 diabetes (T2D) and Crohn's disease [3], and are therefore not specific for lupus but may indicate a general imbalanced state [4]. In terms of total levels of faecal bacteria, as well as abundance of each phylum separately, no significant differences were found. Similar research on the gut microbiota compositions of 45 Chinese SLE patients was consistent with the above results, exhibiting lower Firmicutes and higher Bacteroidetes than healthy controls [5▪▪]. Furthermore, abundance of several genera was significantly different in SLE patients vs. control: *Rhodococcus, Eggerthella, Klebsiella, Prevotella, Eubacterium* and *Flavonifractor* were significantly enriched, while *Dialister* and *Pseudobutyrivibrio* were significantly decreased in SLE patients. In a third study comparing the gut microbiota in 83 SLE patients vs. 16 controls, significant alterations were detected, which included lower species diversity in the SLE group, higher abundance of Proteobacteria and lower abundance of Firmicutes, than the control group. These patterns were seen both in untreated patients, and those receiving medication. The species *Prevotella copri* was more abundant in the SLE group [6▪]. Finally, in a faecal metabolomic study, a reduction in metabolites associated with purine, pyrimidine and amino acid metabolism was found [7].

To date, no study has analysed potential changes in the microbiota of SLE patients specifically during active disease (flares), or compared the microbial profiles in SLE patients during active disease vs. remission. Although this is somewhat difficult technically, as most patients receive medication during active disease, which may alter the microbiota and skew results, it could be of great interest to test whether in fact there are specific microbial fingerprints associated with the active disease state.

THE MICROBIOTA OF MURINE LUPUS MODELS

Some research has been performed on the microbial communities in murine lupus models. When studying germ-free mice in the New-Zealand Black (NZB) lupus-prone model, lower rates and severity of renal disease were found, thereby indicating milder disease symptoms in the germ-free mice. In addition, higher levels of serum antinuclear factor were observed, indicating that these immune complexes still form, but suggesting reduced deposition of these complexes in the kidney [8]. In contrast, no clinical differences were observed between germ-free and conventional mice in the MRL/lpr lupus model [9]. Only when the germ-free MRL/lpr mice were fed an ultrafiltered antigen-free diet, were clinical improvements seen, as manifested by reduced nephritis and smaller lymph node cells, although no differences were seen in levels of autoantibodies. Due to these contrasting results, the role

of microbiota in disease development in mice remains unclear.

Zhang *et al.* [10] reported that in an MRL/Mp-Faslpr (MRL/lpr) model, abundance of lactobacilli decreased, abundance of Lachnospiraceae increased and the overall diversity increased in female lupus-prone mice as compared with controls. Higher levels of Lachnospiraceae and Clostridiaceae were observed at specific timepoints in lupus progression. In addition, differences were found in bacterial composition between males and females in the lupus-prone model. Increased levels of Lachnospiraceae in females were associated with earlier onset and more severe symptoms. Interestingly, when retinoic acid (vitamin A) was given to female lupus-prone mice, lactobacilli levels returned to normal levels, and an improvement in clinical symptoms was seen [10]. This may not be surprising, as vitamin A has been previously shown to both modulate immune host responses and modify the microbial composition [11]. Furthermore, when *Lactobacillus reuteri* was given to mice representing two spontaneous models of lupus (B6Sle.123 and NZBx NZW F1), the probiotic treatment prevented lupus development, increased survival and increased levels of Tregs [12]. A second mouse model of lupus-prone SNF1 mice showed that a more severe disease was correlated with higher levels of Bacteroidetes; however, no disease-associated signatures were observed [13▪].

SEVERAL PATHWAYS MAY LINK THE MICROBIOTA AND SYSTEMIC LUPUS ERYTHEMATOSUS

As with other autoimmune diseases, the hygiene hypothesis may explain the increase in SLE disease frequency in the past century. The hygiene hypothesis postulates that due to advances in medicine and increased hygiene (especially in the western world), we are significantly less exposed to microorganisms and parasites. This reduced exposure leads to an underutilized immune system that no longer needs to fight as many infections, thereby increasing self-attacks, and raising rates of allergies and autoimmune disease. This model is consistent with the observation that the frequency of SLE has risen dramatically in the past century, especially in western countries, and that SLE frequency is much lower in West Africa than in Africans living in Europe or the USA [14▪▪]. The hygiene hypothesis has led to treatments for autoimmune disorders using parasites, such as helminths. Helminths and their derivatives have shown to be effective for other autoimmune disorders such as IBD, T1D, MS and RA [15]. In a mouse model of SLE (NZB/NZWXF1), when the effects of a *Toxoplasma gondii* parasitic infection were tested, milder renal symptoms and prolonged life span were observed, as well as lower levels of interleukin (IL)-10 and the pro-inflammatory cytokine, interferon gamma [16]. This is consistent with a study that showed protection against kidney disease by a parasitic worm-derived immunomodulator (glycoprotein ES-62) in a model of SLE [17]. Therefore, parasite-derived treatments aimed at modulating the immune system may be promising for SLE, and should be tested in future studies. On the contrary, it has been reported that schistosomiasis in mice can lead to the production of antinuclear antibodies, promoting SLE. Thus, additional research is required to understand the role of allergens and immunogens in autoimmune disease [18].

One of the major features of SLE is T-cell activation, which promotes the formation of self-antigen/antibody complexes. It was proposed that microbiota may influence this T cell activation through molecular mimicry. This was demonstrated using a synthetic protein derived from *Capnocytophaga ochracea* (an oral microbe), which was able to activate Ro60-reactive T cells. Ro60 was chosen for study, as autoantibodies against Ro60 are present in lupus patients [19].

Finally, the microbial populations may affect levels of host hormones, playing a role in disease, as well. As in many other autoimmune diseases, lupus is much more common in women of childbearing age vs. men, suggesting a role of sex hormones in the disease. It has already been shown that the female hormone oestrogen can exacerbate disease [20], and it remains to be discovered whether testosterone plays a protective role in males. In other autoimmune disease states, such as T1D, it was shown that testosterone indeed has a protective effect [21] and that this role is mediated by the microbiota [22]. This raises the possibility that microbiota may be involved in the sex bias in SLE, as well. Differences in the gut microbial compositions between female and male mice in the BWF1 lupus model have also been described. In this model, females develop disease early in life, while males are protected or develop disease at a more advanced age. The clinical sexual difference is mediated by hormones, as castrated males develop early disease in a manner similar to females. Importantly, when female BWF1 mice were fed with faeces from male BWF1 mice, the resulting faecal transplant dramatically improved survival, mitigated renal symptoms and reduced anti-dsDNA antibody production [23]. These results reinforce the role of microbiota in the sexual bias of SLE disease development, although they are probably not the only

factor. Studies have shown that there are X-linked immune-related genes that also contribute to higher disease susceptibility in females. Expression of Toll-like receptor genes, specifically *TLR8*, from both copies of the X chromosome in females increases the formation of the SLE-related IgG autoantibodies, as well as increasing IFN-α levels [24▪].

CONCLUSION

Data available to date support an interconnection between the microbiota composition and SLE. However, given some inconsistencies in the results of human studies, more research is needed to fully unravel this connection. In addition, observation of the microbial communities during disease flares as opposed to regression may elucidate the specific changes in the microbiota related to SLE. Understanding the pathways through which the microbiota impacts the disease state, most likely via hormones and the immune system, may help in the future development of treatments, including diet-based and probiotic interventions.

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Conflicts of interest

There are no conflicts of interests.

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Vitamin D and rheumatoid arthritis: an ongoing mystery

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Purpose of review
In recent years, there has been a growing interest in the value of vitamin D and its effects on autoimmunity. The aim of this review is to summarize the current knowledge on the association between vitamin D and rheumatoid arthritis (RA) in terms of prevalence, disease activity, clinical expression, serology and gene polymorphisms of vitamin D receptors.

Recent findings
Studies have shown contrasting findings concerning the association between vitamin D levels and RA. Vitamin D seems to have immunomodulatory properties. Therefore, low vitamin D levels could contribute to increased immune activation. However, the potential role of vitamin D supplementation in preventing RA manifestation and its beneficial role as a component of RA treatment remain controversial. The relationship between RA susceptibility and vitamin D polymorphisms is also unclear.

Summary
Despite advancements synthesized by some recent meta-analyses, the relationship between vitamin D and RA requires further evaluation. Further research is needed to confirm the relationship between RA susceptibility and vitamin D polymorphisms and to determine whether vitamin D plays a role in preventing the manifestation of RA. Finally, additional studies are required to determine the impact and optimal amount of vitamin D supplementation in the treatment of RA patients.

Keywords
autoimmunity, gene polymorphism, immunomodulation, rheumatoid arthritis, vitamin D

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic inflammation involving the joints, synovial membrane, and occasionally, extra-articular organs. RA prevalence ranges from 0.4 to 1.3% worldwide [1,2], increasing with age and being more common among women [3,4]. RA causes a high disability rate and may lead to premature death [5]. Inflammatory arthritis which has a substantial socioeconomic burden is mostly caused by RA [6]. Still, the cause of RA has yet to be elucidated.

Recently, vitamin D has been shown to possibly serve as a therapeutic agent in RA patients [7]. Infection and autoimmune responses play a main role in RA development and progression, as well as genetic and environmental factors [8]. Antibodies to citrullinated peptide antigens [9,10] activate Th-1 cells and stimulate secretion of interleukin (IL)-1, IL-6 and tumor necrosis factor (TNF)-α [11,12], which serve as mediators of the continuous activation process of B cells [11–13]. As such, therapies like anti-TNF-α agents can decrease bone and cartilage damage by cell-specific targeting of cytokine activity [14].

Vitamin D can decrease IL-17, IL-6, IL-1 and TNF-α production inhibiting Th1 cells, as well as the release of IL-2 and interferon γ by $CD4^+$ cells,

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KEY POINTS

- From a biological standpoint, it has been hypothesized that vitamin D could have immunomodulatory properties and that, as such, low vitamin D levels could contribute to increased immune activation, thus playing a role in RA pathogenesis.
- Studies have shown contrasting findings concerning the association between vitamin D levels and RA, both in terms of the potential impact of vitamin D supplementation on RA and the relationship between RA susceptibility and vitamin D polymorphisms.
- Further research is needed to confirm the relationship between RA susceptibility and vitamin D polymorphisms and to determine whether vitamin D plays a role in preventing the manifestation of RA.

implicated in the etiopathogenesis of RA [15,16]. Vitamin D may also inhibit the proliferation of B cells and induce apoptosis, leading to reduced autoantibody production due to decreased plasma cell production and immunoglobulin class switching [17]. Moreover, vitamin D decreases autoreactivity by modulating the proinflammatory and anti-inflammatory cytokines secreted by antigen-presenting cells (APCs) [18,19]. Polymorphisms of the vitamin D receptor (VDR) and 1-α-hydroxylase [20] genes can also confer susceptibility.

THE CORRELATION BETWEEN VITAMIN D AND RHEUMATOID ARTHRITIS

Several interventional studies have evaluated the relationship between vitamin D insufficiency and RA (Table 1) [7,11,21–49]. Yang *et al.* [7] investigated the effect of vitamin D supplementation on RA, enrolling two groups of patients: one with sufficient vitamin D amount and one with vitamin D deficiency. The latter group was further divided into a subgroup receiving vitamin D treatment (α-calcidol, 0.25 μg twice/day) and one under no pharmacological treatment. All groups were followed up for 2 years, and their visual analogue scale (VAS), as well as inflammatory biomarkers [C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)] and the number of painful and swollen joints were recorded every 2–3 months. No difference was found between the vitamin D insufficient subgroups. However, RA flare rate in the vitamin D sufficient group was lower compared with the vitamin D-deficient subgroup receiving no treatment.

Chandrashekara *et al.* [43] evaluated the use of vitamin D supplementation in 150 RA patients under disease-modifying antirheumatic drugs for at least 3 months. Disease activity score with the 28 Joints-CRP (DAS28-CRP) and vitamin D levels were measured. A total of 49% of patients showed a DAS28-CRP more than 2.6 and vitamin D levels less than 20 ng/ml, and therefore, received vitamin D supplement of 60 000 IU/week for 6 weeks, followed by 60 000 IU/month for a total duration of 12 weeks. A significant improvement in the mean DAS-28-CRP was found (3.68 at baseline versus 3.08 after vitamin D treatment). Vitamin D significantly increased from a mean of 10.05 to 57 ng/ml.

A meta-analysis by Song *et al.* [49], pooling together three cohort studies (215 757 participants and 874 incident RA cases) and eight studies (2885 RA patients and 1084 controls), showed a 24.2% lower risk of developing RA with higher vitamin D intake. Considering vitamin D uptake, the relative risk (RR) of suffering from RA was 0.76 [95% confidence interval (CI) 0.58–0.94], whereas considering vitamin D supplement intake, RR was 0.76 (95% CI 0.63–0.93).

Varenna *et al.* [42] assessed the relationship between vitamin D supplementation and age and bone density. More than one-half of the population was not taking supplements. However, among those taking supplementation, more than one-third were taking insufficient dosages (≤440 IU/day). Among those taking the recommended daily dose of at least 800 IU, approximately 30% were still unable to reach adequate vitamin D levels, probably because of a decreased sun exposure and/or to a higher health assessment questionnaire (HAQ) score.

Atwa *et al.* [22], recruiting 95 individuals (55 cases and 40 controls), found that 25(OH)D levels were significantly decreased in RA patients (15.45 ± 6.42 versus 24.55 ± 11.21 ng/ml).

The prevalence of vitamin D deficiency was evaluated in 1191 RA patients versus 1019 controls [32]. A total of 55% of the RA patients were not taking supplementation and, within this group, only 52% were vitamin D deficient, similarly to healthy controls. However, many RA patients who received supplementation still remained vitamin D deficient. In addition, vitamin D inversely correlated with disease activity and the Steinbrocker functional state. When adjusting vitamin D levels for BMI and sun exposure time, the negative association between disease activity and vitamin D levels remained significant.

A prospective cohort study [45] assessed the association between vitamin D and RA activity. Twenty-nine thousand three hundred and sixty-eight women without a history of RA, aged 55–69, were observed. Their diet included supplemental vitamin D usage. During the 11-year follow up,

Table 1. A comprehensive overview of the studies focusing on vitamin D and rheumatoid arthritis

Vitamin D and RA correlations								
Reference	**Study design**	**Year**	**No. of RA patients**	**VD deficiency in RA**	**No. of controls**	**VD deficiency in controls**	**Correlation with activity**	**Correlation with other factors**
Observational studies which found a correlation								
Abourazzak *et al.* [21]	Retrospective	2015	170	VD insufficiency and deficiency were 64.5 and 35.5% successively			VD inversely correlates with DAS28 ($P=0.009$), physical disability (HAQ) ($P=0.001$) and severity of the disease ($P<.001$)	
Atwa *et al.* [22]	Cross-sectional study	2013	55	15.45 ± 6.42 ng/ml	40	24.55 ± 11.21 ng/ml		Not correlated with TNF-α, CRP, ESR, DAS28 or PASI
Azzeh *et al.* [23]	Retrospective	2015	102				VD inversely correlates with DAS28 ($r=-0.277$, $P=0.014$)	VD < 12.3 ng/ml predicted high-disease activity, and VD > 17.9 ng/ml predicted low-disease activity
Baykal *et al.* [24]	Retrospective case–control	2012	55	90.9% of patients had VD <30 ng/ml; 72% of patients had VD <20 ng/ml	45		VD inversely related to incidence of RA. No association found between disease activity and VD	
Cutolo *et al.* [25]	Retrospective case–control	2006	64 Estonian 54 Italian	Winter 35.1 ± 1.9 Summer 46.4 ± 2.3; Italy 58.9 ± 5.4 65.2 ± 5.4 nmol/l	30 35	43.3 ± 2.6; summer 47.4 ± 3.1 54.5 ± 5.5, 68.9 ± 6.1	Much lower VD in north versus south both in RA patients and controls	VD inversely correlates to DAS28
Haque *et al.* [26]	Retrospective	2010	62	61% were VD deficient			VD inversely associated with DAS28 (0.38), pain (–0.49) and HAQ (–0.54)	
Higgins *et al.* [27]	Retrospective	2013	176	Mean VD level was 39.42 nmol/l			Negative relationship between VD and VAS (coefficient = 0.249, $P=0.013$)	No correlation between VD and DAS28
Kerr *et al.* [28]	Retrospective	2011	850	The VD insufficiency and deficiency were 84 and 43%, respectively				Men only mean age 64 in study
Kostoglou-Athanassiou *et al.* [29]	Cohort study	2008	44	VD level 15.26 ± 1.07 ng/ml	44	VD level 25.8 ± 1.6 ng/ml	VD deficiency highly prevalent in RA	
Kostoglou-Athanassiou *et al.* [29]	Retrospective case–control	2012	44	15.26 ± 1.07 ng/ml	44	25.8 ± 1.6 ng/ml	VD levels negatively correlated to the DAS28 score, with correlation coefficient being –0.084	Levels of VD negatively correlated to CRP and ESR
Moghim *et al.* [30]	Retrospective	2012	158 87 active 71 silent RA	The VD levels in patients with active RA were lower than in those with silent RA (49.38 ± 38.2 versus 64.64 ± 43.61 nmol/l; $P=0.022$)				
Oelzner *et al.* [31]	Retrospective	1998	96				VD negatively correlated to CRP	
Rossini *et al.* [32]	Retrospective case–control	2010	1191	52%	1019	58.7%	VD inversely correlated to disease activity and (DAS28)	33.3% of supplemented were still VD deficient
Raczkiewicz *et al.* [33]	Population-based study	2015	97	76.3% of patients			Negative correlation between VD levels and DAS28 score	

Table 1 (*Continued*)

Vitamin D and RA correlations								
Reference	**Study design**	**Year**	**No. of RA patients**	**VD deficiency in RA**	**No. of controls**	**VD deficiency in controls**	**Correlation with activity**	**Correlation with other factors**
Sabbagh *et al.* [34]	Retrospective case–control	2013	60	(64.8 ± 29.8)	56	(86.8 ± 37.7)	RA cases with low VD had higher risk of disease activity (OR = 5.15 95% CI 1.16, 22.9; $P = 0.031$)	
Turhanoğlu *et al.* [11]	Retrospective case–control	2011	65	104.87 § 60.08 nmol/l	40	105.72 § 38.06 nmol/l	VD negatively correlated with DAS28, CRP and HAQ (respectively, $r = -0.431$, $P = 0.000$, $r = -0.276$, $P = 0.026$ and $r = -0.267$, $P = 0.031$)	VD levels in patients not lower than the controls
Observational studies which did not find a correlation								
Baker *et al.* [35]	Retrospective	2012	499	48% VD <20 ng/ml			VD deficiency not associated with greater DAS28 [β–0.021 (95% CI– 0.22,0.18)]	
Braun-Moscovici *et al.* [36]	Retrospective	2011	121				No correlation between VD levels and DAS-28	
Craig *et al.* [37]	Retrospective	2010	266	50% had VD ≤37.5 nmol/l			VD deficiency is common in new-onset RA	VD does not correlate with severity of disease
Matsumoto *et al.* [38]	Retrospective case–control study	2015	208	16.9 ng/ml	205	19.5	Low VD correlates with RA but not disease activity	
Pakchotanon *et al.* [39]	Cross-sectional study	2013	239	28.79 ng/ml was the mean VD level			No association between VD and disease activity	
Quraishi *et al.* [40]	Retrospective	2013	45	VD levels were 20–30 ng/ml, <20 ng/ml in 36 and 29%, respectively			No association between VD and disease activity	
Sahebari *et al.* [41]	Retrospective case–control study	2014	99				No correlation between VD levels and DAS-28	
Varenna M *et al.* [42]	Retrospective	2012	1168	56% not taking VD supplements			VD deficiency is common even in those taking supplements	
Interventional Studies								
Reference	Study design	Year	No. of RA patients	Vitamin D deficiency in RA	No. of controls	VD deficiency in controls	Correlation with activity	Correlation with other factors
Interventional studies which found a correlation								
Chandrashekara *et al.* [43]	Nonrandomized	2015	150	73 (49%)			Supplementation of VD in RA patients contributed to significant improvement in disease activity	
Dehghan *et al.* [44]	Double blinded, randomized controlled trial study	2014	80 Allocated to placebo or VD treatment	All had a VD of < 30 ng/dl			A low VD level was not identified to be a risk factor for RA severity or flare ups	
Merlino *et al.* [45]	Prospective cohort study	2004	152 Women developed RA from a starting 29 368				VD negatively correlates with development of RA. RR of 0.67 Inverse association with supplements or diet high in VD	

Table 1 (*Continued*)

Vitamin D and RA correlations								
Reference	**Study design**	**Year**	**No. of RA patients**	**VD deficiency in RA**	**No. of controls**	**VD deficiency in controls**	**Correlation with activity**	**Correlation with other factors**
Yang *et al.* [7]	Randomized controlled trial	2015	377 patients split into normal VD group and VD-deficient group. Half of deficient group were treated with VD	192 (50.9%)	88	20.9±8.6	The flare of 16.7, 19.0 and 29.5% for the normal VD levels (n=168), VD-treated subgroup (n=84) and non-VD-treated subgroup (n=88), respectively	
Interventional studies which did not find a correlation								
Costenbader *et al.* [46]	Prospective cohort study	2008	*755*		121700		Diet high in VD and supplements does not influence the incidence of RA	
Salesi *et al.* [47]	Double blind trial	2012	117 50 cases remained in the VD group and 48 in control by the end of the study				VD supplement showed no significant improvement in efficacy outcomes compared with placebo	Both groups received MTX. Moderate/major response in VD group was 76/44% compared with 64.6/33.4% in placebo group
Systematic reviews and meta-analyses								
Lin *et al.* [48]	Meta-analysis of observational studies	2016	2148	VD in RA patients was 13.21 nmol/l less than that in controls	1991		VD compared with DAS28 was –0.13 25OHD was also inversely associated with CRP levels	
Song *et al.* [49]	Meta-analysis of interventional studies	2012	2885 from eight studies of association between RA and VD. three cohort studies with 215757 patients and 874 incident cases of RA		1084		Vitamin D levels are inversely associated with RA activity	Increased incidence of RA in VD-deficient patients

CRP, C-reactive protein; DAS-28, disease activity score 28 joints; def, deficiency; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; MTX, methotrexate; RA, rheumatoid arthritis; TNF, tumor necrosis factor; VD, vitamin D.

152 RA cases were confirmed. Analysis of vitamin D supplementation was stratified into three ranges: less than 221.4 IU/day, 221.4–467.6 IU/day and at least 467.7 IU/day. Higher vitamin D intake was inversely associated with RA risk. Conversely, Costenbader *et al.* [46] concluded that increased vitamin D intake (≥400 IU/day) was not associated with an increased RA risk. Other studies [29] have shown that lower vitamin D was associated with higher RA disease activity.

Although many studies have suggested possible association between low vitamin D and RA, others have shown no association (Table 1). Salesi and Farajzadegan [47] recruited RA patients with active disease under methotrexate therapy. Patients were allocated to a group receiving 50 000 IU/week of vitamin D or to the placebo group. No significant difference was demonstrated in terms of disease severity. Furthermore, no significant difference could be found between calcium, phosphorus and alkaline phosphatase levels between the two groups before and after intervention.

VITAMIN D AND RHEUMATOID ARTHRITIS ACTIVITY, FLARES AND REMISSION

Although some studies have shown that vitamin D deficiency may increase RA disease activity, flare rates and recurrence [21,24,43,50–53], other studies have shown no relationship [27,35,36,38–41,44] (Table 1).

A meta-analysis by Lin *et al.* [48] synthesized 24 studies, pooling together 3489 patients. Lower vitamin D levels were demonstrated in RA patients compared with controls [mean difference: −16.52 nmol/l (95%CI: −18.85 to −14.19 nmol/l)]. Negative associations were found between vitamin D levels and RA disease activity both in terms of DAS-28 [$r = -0.13$, (95% CI −0.16 to −0.09)] and CRP [$r = -0.12$, (95% CI −0.23 to 0.00)].

Another study [33] showed that low levels of vitamin D were more prevalent in RA patients and were associated with disease activity and worse quality of life.

Baykal *et al.* [24] recruited 55 RA patients and 45 controls. Significantly decreased vitamin D and increased parathyroid hormone levels were found in RA patients compared with controls. However, 25(OH)D levels did not correlate with RA disease activity (DAS-28, CRP and ESR).

A study [26] recruited 62 RA patients, 61% of which had deficient vitamin D levels. In those with active disease (DAS-28 ≥2.6), vitamin D levels were found to be significantly moderately and inversely associated with the DAS-28, pain and HAQ. However, such associations could not be found in patients in remission (DAS-28 <2.6). Vitamin D-deficient patients with active RA were six times more likely to be moderately or severely disabled (HAQ ≥1.25). Accordingly, vitamin D deficiency was more prevalent among RA patients and associated with higher DAS-28 scores, pain and disability.

Abourazzak *et al.* [21] evaluated 170 Moroccan patients. Vitamin D insufficiency and deficiency were found in 64.5 and 35.5% of patients, respectively. Vitamin D levels were inversely associated with the DAS-28, HAQ scores and disease severity. Another study [23] found a significant inverse correlation between serum 25(OH)D levels and DAS-28. Furthermore, vitamin D levels less than 12.3 ng/ml predicted high disease activity, whereas levels more than 17.9 ng/ml were associated with low disease activity. Turhanoğlu *et al.* [11] showed significantly decreased vitamin D levels alongside with increasing disease activity and decreasing functional capacity in 65 Turkish RA patients.

Cutolo *et al.* [25] found significantly lower vitamin D levels in RA patients from Northern versus Southern Europe. Vitamin D significantly negatively correlated with DAS-28. Another study [54] confirmed the role of vitamin D deficiency in autoimmune rheumatic disease, including both initial disease development and worsening of an existing disease. Kostoglou-Athanassiou *et al.* [29] found vitamin D deficiency to be more prevalent among RA patients. Another study [30] reported that vitamin D inversely correlated with RA disease activity. Another study [31] demonstrated acceleration of the arthritic process in RA possibly caused by decreased vitamin D levels. Significantly lower vitamin D levels were found in patients with active RA or poorly responding to treatment, with the highest Steinbrocker functional state. Similar results were obtained by Sabbagh *et al.* [34] as well.

Craig *et al.* [37] found that vitamin D insufficiency was more prevalent among African Americans with recent-onset RA. However, in multivariate analyses, no significant association was found between vitamin D levels and baseline pain, swollen joints and DAS-28.

A study of 499 participants [35] found no correlation between vitamin D and RA disease activity, vander Heidje-Sharp scores and inflammatory biomarkers. A double-blind randomized controlled study [44] conducted on 80 RA patients concluded that low levels of vitamin D were not a risk factor for RA disease activity or recurrence. Another study [41] of 99 patients found no correlation as well. Braun-Moscovici *et al.* [36] conducted a study of 121 patients, which showed no association between vitamin D levels and disease activity, duration,

treatment and type. However, there was a high incidence of vitamin D deficiency in patients with inflammatory joint disease.

Higgins *et al.* [27] investigated whether low levels of vitamin D affected the patients' perception of pain, measured by VAS, rather than the severity of the disease, measured by the disease activity score (DAS-28) as done in previous studies. The study showed a significant inverse association between vitamin D and VAS score, raising the possibility that the increased RA severity in vitamin D-deficient patients may be due to pain perception and not merely due to the disease itself.

A randomized double-blind placebo controlled study observed a synergistic effect of high vitamin D doses together with analgesics to provide better musculoskeletal pain relief [55]. However, another study [35] showed that vitamin D levels did not affect response to treatment.

VITAMIN D AND RHEUMATOID ARTHRITIS GENE POLYMORPHISMS

Vitamin D (calciferol) comprises fat-soluble secosterols (steroids containing a broken ring) with varying activity levels [56]. Vitamin D_3 (cholecalciferol) can be produced in the human skin from 7-dehydrocholesterol or can derive from animal-based foods. However, to become biologically active, vitamin D requires two enzymatic hydroxylation reactions, occurring in the liver and kidney, mediated by 25-hydroxylase and 1α-hydroxylase, respectively [57].

Vitamin D plays a main role in calcium homeostasis as a regulator of intestinal calcium absorption [58]. After entering a target cell and binding a nuclear receptor (VDR), the hormone–receptor complex binds to specific DNA sequences and influences transcription factors of effector genes [56,59]. VDR can be found in the brain, skeletal muscle, breasts, prostate, colon, skin and APCs [60–66]. This is not surprising as vitamin D plays a role in immune regulation [67–69] (Fig. 1), decreasing immune activity influencing immunoglobulin production by B cells, proliferation of T cells, cytokines release, cytotoxic effects of natural killer cells and cytotoxic T cells [70] (Fig. 1). Genes encoding VDR (chromosome 12) play an important role in the immune system regulation as well, with the Th-1 cells in particular [71]. A number of VDR mutations and deletions have been correlated with a variety of diseases, with more than 63 abnormalities

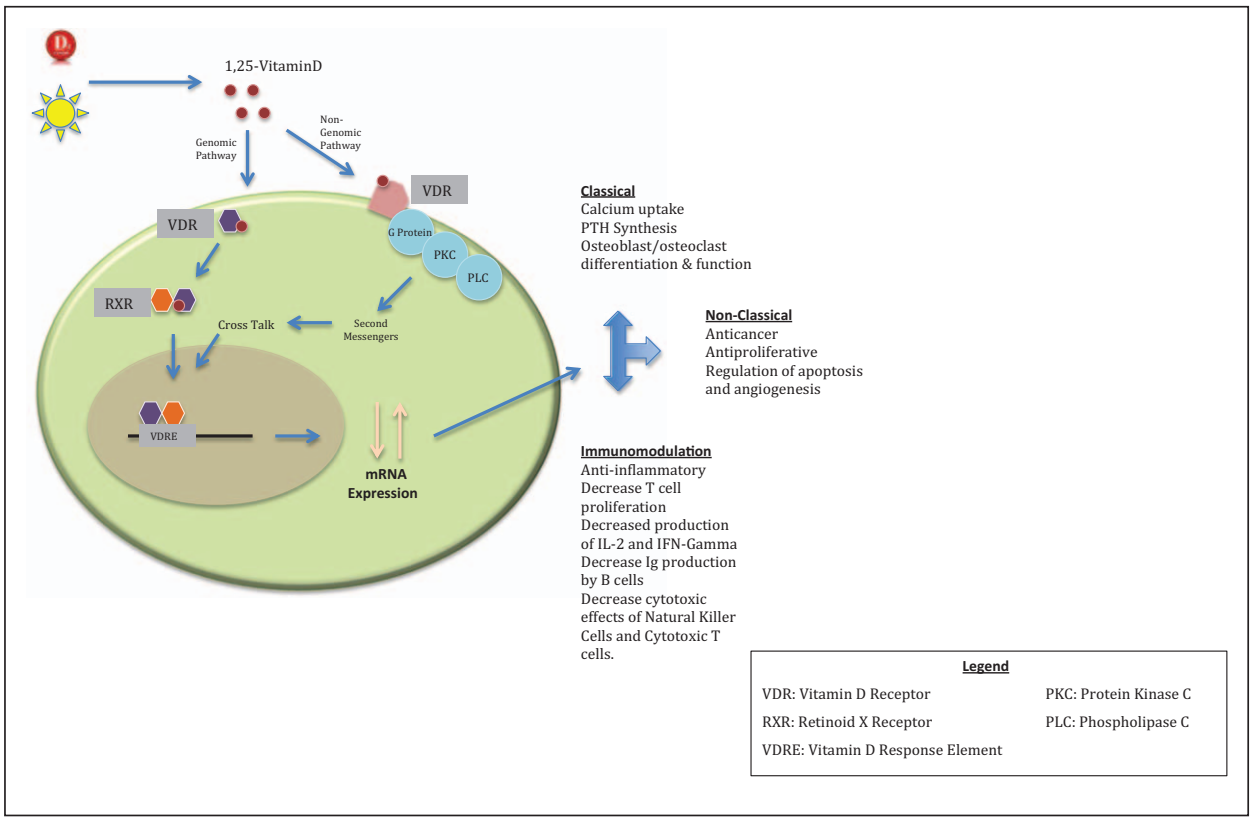

FIGURE 1. Vitamin D signal pathway. 1,25-vitamin D binds to its receptor (VDR) which dimerizes with the retinoid X receptor (RXR) to bind vitamin D response elements (VDRE) in target genes. This complex activate target genes that lead to diverse functions of the vitamin D.

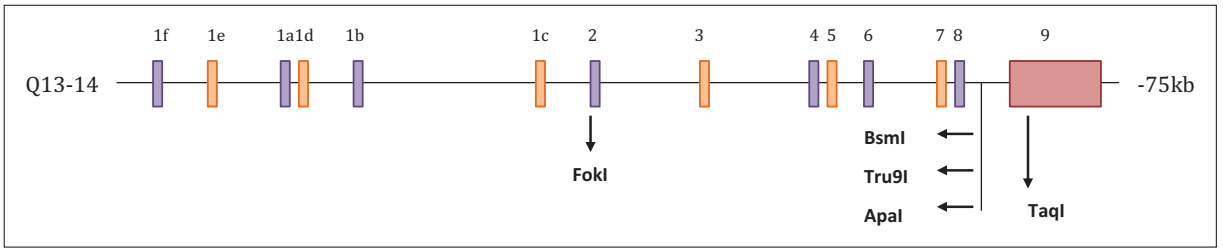

FIGURE 2. Chromosome 12q – VDR gene location and various polymorphisms.

discovered so far [72], which prevent VDR from binding the active form of vitamin D [73]. The most common mutations associated with RA include the FokI, BsmI, TaqI and ApaI genes [72] (Fig. 2).

However, many studies have reported conflicting results regarding the association of RA development and VDR (Table 2) [70,74–78,79▪,80,81,82▪,83▪▪]. A recent meta-analysis [82▪] found that FokI

Table 2. A comprehensive overview of the studies focusing on the relationship between vitamin D and rheumatoid arthritis gene polymorphisms

Vitamin D and RA gene polymorphisms							
Reference	**Study design**	**Year**	**RA patients**	**Controls**	**Association between RA and TaqI**	**Association between RA and FokI**	**Association between RA and BsmI**
Garcia-Lozano JR *et al.* [74]	Retrospective case–control	2001	82	200	Weak association between TaqI and RA		Absence of BsmI shows early form of RA
Gómez-Vaquero *et al.* [75]	Retrospective	2007					Among patients with RA, the bb genotype of the BsmI polymorphism of the VDR gene is associated with less severe disease
Hitchon *et al.* [76]	Retrospective case–control	2012	448	704		The Fok1 significantly associated with RA. Comparing patients with RA to unaffected NAN controls, the Fok1 was associated with RA using both genotypic	
Hussein *et al.* [77]	Retrospective case–control	2015	200	150			BsmI was found to not increase susceptibility to RA
Karray *et al.* [70]	Retrospective case–control	2012	131	152		RA group showed higher prevalence of FokI polymorphism alleles than in the controls ($P=0.001$ and $P=0.005$, respectively)	
Milchert *et al.* [78]	Retrospective case–control	2010	102	57			No significant correlation was found between BsmI VDR gene polymorphism and RA susceptibility or activity. BsmI polymorphism correlated only with RA functional status
Saad *et al.* [79▪]	Case–control	2015	105	80		No significant differences for FokI and the presence of RA disease	
Tizaoui K *et al.* [80]	Retrospective case–control	2014	106	153	No association reported between VDR ApaI and TaqI polymorphisms with RA risk ($P>0.05$)		
Systematic reviews and meta-analysis							
Lee *et al.* [81]	Meta-analysis of case–control studies	2011	851	1064		Association between the F allele and RA was 1.502 (95% CI = 1.158–1.949)	
Song *et al.* [82▪]	Meta-analysis of case–control studies	2015	923	912		Although VDR FokI polymorphism was not associated with RA and the F allele in the entire studied cohort (odds ratio = 1.1740, 95%), in Europeans it was associated with the risk of RA	
Tizaoui *et al.* [83▪▪]	Meta-analysis of case–control studies	2015	1703	2635	TaqI polymorphism significantly associated with RA disease in homozygous, codominant and allele contrast models	Significant association between FokI polymorphism and RA risk in the recessive, dominant and allele contrast models ($P=0.045$, $P=0.027$ and $P=0.013$, respectively)	Association between BsmI polymorphism and RA risk was marginal in the dominant, codominant and allele contrast models ($P=0.057$, $P=0.071$ and $P=0.069$, respectively)

CI, confidence interval; RA, rheumatoid arthritis; VD, vitamin D; VDR, vitamin D receptor.

polymorphism demonstrated no association between RA and the F allele. However, a significant association was found between the F allele and RA in European individuals. Conversely, no association was found between RA and VDR BsmI B allele and TaqI T allele polymorphisms in Europeans [82▪]. Another meta-analysis conducted by Tizaoui and Hamzaoui [83▪▪] found a significant association between TaqI polymorphism and RA disease in homozygous, codominant and allele contrast models. Marginal association was demonstrated between BsmI polymorphism and RA risk in the dominant, codominant and allele contrast models. However, significant association was found between FokI polymorphism and RA risk in the recessive, dominant and allele contrast models.

A meta-analysis by Lee *et al.* [81] found that VDR BsmI and TaqI polymorphisms had no association with RA in all individuals, either Europeans or Asians. Nevertheless, significant associations were demonstrated between the F allele, the FF genotype and the FF versus the ff genotype of the FokI polymorphism and the development of RA in Europeans. Additional studies [70,76] have found a significant relationship between the FokI polymorphism and RA.

Milchert [78] obtained no correlation between BsmI polymorphism and RA susceptibility; however, BsmI polymorphism correlated with RA activity and progression, a relationship confirmed by other studies as well [75,77]. In other studies, BsmI was again found to not increase RA susceptibility [70,84]. However, Garcia-Lozano *et al.* [74] found a weak association between the BB/tt genotype, defined by the BsmI and TaqI restriction site polymorphisms, and an early-onset RA in female patients. Another study [80] showed no association between TaqI, ApaI and RA. Cavalcanti *et al.* [85] examined five VDR single nucleotide polymorphisms and found that rs4760648 and rs3890733 were associated with RA susceptibility. An association between *TNFB*, BsmI, TaqI, *MTHFR* (C677T, A1298C), *TGFβ1* and ApaI polymorphisms and RA was demonstrated by a case–control study [79▪], which, conversely, identified no association between FokI and RA susceptibility.

CONCLUSION

Vitamin D plays an important role in immunomodulation. This occurs through different possible mechanisms including modification of cytokines and alteration in immune cells activation, proliferation and destruction [18]. Studies have identified decreased serum vitamin D levels in patients with RA and inverse association between vitamin D levels and RA disease activity, particularly in developing nations [41]. However, the potential role of vitamin D supplementation in preventing RA manifestation and its beneficial role as a component of RA treatment remain controversial. Adding vitamin D to the traditional RA pharmacological regimen has been found beneficial in many studies, whereas other studies have failed to replicate such finding. The relationship between RA susceptibility and vitamin D polymorphisms is also unclear.

As such, the relationship between vitamin D and RA requires further evaluation. Further research is needed to confirm the relationship between RA susceptibility and vitamin D polymorphisms and to determine whether vitamin D plays a role in preventing the manifestation of RA. Finally, additional studies are required to determine the impact and optimal amount of vitamin D supplementation in the treatment of RA patients.

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Conflicts of interest

The authors declare that they have no competing interests.

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- ▪ of special interest
- ▪▪ of outstanding interest

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Chikungunya virus and autoimmunity

Amir Tanay

Purpose of review
Chikungunya virus (CHIKV) is a mosquito-borne alphavirus. Fever, rash and severe arthralgia are the hallmarks of chikungunya fever (CHIKF), the disease caused by this virus. The acute course of the disease usually lasts few weeks to months. Chronic, relapsing or persistent arthralgia and arthritis have been described mimicking rheumatoid arthritis (RA), requiring immunosuppressive drugs.
The purpose of this review is to characterize both the chronic clinical course of CHIKF-associated arthritis and the immunological pathogenic mechanisms involved.

Recent findings
The effect of postepidemic chronic persistent rheumatic course on the functional status of affected individuals, affecting large populations, has been studied. One-third of affected individuals had persistent pain months to years postepidemic and the identified risk factors for functional disability were identified. Inflammatory biomarkers associated with disease severity of RA such as interleukin 6 (IL6), and relevant chemokines have been found to correlate with the severity of postepidemic chronic disease. There are conflicting reports on antinuclear antibodies (ANAs) as well as rheumatoid factor and anti-citrullinated peptide antibody (ACPA) sero-positivity during infections.
According to a recent study, eight out of 10 infected individuals developed chronic persistent rheumatic course and met classification criteria for seronegative RA.
In a flow cytology analyses, these eight patients, similar to a group of RA patients, had a greater percentage of activated and effector $CD4^+$ and $CD8^+$ T cells than healthy controls.

Summary
Patients with CHKV infections may have a chronic persistent course of musculoskeletal disease, overlapping clinical and immunologic features with RA patients. In the appropriate setting and awareness, CHIKV infection should be considered when a patient is evaluated with a new symmetric polyarthritis.
The question to be raised: Is it possible that in genetic prone individuals and in a particular environmental and infectious setting, such as CHIKF outbreak, an autoimmune disease will emerge?

Keywords
autoimmune disease, chikungunya virus infection, chronic persistent polyarthritis, rheumatoid arthritis

INTRODUCTION

Chikungunya fever (CHIKF) is a systemic viral disease characterized by fever, acute arthritis myalgia and rash. Acute symptoms can last for few weeks, but the articular symptoms and pain can persist for months and even years [1]. It is endemic in Africa and Southeast Asia where during the past 60 years several outbreaks and epidemics occurred [2,3▪]. Over the past 10 years, it has been reported also in the Caribbean region and the Americas [1]. Chikungunya virus, family Togoviridae, genus *alphavirus*, is a single-stranded RNA virus that is transmitted by mosquitoes in an epizootic cycle between small mammals, large mammals and humans [1]. The vectors *Aedes aegypti* (AAe) and *Aedes albopictus* (AAl) spread globally over the years contributing to the emergence of CHIKF outbreaks and epidemics in East Africa, southern and southeast Asia, spreading further to Central America [4]. In rural regions, the burden of chronic manifestations of the disease was reported in 36% of the CHIKF-affected individuals [5]. International travel contributes to the appearance of CHIKF among Western tourists, returning from popular sites infested by CHIKV and its vectors [6,7]. Recently, a chronic course of the musculoskeletal disease was reported in such patients in the United States, demonstrating biologic markers of inflammation and immune

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KEY POINTS

- Chikungunya fever emerges as a global vector borne disease, spreading globally with large outbreaks and a very high attack rate affecting millions of individuals.
- Fifty percent of individuals with Chikungunya fever may have a long-term arthralgia and arthritis.
- Chikungunya fever associated arthralgia and arthritis can mimic rheumatoid arthritis.
- Mild to moderate/severe disability is seen in most Chikungunya fever associated arthralgia and arthritis.
- Both the innate and adaptive immune systems are involved in the pathogenesis of the chronic rheumatic sequelae of Chikungunya fever.

activation not unlike those seen in autoimmune diseases such as rheumatoid arthritis (RA) [2].

In this review, the chronic persistent course of rheumatic sequelae will be characterized and its immunologic pathogenic mechanisms will be described.

DISABILITY AND PERSISTENT PAIN FOLLOWING CHIKUNGUNYA FEVER

A cross-sectional survey was performed in a large Indian rural population of 98 000, 18 months after the epidemic of 2008–2009. The investigators used Heath Assessment Questionnaire- Disability Index (HAQ-DI). Assessed were musculoskeletal complaints, functional disability and risk factors predicting severity of disability [3▪,4,5].

Out of a total of 3869 individuals interviewed, 1195 gave a positive history of CHICV infection (epidemiological or serologically confirmed). Of those, 48.65% had persistent pain 18 months after the epidemic. Mild disability was observed in most (60.6%) and 16.2% had moderate to severe disability. Of note was the fact that 53.5% of those with persistent pain were individuals with a history of a rheumatic musculoskeletal disorder (RMSD). Ten percent smoked. And 12.4 and 10.2% had hypertension and diabetes mellitus, respectively. The factors affecting the severity of the disability on the HAQ-DI and the respective odds ratios were female sex 1.44 [95% confidence interval (95% CI) 1.02–2.04]; previous RMSD 2.27 (95% CI 1.54–3.35); joints swelling in the acute stage 1.72 (95% CI 1.19–2.49); involvement in the persistent pain of: joints and soft tissue 3.74 (95% CI 2.21–6.34); joints only 2.14 (95% CI 1.27–3.61); vegetarian diet 4.73 (95% CI 2.03–10.99).

Several other reports from the same region showed similar findings of persistent pain and chronic course following the epidemic [5,6].

LATE SEQUELAE OF CHIKUNGUNYA FEVER MASQUERADING AS RHEUMATOID ARTHRITIS

Eight out of ten American travellers who were infected by CHICV while visiting Haiti in June 2014 developed persistent symmetric polyarthritis (lasting 4–5 months postinfection at the time of the study) who met the American College of Rheumatology/European League Against Rheumatism 2010 criteria for (seronegative) RA)ACR/EULAR-CR-RA) [2]. Cytometric analysis of peripheral blood mononuclear cells (PBMNCs) revealed that early untreated RA patients control group and the CHIKV-infected patients had greater percentages of activated and effector $CD4^+$ and $CD8^+$ T cells than healthy controls. The authors concluded that patients with persistent arthritis and patients with RA have not just clinical similarities but also resemble closely RA patients in the T cell phenotype. In an earlier study, Bouquillard and Combe [7] describe 21 new cases of RA following CHICF epidemic in the Indian Ocean islands. All fulfilled 1987 ACR-CR; Sixty one percent were women; The mean time to RA diagnosis was 10 months postepidemic (ranging 4–18 months); At 21 months, 81% had erosions and joint space narrowing; rheumatoid factor and anticitrullinated protein antibody (ACPA) were positive in 57 and 28%, respectively; HLA DRB1*04 or −*01 was found in 66%. The authors concluded that the outcome was severe. Most of the patients requiring Methotrexate and four patients had to be switched to TNF blockers. The authors suggested that viral infection had a role in the initiation of RA in these cases.

In another recent retrospective study from Colombia, a follow-up of 39 patients with CHICF was conducted for a period of 12 months, starting from their acute infection. The incidence rate of chronic inflammatory arthralgia was 89% [8].

IMMUNOPATHOGENIC MECHANISMS IN CHRONIC PERSISTENT CHIKUNGUNYA FEVER ASSOCIATED JOINT DISEASE

There is evidence of persistent CHIKV infection in humans suffering from chronic Arthralgia and arthritis, yet little is known about its pathogenesis [9].

In mouse models, CHIKV-RNA was detectable and seemed to persist in joint tissues for at least 16 weeks postinfection.

In RAG1−/− mice, which lack T and B cells, infection with CHICV resulted in increased viral burden in many tissues, compared with wild-type mice, suggesting that the adaptive immunity plays an important role in the persistence of CHIKV infection. Yet, at the same time, there was a histopathological evidence for synovitis and arthritis in both RAG1−/− and wild-type mice. This suggests that associated arthritis is not mediated solely by the adaptive immune system [10].

The role of monocytes and macrophages in the inflammatory responses of acute and chronic CHKF-related arthritis may be very important. The replication of the virus is blocked effectively by type I interferon response that requires sensing by non-myeloid cells. Macrophages are probably involved in the clearance of infected cell debris. This in turn can trigger pro-inflammatory responses that might account for the chronic joint pain [1].

Miner *et al.* [2] have found that patients with CHIKF-related chronic arthritis and patients with early untreated RA resemble each other in several immune profiles in the peripheral blood: in natural killer cells (NK) and in naive, activated and effector T killer and T helper cell populations. The numbers of these cell populations in these two groups were higher than in healthy controls, yet NK cell percentages were significantly higher only in patients with CHIKV-related arthritis than in healthy controls. A consistent trend towards increased L-selectin (CD62L) expression on $CD4^+$ T cell subsets was observed in RA patients when compared with healthy controls and CHIKV-infected patients. These results suggest that patients with CHIKV infection and patients with RA share a similar immune response phenotype with subtle different trends. Prospective characterization of T cell phenotype in such patient groups may help to determine whether the T cell activation status correlates with clinical disease activity [2].

Another clinical study of the pathophysiology of acute CHIKV infection was conducted, based on a rural population survey done during the 2006–2009 Indian epidemic.

Th1 and Th2 cytokine profiles and anti-CHIKV specific antibodies were determined. An intense upregulation of a number of pro-inflammatory markers, with a Th1 profile, was observed: Interferons (IFN-α, IFN-β and IFN-gamma), tumour necrosis factor-α (TNF- α), interleukin-1β (IL-1β), interferon gamma-induced protein-10 (CXCL-10/IP-10) and monocyte chemoattractant protein-1 (MCP-1), as well as of anti-inflammatory cytokines with Th2 profile: interleukin-4 (IL-4), interleukin-10 (IL-10) and interleukin-13 (IL-13). These findings were demonstrated during the acute infection period in individuals with a typical self-limited disease. Interestingly, early persistent anti CHIKV specific IgM and lower specific IgG together with intense TH2 cytokine response was associated with persistent rheumatic phenomena. A further investigation of virus markers, cytokines and immune responses (cellular and humoral) would be required to establish a concrete causal and contributory relationship with the clinical course [11].

Recently, Miner *et al.* [12▪] used a combination of abatacept, a CTLA4-Ig, which blocks T cells costimulation and which is used routinely in the clinical practice of RA treatment, in tandem with a human neutralizing anti CHIKV antibody on a mouse model of CHIKV-induced chronic arthritis. They were able to show a significant reduction of the accumulation of infiltrating T cells in joint tissues, a reduction of levels of pro-inflammatory cytokines and chemokines along with improvement in joint swelling of arthritic animals. This combined effect was larger than that of each of the two modalities used separately. Repurposing these clinically available therapies may provide new therapeutic options for CHIKF-induced chronic arthritis patients [12▪].

CONCLUSION

Chikungunia disease is a globally re-emerging infectious Mosquito-borne disease, moving fast over the continents, encompassing its ancestral cradle in eastern sub-Saharan Africa, South-East Asia, Indian Ocean islands, the Caribbean region, the Americas and appearing sporadically also in Europe.

The wide and rapid spread of CHIKF was facilitated by various factors such as point mutations in genes encoding for envelope protein that enables enzootic and epizootic cycles with new mosquito species resulting in a wider geographic distribution; growing urbanization phenomenon in the Tropics resulting in denser encounter between human and urban mosquito populations; the global invasion of *Aedes albopictus*, a mosquito that now serves as a second CHIKV vector in addition to *Aedes aegypti*; and recently, another CHIKV strain spread through northern South America and Florida, where locally acquired cases have been reported. Yet, generally speaking, the intense air travel with putative infected travellers did not initiate local transmission in the Americas during the 2006–2009 outbreaks.

It is likely that millions of unexposed population groups lacking 'herd immunity' will be at risk in these densely mosquito-infested areas [1].

The major CHIKF-related impact and the substantial economic burden of CHICF root in both, the high attack rate of the acute disease and its main sequelae, the chronic arthralgia and arthritis, with

an average incidence rate of over 50% of infected individuals. In susceptible individuals, the arthritis is incapacitating, erosive and may mimic RA, necessitating prolonged therapy with disease-modifying antirheumatic drugs and corticosteroids [3▪,2,9].

The best way to probe into the pathogenesis of autoimmune diseases such as RA and systemic lupus erythematosus (SLE) is to review the seminal article by Shoenfeld *et al.* [13]. 'The Mosaic of Autoimmunity', specifically, is the chapter dealing with environmental factors. The authors discuss microbial agents as the most important environmental contributors to the development of autoimmune disease [13,14].

Shoenfeld *et al.* [13] discuss five main mechanisms that can lead to an autoimmune disease:

(1) Molecular mimicry: The microbial agent incorporates an epitope that is homologous to a structure of a self-antigen.
(2) Epitope spreading: Over-processing and over-presentation of antigens by antigen-presenting cells (APCs), occurring locally during an inflammatory state, causes the priming of a protean number of T cells with many specificities.
(3) Polyclonal activation: Infected B cells proliferate and increase antibody production with resulting circulating immune complexes, hence causing damage to various tissues.
(4) Bystander activation: Enhanced cytokine production results in expansion of autoreactive T cells reaching a critical number sufficient to induce clinically overt disease.
(5) Microbial superantigens can bind to the T cell receptor beta chain nonspecifically and in tandem bind to a large variety of major histocompatibility complexes class 2 (MHC2) molecules on the surface of different cells, thus enabling the induction of an autoimmune reaction.

Epstein–Barr virus (EBV) infection is the most established example of a relationship between viral infection and an autoimmune disease. In SLE, a molecular mimicry was found between EBV nuclear antigen-1 and antidsDNA, anti-Ro and anti-LA antibodies. EBV has also been associated with RA, multiple sclerosis, Sjoegren's syndrome, autoimmune thyroiditis, autoimmune hepatitis and Kawasaki disease.

There were conflicting reports as to the prevalence of autoantibodies in patients with CHIKF-chronic arthritis. Schlite *et al.* found none [15], whereas others have inconsistently reported on ANA, rheumatoid factor and ACPA positivity and relevant shared epitope polymorphisms [7,16].

Is CHIKF-chronic arthritis an autoimmune disease? Well, it does not fulfil all the revisited Rose–Witebsky postulates of an autoimmune disease [17]. First, we do not have as yet direct evidence for reproduction of an autoimmune disease through transfer of pathogenic antibody or pathogenic T cells. Second, we do not even have a concrete indirect evidence based on reproduction of an autoimmune disease in experimental animals. Third, we do have some circumstantial evidences from clinical clues outlined above.

The determination of whether persistent chikungunya virus replication, lack of virus antigen clearance or both contribute to chronic arthralgia symptoms requires further studies with animal models and human samples.

The innate and adaptive immune responses to acute chikungunya virus infection have received much attention, yet the pathogenesis of chronic arthralgia and the basis for the variation in long-term outcomes among patients remain elusive. These issues will require large and systematic patient cohort studies, compilation of detailed clinical data and analyses of blood and tissue.

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Conflicts of interest

There are no conflicts of interest.

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Body composition assessment in the prediction of osteoporotic fractures

Mélany Hars and Andrea Trombetti

Purpose of review
To give an overview of recent research findings and insights on the role of body composition assessment in fracture risk prediction.

Recent findings
While there is to date little doubt that bone mineral density (BMD) is a main pathogenic factor of osteoporotic fractures, recent studies have emphasized the independent contribution of body composition components, especially lean mass, to fracture risk. In this article, we address body composition changes with aging, before to focus on recent studies addressing the contribution of lean and fat mass to fracture risk, together with some hypothesized mechanisms and clinical implications.

Summary
Recent compelling evidence suggest that clinicians should recognize the potential role of muscle wasting in determining fracture risk among older adults and that measures of lean mass, especially appendicular lean mass – which can be assessed simultaneously with the BMD measurement – should be considered in fracture risk assessment beyond BMD and clinical risk factors. More evidence is needed to support certain fat-related indicators in fracture risk prediction, but regional adiposity measures appear promising. Further studies in the field should help to elucidate whether interventions effective at attenuate, prevent, or ultimately reverse skeletal lean mass loss or fat accumulation, may prevent fractures.

Keywords
body composition, dual-energy X-ray absorptiometry, fat, fracture, skeletal muscle

INTRODUCTION

Osteoporotic fractures are common and remain a major public health challenge [1–8]. Bone mineral density (BMD), as assessed by dual-energy X-ray absorptiometry (DXA), has largely been accepted as the standard measure for the diagnosis of osteoporosis (Fig. 1). Although it is well established that a T-score of −2.5 or less – that is, osteoporosis as defined by the World Health Organization (WHO) criteria – is associated with a substantial increase in fracture risk, BMD measurement alone does not reliably predict the fracture risk, a bulk of fractures occurring in patients with a T-score higher than -2.5 [9,10]. This raised the need to identify and consider other risk factors besides BMD to improve the identification of high fracture risk individuals. In 2008, a WHO task force introduced the Fracture Risk Assessment Tool (FRAX, www.shef.ac.uk/frax/), which incorporates independent clinical risk factors for fracture, including body mass index (BMI), combined with BMD if available, to predict individual 10-year risk of hip or major osteoporotic fracture [11]. Recent studies have begun to emphasize the potential role of body composition components and their regional distribution, including lean and fat tissues, to fracture risk. In this article, we address recent findings and insights on the contribution of lean and fat mass to fracture risk, together with some hypothesized mechanisms and clinical implications.

BODY COMPOSITION CHANGES WITH AGING

A hallmark of the aging musculoskeletal system is the progressive loss of skeletal muscle mass, termed

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KEY POINTS

- Low lean mass (or 'sarcopenia'), as assessed by DXA, has revealed as a contributor to fracture risk among older adults, independently of BMD or clinical risk factors.
- Identification of low appendicular lean mass – which can be assessed simultaneously with the BMD measurement – should be considered in fracture risk assessment beyond usual risk factors.
- More evidence is needed to support certain fat-related indicators in fracture risk prediction, but regional adiposity measures appear promising.

'sarcopenia' by Rosenberg in 1989 [12]. Sarcopenia subsequently evolved to encompass also the parallel muscle function decline – termed 'dynapenia' – that occurs with aging and substantially outpaces muscle mass loss [13–16]. A consensual operational definition of sarcopenia has still not been reached [14–16]. Hence, several clinical definition and diagnosis criteria have been proposed, based on muscle mass alone [17,18], or in combination with muscle function (i.e., muscle strength and/or physical performances) [19–21]. Different thresholds for low muscle mass have been recommended in these definitions – including various derivative indicators of appendicular lean mass (ALM; the sum of lean mass in the arms and legs) (Fig. 1) as assessed by DXA – [22], but data for these candidate criteria for sarcopenia against hard outcomes are still sparse.

A concomitant increase in whole-body and regional fat deposits is also a typical manifestation of aging, even without changes to body weight [23–26]. Fat is redistributed from subcutaneous to visceral depots, with an increase in abdominal fat and fat deposition in ectopic sites (e.g., skeletal muscle or bone marrow) [26–30]. Obesity characterizes the abnormal accumulation of body fat and has been defined by the WHO as a BMI of 30 kg/m^2 or more [31]. However, it is well known that BMI is an imperfect proxy of body fatness mainly because it does not differentiate between lean from fat tissue. Also, there is compelling evidence that the distribution and type of excess fat may be more relevant to health than the total amount of body fat or the classification of obesity [23,26,32–36]. Especially, visceral adipose tissue (VAT) has been related to the development of numerous negative health outcomes, including mortality [37].

Body composition assessment – or the measurements of amount and distribution of body fat and fat-free tissues – extends beyond BMI [38]. DXA has gained interest and acceptance as a reference method, particularly because of its wide availability, relatively low cost, fast acquisition time, and low radiation exposure, compared to other available techniques including magnetic resonance imaging and computed tomography (CT), the gold-standard technique [9,22,39–41]. In order to discriminate between different types of adipose tissue, new tools have been developed, allowing in particular VAT measurements (Fig. 1) [40,42,43].

RECENT INSIGHTS INTO THE CONTRIBUTION OF LEAN AND FAT MASS TO FRACTURE RISK ASSESSMENT

Studies investigating the association between body composition components and fracture risk have mainly focused on bone health, especially BMD as a surrogate marker for future fracture risk. Both lean and fat mass have been positively correlated with BMD, but their relative contribution has been highly controversial [44]. In a meta-analysis of 44 studies ($n = 20\,226$; 75% women; age 18–92) Ho-Pham *et al.* [44] reported prominent effect of lean mass on BMD as compared to fat mass, when combined men and women. Beyond bone density, several studies have reported positive association between lean mass and bone geometry, microarchitecture and strength estimates [45–48].

Regarding fat, the relationship with bone health appears more controversial and complex, the different patterns of distribution and types of fat-tissue depots likely influencing this relationship, and requires further elucidation [45,49,50▪▪,51–55]. Recent evidence suggests a positive association between fat mass and especially trabecular microarchitecture [45]. Also, some studies are in favor of a protective or neutral effect of subcutaneous depots, but a negative effect of VAT on bone structure, microstructure and strength [52–54].

Studies addressing the independent contribution of lean mass to future fracture risk are scarce. Recently, the predictive value of low lean mass, as defined by several thresholds used in various operational definitions of sarcopenia, against fractures, was examined for the first time, in a large homogeneous cohort of 65-year-old community-dwellers ($n = 913$; 80% women; mean age 65 ± 1 years) from the GERICO study [56▪]. Low lean mass, as defined by Baumgartner thresholds, was found to be associated with higher fracture risk over 3 years, independently of FRAX probability with BMD [odds ratio (OR), 2.32; 95% confidence interval (CI), 1.04–5.18] or low BMD (Fig. 2). It also added significant predictive value beyond FRAX (likelihood ratio test for nested models, 4.28; $P < 0.039$). In this study, data were likely to be influenced by the sarcopenia

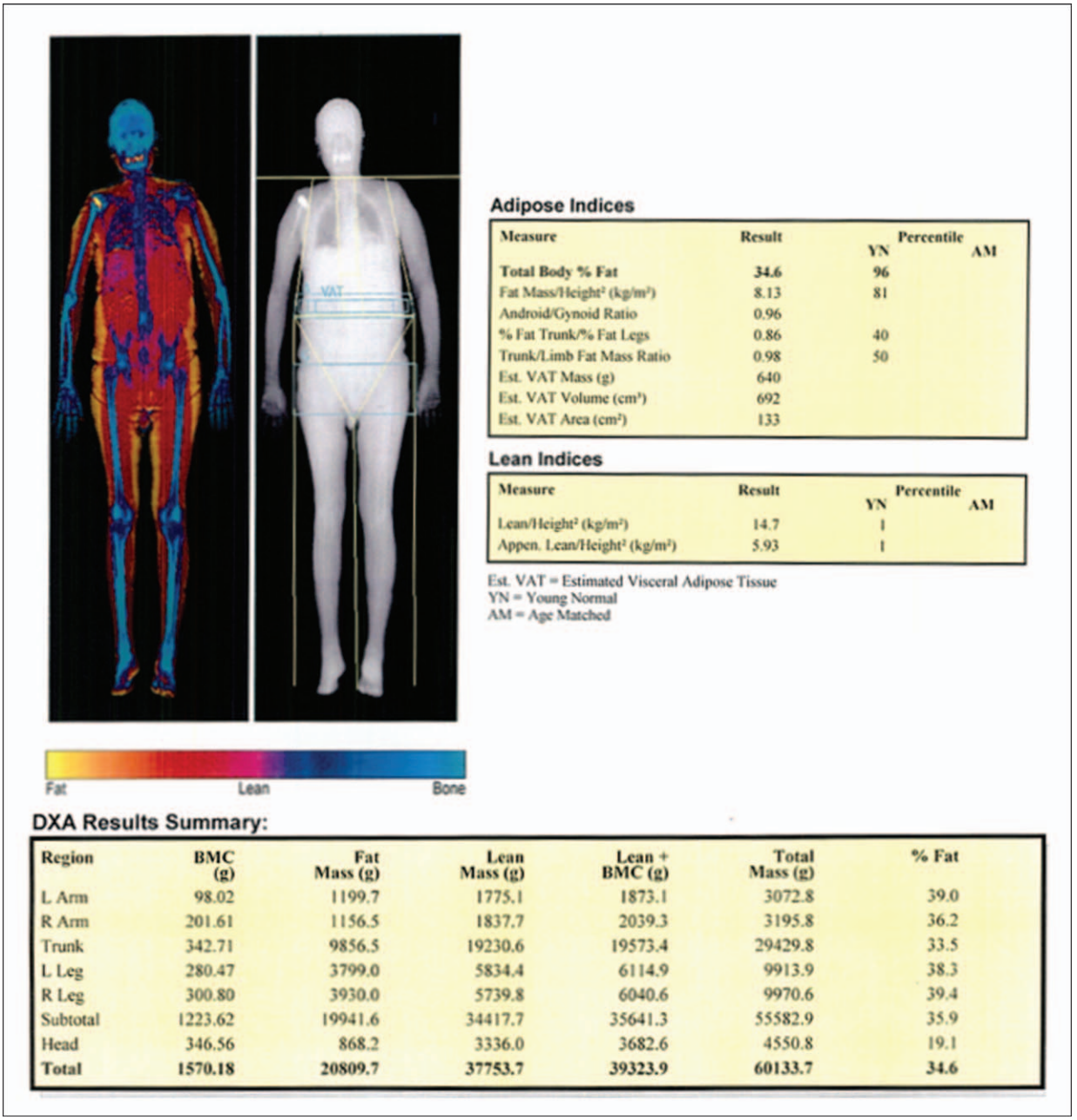

FIGURE 1. DXA scan of an 88-year-old Caucasian male with a diagnosis of sarcopenia, according to Baumgartner *et al.* threshold (i.e., appendicular lean mass/height^2 below 7.26 kg/m^2). DXA = dual-energy X-ray absorptiometry.

definition applied. More recently, Sornay-Rendu *et al.* [57▪▪] showed among postmenopausal women ($n = 595$; mean age 66 ± 8 years) enrolled in the OFELY cohort and followed-up over 13 years, that each SD increase of lean mass indices (i.e., total lean mass/height^2 and ALM/ height^2), were associated with significantly decreased fracture risk, independently of BMD and clinical risk factors including falls (adjusted hazard ratios of 0.76 for both of $P \leq 0.02$), and with a predominant role of ALM on fracture risk.

These recent findings contrast with few previous studies having failed to find any independent association between low lean mass and fracture incidence [58–63]. Even, in one recent nested case-cohort study, lower ALM/height^2 was paradoxically protective of hip fracture risk in men after accounting for hip BMD, but this remains to be fully investigated [64]. The discrepancies between recent study findings and those of earlier researches are likely to be explained by the focus of hip fractures only or the methodologies employed including failure to take into account ALM [57▪▪].

Recent findings also provided first insight into an additive risk of low lean mass and osteoporosis

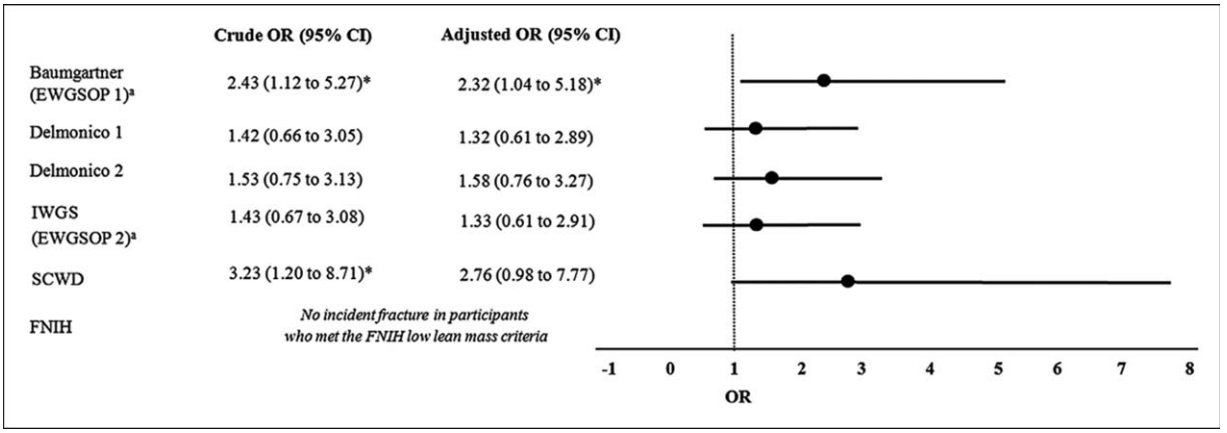

FIGURE 2. Crude and adjusted OR for the association between low lean mass thresholds, as proposed in different operational definitions of sarcopenia, and incidence of low trauma fracture over a 3-year follow-up ($n = 913$). Adjustment was made for gender, age, length of follow-up and FRAX probability with femoral neck BMD. OR = odds ratio; CI = confidence interval; EWGSOP = European Working Group on Sarcopenia in Older People; FRAX = Fracture Risk Assessment Tool; IWGS = the International Working Group (IWGS) on sarcopenia; SCWD = Society on Sarcopenia, Cachexia, and Wasting Disorders; FNIH = Foundation of the National Institutes of Health sarcopenia project. [a]The EWGSOP recommended two different options for low lean mass threshold. *$P < 0.05$. Adapted from [56▪].

(i.e., sarco-osteoporosis) or low lean mass and obesity (i.e., sarcopenic obesity) for fracture risk. In Hars *et al.* [56▪] study, the coexistence of sarcopenia and densitometric osteoporosis was associated with a 3.4-fold increase in low trauma fracture risk. When defining sarcopenia as a combination of low lean mass and function, Chalhoub *et al.* [65] and Yu *et al.* [58], also highlighted a potential strong role of sarco-osteoporosis in fracture risk in older men. Scott *et al.* [66▪▪] investigated the associations between sarcopenic obesity (i.e., with sarcopenia and obesity defined as the lowest sex-specific tertiles for ALM and the highest sex-specific tertile for total fat mass, respectively) and its components with incident fractures ($n = 1089$; 51% women; mean age 62 ± 7 years). Sarcopenic obese older men had over threefold higher rates of nonvertebral fractures over 10 years compared with both nonsarcopenic nonobese or obese alone counterparts, after accounting for total hip BMD. Sarcopenic obese women also had higher fracture rates compared with obese alone, but this was mediated by BMD. In another cohort, Scott *et al.* [67] also revealed the negative impact of the coexistence of sarcopenia, defined as a combination of low lean mass and function, and obesity on fracture, but data were likely to be influenced by the sarcopenia definition retained.

Relatively few prospective studies have investigated the independent contribution of fat mass to the risk of fracture, and even fewer, the impact of different distribution and type of excess fat. Most studies in the field have focused on BMI despite it represents an imperfect measure of body fatness. Low BMI has been well documented as a risk factor for fracture, especially low BMI being a significant BMD-independent risk factor for hip fracture [68]. Conversely, high BMI has been widely accepted to be protective against fractures, however, some studies have revealed that fractures are frequent in obese individuals and suggested that obesity increases fracture risk at certain location independently of BMD [35,68–74]. Recent data regarding the relationship between high BMI and fracture risk, not all unanimous, have suggested that this relationship differ by anatomic site and gender [68,75,76]. Especially, some evidence point positive association between BMI and the risk of humerus or ankle/lower leg fractures in women [68,77]. In males, data are less available.

The prospective association between fat-related indices (i.e., direct assessment of body composition) and fractures has not been well documented. Some studies, including a large one by Leslie *et al.* [61,62] ($n = 40\,050$ women and 3600 men, age ≥ 50 years), have shown that lower fat mass is predictive of hip and osteoporotic fractures, but the associations were lost when considering BMD or FRAX probability.

Emerging data suggest that regional adiposity measures might add predictive information over and above BMD, despite data still remain controversial. More importantly, most of the studies fail to adequately consider the role of potential confounding and mediating factors making it difficult to determine the true independent contribution of these regional fat storages. Especially, a growing body of studies has focused on indicators of abdominal obesity as assessed by DXA. Recently, Sornay *et al.* [57▪▪] showed that increased visceral and

subcutaneous abdominal fat mass were associated with decreased major osteoporotic fractures risk in postmenopausal women ($n = 595$; mean age 66 ± 8 years), but the association was weakened after adjustment for BMD and did not persist after accounting for competing risk of death. Conversely, in Machado *et al.* [78▪] study ($n = 433$ women; men age 73 ± 5 years), higher VAT had a significant association with incident nonspine fractures over 4.3 years but only in nonobese women, even after adjustment for BMD.

In recent years, the fatty degeneration of thigh muscles has also gained attention. Lang *et al.* [60] reported that decreased thigh muscle Hounsfield unit values obtained by CT-lower values indicating greater fatty infiltration of muscle – was associated with increased risk of hip fracture in men and women, independently of BMD. At thigh level, decreased DXA-derived subcutaneous fat thickness was also recently been found to be strong contributors to hip fracture risk in men and women, independently of BMD and other clinical risk factors [64].

HYPOTHESIZED MECHANISMS

Low lean mass may act on fracture through increased fall risk. Low muscle mass may lead to reduced muscle strength and physical impairments and in turn increase the risk of falls. In a recent retrospective longitudinal study comparing several operational definitions of sarcopenia as predictor of prospective incidence of falls, falls risk was selectively predicted by the Baumgartner *et al.* [79] thresholds. Only few studies have investigated the direct contribution of fat mass to falls, while numerous studies have shown that high BMI imparts an increased fall risk [80]. Recently, it was shown in the CHAMP study, that both nonsarcopenic and sarcopenic obese older men (with sarcopenia defined using EWGSOP definition) [21] had significantly higher 2-year fall rates compared with with nonobese men [67]. While adiposity may cushion the fall impact at some bone sites, the site-specific association found in certain studies may conceivably be largely explained by a different fall mechanism in obese individuals [71], with greater impact forces during a fall associated with increase weight for humeral fractures, and excessive stresses over time on bones/joints because of higher loads (e.g., increased joint torque) for ankle fractures.

There is emerging research in the connections between muscle, fat, and bone, as evidenced in several recent reviews [35,38,81–90]. Main mechanisms behind the adverse effect of muscle loss on bone status include decreased mechanical stimuli, followed by a deregulation of systemic signals

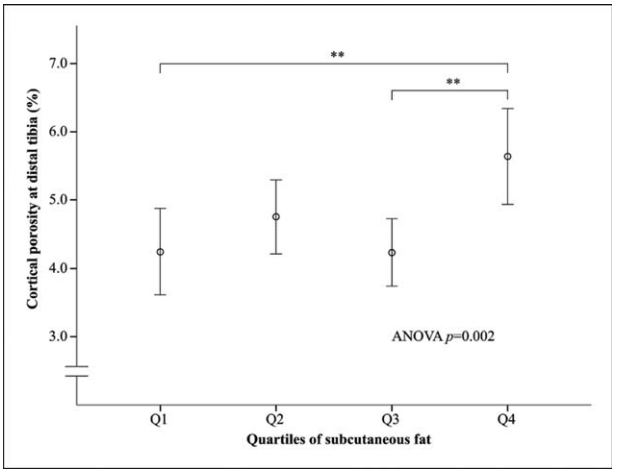

FIGURE 3. Mean values of cortical porosity (%) with 95% confidence interval divided into quartiles of tibia subcutaneous fat, in 200 older women assessed by high-resolution peripheral quantitative computed tomography. $^{**}P < 0.01$. Adapted from [50▪▪].

including sex hormones and regulating metabolism hormones, and a modulation of expression of local factors, including proinflammatory cytokines (e.g., interleukin-6, tumor necrosis factor-alpha) [87]. If the protective effect of fat on bone may mainly be attributed to greater mechanical load and hormonal factors (e.g., increased secretion of insulin and amylin from pancreatic β-cells, increased levels of sex-hormones, increased aromatization of androgen to estrogen), certain adipokines such as the leptin and adiponectin have shown both positive and negative effects on bone, whereas fat may exert a negative effect on bone by increased proinflammatory cytokines and imparting insulin resistance, especially for VAT [89]. Of note, recently, it was shown recently that VAT may not have a prominent effect on bone microarchitecture and skeletal strength independently of BMI or weight, suggesting that the increased risk for fractures associated with higher VAT found in certain studies may be attributable to other factors, especially skeletal loading [51]. As opposed to this, Sundh *et al.* [50▪▪] recently showed that only local adipose tissue (i.e., subcutaneous tibia fat) was inversely associated with cortical density and positively associated with cortical porosity at distal tibia, suggesting a local adverse effect of adipose tissue on bone, rather than systemic (Fig. 3).

Finally, recent studies have also emphasized the role of bone marrow adiposity in skeletal health and metabolism [91–94].

CLINICAL IMPLICATIONS

The evidence aforementioned suggest that clinicians should recognize the potential role of muscle

wasting in determining fracture risk among older patients and that measures of lean mass, especially ALM – which can be assessed simultaneously with the BMD measurement – should be considered in fracture risk assessment beyond BMD and clinical risk factors. This is also the case for obese patients who may be at exacerbated risk of fracture. Further studies should help to determine the contribution of lean mass in refinements of FRAX and other fracture prediction models.

The actual available evidence, especially from recent comparisons of sarcopenia definitions against falls and fractures, suggest that Baumgartner definition (i.e., based on ALM/height^2 two standard deviations below the mean of a young reference group, an analogy with osteoporosis; 5.45 kg/m^2 in women and 7.26 kg/m^2 in men) [17] may represent a reasonable approach of sarcopenia, particularly among nonobese older adults, although more validation studies are required [79,95]. Of note, the inclusion of functional measures in the definition of sarcopenia did not confer a better predictive value for incident falls [79]. Furthermore, without denying or minimizing the importance of functional measures, a sarcopenia definition based on low ALM/height^2 alone is suggested as particularly suitable for early diagnosis and intervention due to the low prevalence found when using a composite definition of sarcopenia combining both low muscle mass and function [95]. For example, in two homogeneous cohorts of 68-year and 63-year-old men and women – that is, the GERICO cohort ($n = 767$) and a nationally representative British birth cohort ($n = 1566$), respectively – [96,97], low lean mass (i.e., ALM/height^2) prevalence ranged from 10.7 to 30.7%, whereas the prevalence of low lean mass combined with either weakness or slowness was considerably lower, between 1.3 and 7.3%, with overall higher prevalence found in women. This higher prevalence gives more sensitivity for screening purpose, and thus a better chance to offer preventive interventions. Given the recent establishment of an ICD-10 (M62.84) code for sarcopenia, major steps forward are expected in the near future, especially regarding candidate criteria for sarcopenia, which should help to refine clinical recommendations [15].

More evidence is needed to support certain fat-related indicators in fracture risk prediction, but regional adiposity measures appear promising. Future work, especially using more appropriate imaging techniques as CT and comprehensive sets of risk factors, are needed to shed light on the role of fat accumulation and distribution on future fracture risk.

The lack of association found in certain studies does not imply that body composition assessment may not be useful for a given set of patients and should not contradict the importance of soft tissues in the pathogenesis of osteoporotic fractures.

CONCLUSION

Recent studies have begun to emphasize the independent contribution of low lean mass to fracture risk among older adults, suggesting that identification of low lean mass – which can be assessed simultaneously with the BMD measurement – should be considered in fracture risk assessment beyond BMD and clinical risk factors. Further studies in the field should help to elucidate whether interventions effective at attenuate, prevent, or ultimately reverse lean mass loss or fat accumulation, may prevent fractures.

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Conflicts of interest

There are no conflicts of interest.

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Skeletal assessment with finite element analysis: relevance, pitfalls and interpretation

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Purpose of review
Finite element models simulate the mechanical response of bone under load, enabling noninvasive assessment of strength. Models generated from quantitative computed tomography (QCT) incorporate the geometry and spatial distribution of bone mineral density (BMD) to simulate physiological and traumatic loads as well as orthopaedic implant behaviour. The present review discusses the current strengths and weakness of finite element models for application to skeletal biomechanics.

Recent findings
In cadaver studies, finite element models provide better estimations of strength compared to BMD. Data from clinical studies are encouraging; however, the superiority of finite element models over BMD measures for fracture prediction has not been shown conclusively, and may be sex and site dependent. Therapeutic effects on bone strength are larger than for BMD; however, model validation has only been performed on untreated bone. High-resolution modalities and novel image processing methods may enhance the structural representation and predictive ability. Despite extensive use of finite element models to study orthopaedic implant stability, accurate simulation of the bone-implant interface and fracture progression remains a significant challenge.

Summary
Skeletal finite element models provide noninvasive assessments of strength and implant stability. Improved structural representation and implant surface interaction may enable more accurate models of fragility in the future.

Keywords
bone, dual x-ray absorptiometry, finite element, orthopaedic implants, quantitative computed tomography

INTRODUCTION

Musculoskeletal disorders including osteoporosis and arthritis lead to pain, loss of mobility and fracture. Despite the various contributors to fragility such as bone mass, structure and collagen quality, the current standard for fracture risk assessment is a dual-energy x-ray absorptiometry (DXA) measurement of areal bone mineral density (aBMD) [1,2]. This measure captures only 50–80% of the variability in bone strength [3], and therefore many patients at risk of fracture go undiagnosed [4,5]. Volumetric BMD (vBMD) obtained from quantitative computed tomography (QCT) is more effective at assessing bone strength than aBMD [6,7]; however, it does not capture the bone geometry, microstructure and external forces that also contribute to fracture. The finite element (FE) method is a numerical method in which a loaded structure is divided into smaller elements and the stresses and strains for each element calculated. Finite element models of bones and joints are created using geometrical and material parameters obtained from imaging modalities such as QCT. Since the 1970s, finite element models have been developed to study bone and joint disease, fragility and implant design. The purpose of this review is to provide an overview of the applications of the finite element method for predicting bone fragility, disease progression, therapeutic efficacy and orthopaedic implant stability. The current limitations and challenges of the method will be

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KEY POINTS

- Finite element models enable the noninvasive assessment of bone and joint response to loading. Finite element-predicted biomechanical behaviour agrees well with controlled experimental tests, but has not been shown conclusively to be superior to bone mineral density (BMD) for the prediction of fracture in clinical studies.
- Finite element models have been used extensively to study orthopaedic implant stability; however, the accurate simulation of the bone-implant interface and fracture progression remains a significant challenge.
- Finite element models that simulate a rheumatoid arthritis condition may help to explain the biomechanical influences on disease progression, but much work is still required to validate the current models.
- High-resolution imaging modalities and advanced image processing techniques may improve bone structural representation and the ability for finite element models to predict bone fragility and orthopaedic implant stability in the future.

discussed and an outlook on potential future improvements and applications will be given.

GENERATION OF FINITE ELEMENT MODELS FROM MEDICAL IMAGES

Most skeletal finite element models are created from CT images and this procedure is shown in Fig. 1. The site of interest is isolated by manually tracing 2D slices or automated methods such as statistical shape modelling [8]. A meshing procedure is then applied to create elements, usually in the shape of tetrahedrons or hexahedrons [9]. Shell or pentahedral elements can also be used to represent the cortex [9,10]. Each element in an finite element mesh can have unique mechanical properties and empirical relationships have been developed to derive preyield and postyield behaviour from BMD [11–17]. External forces and fixations are applied to the nodes of specific elements and are known as boundary conditions. Boundary condition choice can greatly affect the results, where deviations from 41% underestimation to 65% overestimation of stiffness have been observed [18▪]. A number of studies have examined the effect of loading direction

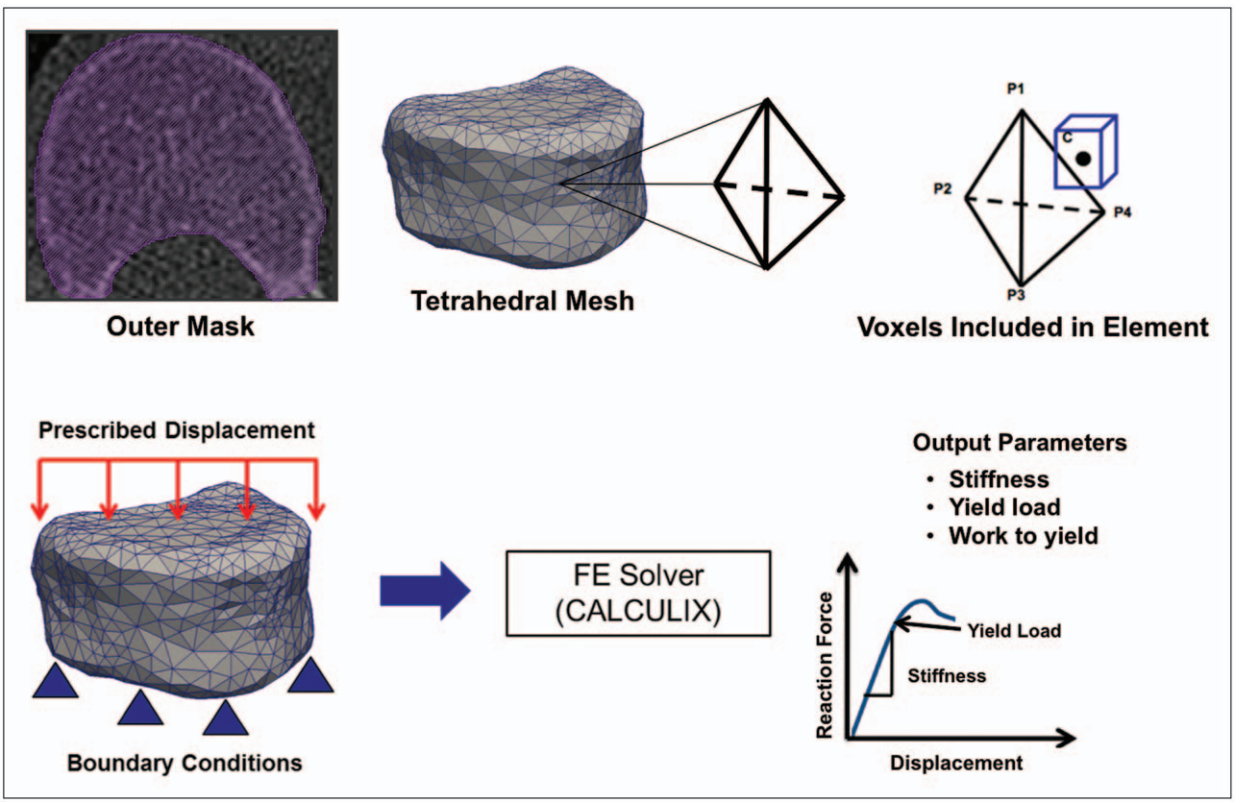

FIGURE 1. Conversion of a QCT image of a vertebra to an finite element model. Top: The vertebral body is selected (outer mask) and converted to a mesh of tetrahedral elements. The mechanical properties of each element are determined from the vBMD of the voxels within the element. Bottom: Boundary conditions are applied to fix nodes and prescribe displacements. This is then passed into a solver to calculate parameters such as whole bone stiffness and yield load. Adapted with permission [48▪].

[19,20,21▪,22], and stance versus fall configuration [19,22,23▪▪,24–26] on fracture risk at the hip. Femoral fracture risk increases with posterolateral impact during a fall [19,26,27] and with posterior loading during stance [19], and models simulating multiple loading directions can improve fracture discrimination [22,28]. All input data are passed into a solver, which calculates the local reaction forces, displacements, stresses and strains.

PREDICTION OF BONE FRAGILITY AND FRACTURE

Finite element-predicted mechanical behaviour correlates well with mechanical tests of excised vertebrae (49–86% of variance explained) [29–31] and femora (74–95% of the variance explained) [11–15,32–36] and explains 18–40% more of the variance in vertebral strength [29,31,37] and at least 10% more variance in femoral strength [38] than BMD. In retrospective studies of postmenopausal women with and without fracture, the odds ratios for vertebral strength were numerically higher than those for aBMD and vBMD [39,40], whereas femoral strength was significantly associated with fracture status after adjusting for aBMD [21▪]. Two prospective studies have enabled the comparison of finite element analysis to BMD methods. The osteoporotic fractures in men (MrOS) cohort consisted of men aged 65 and older assessed at baseline and a mean follow-up of 4.5 years [41]. The Age, Gene/Environment Susceptibility-Reykjavik Study (AGES/Reykjavik) consisted of men and women born between 1907 and 1935, assessed at baseline and a 4- to 7-year follow-up [42]. In vertebral finite element models, superior fracture prediction was detected compared to aBMD but not vBMD in the MrOS cohort [43], whereas in the AGES/Reykjavik cohort, strength and load-to-strength ratio were associated with fracture, independent of vBMD in men, but not women [44]. Two studies have applied femoral fall models to the AGES/Reykjavik cohort and report somewhat contradicting findings after adjustment for total hip aBMD. Keyak *et al.* [45] report a significant association between posterolateral strength and fracture in men but not women, whereas Kopperdahl *et al.* [44] report significant age-adjusted odds ratios for femoral strength in women but not men. BMD and femoral strength decreased more quickly in the women [46], whereas a larger difference in strength between the fracture and control groups was detected in men [47]. The benefit of finite element models over BMD may therefore be sex specific, which has also been reported in multiple myeloma patients [48▪].

Fragility and increased fracture rate are common complications of glucocorticoid therapy [49], a condition referred to as glucocorticoid-induced osteoporosis (GIO). Rapid microstructural changes in the trabecular network lead to fractures despite BMD values higher than those associated with postmenopausal osteoporosis [50,51]. In a retrospective cohort of male patients with GIO, a vertebral compression model discriminated between fracture and nonfracture groups better than aBMD, but not trabecular vBMD [52]. This may be a result of the finite elements models being unable to pick up microstructural changes such as altered resorption cavity shape [53], deteriorated trabecular structure [54] or increased cortical porosity [55].

Finite elements analyses can simulate tissue degradation to study the progression of rheumatoid arthritis. A particular challenge in rheumatoid arthritis applications is that the whole joint, including cartilage and ligaments is included in the model. Bajuri *et al.* developed a model of the wrist with linear elastic bone elements, large-deformation hyperelastic cartilage elements and linear spring ligament elements [56]. The model was generated from a CT dataset from a healthy volunteer, and a grade IV rheumatoid arthritis condition was simulated by reducing bone stiffness and ligament elements as well as removing cartilage. The rheumatoid arthritis model predicted larger wrist motion and higher stress concentrations at the radioscaphoid and capitolunate joints, similar to clinical observations [57]. The model was further developed to simulate complex changes such as joint dislocation, contact area reduction, bone erosion and total wrist arthroplasty [58]. A model of the cervical spine was created with linear elastic bone elements and hypoelastic cable ligament elements to determine whether there is a biomechanical influence on rheumatoid arthritis progression [59]. The rheumatoid arthritis condition was simulated by sequential reduction of ligament stiffness by 50%, 75% and 100%. Predicted stress reduction in the axis at the transverse ligament-odontoid process junction provided a potential explanation for erosion of the odontoid process, commonly observed in rheumatoid arthritis. However, although both of these models provide results that are supported by clinical findings, no finite element models of rheumatoid arthritis have been compared to excised rheumatoid arthritis specimens for validation.

ASSESSMENT OF THERAPEUTIC EFFICACY

Finite element models have increasingly been incorporated into clinical studies of therapy. In

general, improvements in predicted bone strength are relatively larger compared to bone mineral or volume density [40,60–66], although some report similar changes [67]. It should be kept in mind that the power relationships between BMD and mechanics have been obtained from experimental tests on bone without treatment, and may change with therapy. Nevertheless, finite element models may detect improvements with therapy earlier than BMD. In postmenopausal women given alendronate, strength but not BMD was significantly higher than baseline after 3 months [40], and relative changes remained higher than BMD for 18 months [60]. A number of studies have compared antiresorptive, anabolic and combination therapy. In men with GIOP, vertebral strength increased by 26–47% with teriparatide treatment versus 4–20% with risedronate after 18 months [61,68]. In postmenopausal women [65], teriparatide improved vertebral strength over alendronate after 18 months (+21 vs. +3.7%), but femoral strength improved similarly regardless of alendronate, PTH(1–84) or combination therapy after one year (2.1–3.6%) [69]. In the latter study, PTH increased trabecular but decreased cortical BMD, which was also reported with 18 months of teriparatide therapy [70]. This differential effect appears to occur at the hip but not the spine [64], and has also been observed in micro-finite element models of peripheral sites [71]. Conversely, peripheral but not trabecular vertebral strength increased in postmenopausal women with rheumatoid arthritis under alendronate treatment [72]. Increased peripheral strength was also observed with combined antiresorptive and PTH treatment compared to PTH alone after antiresorptive monotherapy [73]. Thus, improved depiction of the cortical and trabecular compartments in finite elements models could improve the assessment of treatment efficacy. In postmenopausal women given denosumab, increased hip strength was predicted with a fall model of hexahedral elements by 8.6% and vertebral strength by 18.2% after 36 months [74]. These findings were confirmed by a later study of the same dataset using a smoothed tetrahedral finite elements model incorporating both stance and fall conditions [75].

ORTHOPAEDIC IMPLANT STABILITY

Orthopaedic implant failure can result from aseptic loosening, wear, pain, periprosthetic fracture, dislocation and instability [76]. Cemented implants derive primary stability from a layer of bone cement inserted into the cavity prior to implantation, whereas uncemented implants are press-fit and rely on radial force and friction to stay in place. The contact mechanics between the bone and implant are not completely understood, and therefore difficult to replicate in a model. In cemented implants, idealized geometry and elastic material properties of the cement are often used, and the interdigitation depth assumed negligible [77–79]. Some recent developments to more accurately model the initial stress state because of curing [80–84] and incorporating viscoelastic properties [80,85–88] and composite structure [89] have been applied. In uncemented implants, friction coefficients between 0.2 and 0.5 appear to correlate best with experiments [90,91] and are most often used in finite element models. Although uncemented implants could prolong stability through osseointegration, no clear advantage over cemented implants has been observed to date. Micromotion between the bone and implant may be critical, where motions of 40–50 μm encourage osseointegration but those exceeding 150 μm induce fibrous tissue formation [92]. Experimental results suggest that acetabular components with 1 mm diametrical press-fits are optimal [93,94], and press-fits of 0.5–2 mm are most often used [95–100]. Linear elastic material for the bone tissue is typically assumed despite the visco-elastic stress-relaxation properties likely reducing the actual press fit [101]. Stresses that exceed the yield stress of bone have been detected [102–105], suggesting that the effective press-fit is further reduced by plastic deformation. Incorporating visco-elastic and nonlinear behaviour may improve the accuracy of micromotion prediction.

Increasing the press fit raises the radial and pull-out force (experimental indicators of stability) [106▪], but also increases hoop stress and fracture risk. To date, reports of finite elements models that predict periprosthetic fracture are sparse, partly because of the complexity of modelling tissue failure. Periprosthetic fracture risk was assessed in a model of ipsilateral intramedullary femoral implants, where the stems were inserted into a hollow cylinder representing the femoral shaft and loaded in bending [107]. Increased stress in thin cortices and stress concentrations at the stem tip are likely reflective of the clinical situation; however, because of the simplicity of the model, the absolute values are not easily interpreted. Miles *et al.* [108] developed a model of periprosthetic fracture around a hip-stem implant using biphasic and triphasic linear elastic elements and a maximum principal strain criterion for failure. Although crack formation qualitatively matched experimental results, fracture load was overestimated and found to be highly dependent on the friction coefficient, suggesting that homogeneous material stiffness may be too simplified. Another model incorporated BMD-

calibrated inhomogeneous elemental stiffness into a model of femoral stem insertion to predict periprosthetic fracture risk in patients receiving either cemented or uncemented implants [109,110]. Failure in the linear elements was set after reaching a BMD-defined tensile stress. The number of failed elements tended to decrease with increasing BMD, indicating that initial bone quality plays a role on fracture risk. However, crack propagation and structural collapse were not simulated. Because no reports of periprosthetic fracture in any of the patients were given, it is unclear how well the model actually predicted fracture. Nevertheless, the observations suggest that care must be taken with the use of press-fit implants with osteoporotic patients. More sophisticated models that incorporate inhomogeneous BMD and element failure, which are validated with experimental tests could give more insight into this topic.

LIMITATIONS AND CHALLENGES OF FINITE ELEMENT MODELS

CT scans come with higher monetary costs and radiation exposure to the patient, and one potential solution is to build finite element models from DXA scans. 2D and 3D models have been developed from DXA but the benefit over BMD is not yet clear. In tests on excised femur specimens, 2D DXA-based finite element models correlated well with bone strength (74–77% variance explained), but were inferior to 3D models from QCT (80–85% of variance explained) [111▪], and also inferior to aBMD in the fall configuration (80% of variance explained). However, in retrospective studies, a 2D femoral fall model discriminated fracture status independent of aBMD [112,113]. Because 2D DXA-based finite element models are affected by patient position [114], statistical shape and appearance modelling (SSAM) has been used to generate 3D models from DXA images. These correlate well with 3D models generated from QCT in terms of femoral stiffness ($R^2 = 0.85$) [115] and explain at least 83% of the variance in principal strain [116▪▪]. However, no superiority over BMD has been reported. A second solution to minimise costs and radiation exposure is to build finite element models from preexisting CT scans, for example from a colonography or angiography using phantomless calibration [117,118]. Finite element models of the vertebra and femur in which BMD was calculated using air, fat and blood as internal references were applied to patients that underwent CT colonography scans [119▪]. The bone strengths and DXA *T*-scores were in high agreement (85%); however, the performance against BMD was not tested.

FE models based on QCT are limited by the spatial resolution. Voxel widths are typically at least 0.3 mm, meaning the cortical and trabecular structure cannot be fully resolved. The use of high-resolution QCT (HR-QCT) scan protocols [120▪] or multidetector CT (MDCT) [121] shows promise in pushing the boundaries for structural detection in clinical CT, and de-blurring techniques may obtain more accurate depictions of the cortical shell in low-resolution images [122▪▪].

Finite element models based only on CT images do not incorporate change in collagen quality, which influences energy dissipation and microdamage [123]. In osteogenesis imperfecta, collagen defects reduce bone stiffness despite higher mineralization [124], and therefore current finite element models may not be sensitive for this condition. Diseases such as diabetes and RA may increase the accumulation of advanced glycation endproducts (AGEs) in the proteins of various tissues [123,125,126], which leads to microdamage accumulation [127]. Finite element models that incorporate collagen alterations may further improve fragility assessment.

CONCLUSION AND OUTLOOK

Finite element modelling shows promise as a clinical tool for fracture prediction; however, the advantage over BMD measures has not been conclusively shown. Accurate simulation of the bone–implant interface and the visco-elastic and postyield behaviour of bone remains a challenge. Higher resolution imaging or advanced image processing methods for better structural representation, and collagen consideration could improve finite element simulations, enabling this method to become a standard tool to assess bone fragility and orthopaedic implant stability in the future.

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Conflicts of interest

There are no conflicts of interest.

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Osteoporosis in premenopausal women

Bente L. Langdahl

Purpose of review
The scope of this review was to review the newest developments in the context of the existing knowledge on premenopausal bone fragility. Fragility fractures are common in postmenopausal women and men and diagnostic criteria for osteoporosis have been agreed and multiple pharmacological treatments have been developed over the last 25 years. In premenopausal women, fragility fractures and very low bone mass are uncommon and osteoporosis in premenopausal women has therefore attracted much less interest.

Recent findings
Recent studies have highlighted that lifestyle and dietary habits affect premenopausal bone mass. Bone mass may be improved by sufficient intake of calcium and vitamin D together with increased physical activity in premenopausal women with idiopathic osteoporosis. If pharmacological treatment is needed, teriparatide has been demonstrated to efficiently increase bone mass; however, no fracture studies and no comparative studies against antiresorptive therapies have been conducted. Pregnancy affects bone turnover and mass significantly, but pregnancy-associated osteoporosis is a rare and heterogeneous condition.

Summary
The diagnosis of osteoporosis should only be considered in premenopausal women with existing fragility fractures, diseases or treatments known to cause bone loss or fractures. Secondary causes of osteoporosis should be corrected or treated if possible. The women should be recommended sufficient intake of calcium and vitamin and physical activity. In women with recurrent fractures or secondary causes that cannot be eliminated, for example glucocorticoid or cancer treatment, pharmacological intervention with bisphosphonates or teriparatide (not in the case of cancer) may be considered.

Keywords
BMD, fracture, osteoporosis, premenopausal, treatment

INTRODUCTION

The scope of this review is to review and discuss the diagnostic criteria, the pathophysiology and secondary causes of osteoporosis in premenopausal women, the diagnostic work-up and the management of the condition.

DIAGNOSING OSTEOPOROSIS IN PREMENOPAUSAL WOMEN

There is no consensus or international agreement on the diagnostic criteria for osteoporosis in premenopausal women. This is in contrast to the situation in postmenopausal women, wherein osteoporosis is diagnosed based on low bone mineral density (BMD). The WHO criteria for osteoporosis in postmenopausal women; BMD T-score less than −2.5 does not apply to premenopausal women. The relationship between BMD and fracture risk is well established in postmenopausal women; however, this is not the case in premenopausal women wherein the incidence and prevalence of fractures are several folds lower [1–4]. Most guidelines agree that the diagnosis of osteoporosis in premenopausal women cannot be based on BMD alone, but suggest the diagnosis can be considered in premenopausal women with clinically relevant fragility fractures, for example hip fracture or vertebral fractures or in case of other fragility fractures in combination with low bone mass. The International Society for Clinical Densitometry (ISCD) recommends using BMD Z-scores (comparison to age-matched norms) to classify bone mineral density in premenopausal women. ISCD suggests that BMD Z-score better than −2 should be classified as normal BMD and BMD

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KEY POINTS

- The diagnosis of osteoporosis in premenopausal women should be based on the presence of clinically relevant fragility fractures in combination with very low BMD.
- Osteoporosis in premenopausal women is rare and in a large proportion of patients, a secondary cause can be identified.
- There is some evidence for positive effects of sufficient intake of calcium and vitamin D and physical activity on bone mass in premenopausal women, but no evidence for fracture prevention.
- There is little evidence for pharmacological treatment of primary osteoporosis in premenopausal women.
- There are evidence for a positive effect on BMD of bisphophonates in premenopausal women with glucocorticoid-induced or cancer treatment-induced osteoporosis and of teriparatide in glucocorticoid-induced osteoporosis. There is no evidence for fracture prevention in the short term or long term.

Z-score less than or equal to –2 should be classified as 'below the expected range for age'. ISCD also recommends not using T-scores for diagnosing osteopenia or osteoporosis in premenopausal women and not using the diagnosis 'osteoporosis' in premenopausal women without fragility fractures or secondary causes of osteoporosis [4]. The International Osteoporosis Foundation (IOF) suggests using Z-score in children, adolescents and adults below the age of 20 years and in individuals above the age of 20 years in case of delayed puberty. In individuals 20 years and older, IOF recommends using T-score less than –2.5 as a diagnostic criterion for osteoporosis. IOF also recommends using the diagnostic criteria predominantly in premenopausal women with fragility fractures or secondary causes of osteoporosis, but does not exclude using the diagnosis based on BMD only [5]. In clinical practice, BMD should only be measured in premenopausal women with clinically important fractures or secondary causes of low bone mass or fractures. I would suggest using T-score less than –2.5 for diagnosing osteoporosis in these women as this is a cutoff value that many more clinicians will be familiar with.

INTERPRETATION OF FRACTURES AND BONE MASS IN PREMENOPAUSAL WOMEN

Studies have shown that fractures occurring before menopause predict postmenopausal fractures [2]. Studies have also shown that premenopausal women with fractures have lower BMD than premenopausal women without fractures [6–9]; however, there are no longitudinal studies demonstrating that low BMD in premenopausal women predicts future fractures.

Peak bone mass is attained between the age of 20 and 30 years with some variation depending on skeletal site [10–11]. This means that women younger than 30 years may not have reached peak bone mass at all skeletal sites and this should be taken into consideration when interpreting BMD measurements.

Pregnancy and lactation affect bone mass. Pregnancy is associated with a loss of bone mass of 3–5%, lactation for 6 months leads to a further loss of 3–10%. The bone mass is in most cases fully recovered over 6–12 months after stopping lactation [12,13▪,14]. A special form of osteoporosis in premenopausal women is pregnancy-associated osteoporosis. The pathophysiology underlying this condition is not fully understood, but is probably related to the hormonal changes during pregnancy. The classical presentation of this condition is vertebral or sometimes even multiple vertebral fractures during the third trimester, but the condition is heterogeneous [15▪,16,17▪]. Transient osteoporosis of the hip is also seen in relation to pregnancy and lactation [18].

PATHOPHYSIOLOGY AND SECONDARY CAUSES OF OSTEOPOROSIS IN PREMENOPAUSAL WOMEN

Lifestyle and dietary habits are important for bone mass in premenopausal women; vitamin D deficiency, smoking, physical inactivity and lower serum levels of estradial have been found to be associated with lower bone mass in a cross-sectional study from Mexico [19▪]. A recent study from Australia reported some association between self-reported physical activity over the previous three decades and BMD [20▪]. Secondary causes of low bone mass and fracture should always be considered and investigated properly. This is relevant in postmenopausal women, but even more so in premenopausal women as low bone mass and fractures are seen very rarely in healthy premenopausal women. Many premenopausal women with low bone mass or fractures therefore have an underlying disease or are being treated with medications, which influence bone negatively [21–23]. Secondary causes of low bone mass or fractures include amenorrhea, anorexia nervosa, Cushing's syndrome, hyperthyroidism, primary hyperparathyroidism, vitamin D deficiency, malabsorption (celiac disease [24▪],

inflammatory bowel disease and cystic fibrosis), chronic inflammation (rheumatoid arthritis, systemic lupus erythematosus [25▪] and spondyloarthritis), renal insufficiency, liver disease and connective tissue diseases (osteogenesis imperfecta, Marfan syndrome and Ehlers–Danlos syndrome). Medical treatments that may cause low bone mass or fractures are immunosuppressants (glucocorticoids, cyclosporine and methotrexate), antiepileptic drugs, cancer chemotherapy, heparin, gonadotropin releasing hormone (GnRH) agoinists and Selective Estrogen Receptor Modulator (SERMs). The evidence for the negative effect on bone is for some of these treatments less well established [26,27▪,28]. Methotrexate in high doses has negative effects on bone remodeling, whereas low-dose regiments are more likely to be neutral; however, there are case-reports of metotrexate osteopathy with low doses [29]. Cyclosporine is almost always used in combination with glucocorticoids and it is therefore not clear if there are clinically relevant negative effects of cyclosporine on bone. Similarly, high dose or long-term treatment with heparin is associated with bone loss and fractures; however, low molecular weight heparin is in some, but not all studies associated with less negative effect on bone.

Some of these diseases can be treated and some of the treatments can be changed to other treatments more neutral to bone or the dose can be reduced.

In premenopausal women without secondary causes of low bone mass or fractures, genetic factors are the most likely cause [30▪,31▪]. Bone biopsies from women with unexplained low bone mass or fragility fractures have shown thinner cortices, thinner trabeculae and increased intertrabecular spacing [32–34]. Bone remodeling activity was very variable between individual women and some had high remodeling activity and some had very low remodeling activity.

INVESTIGATIONAL CONSIDERATIONS AND WORK-UP IN PREMENOPAUSAL WOMEN WITH FRAGILITY FRACTURES OR VERY LOW BONE MASS

As mentioned above, it is important to identify secondary causes of low bone mass/fractures as some of these may be corrected or treated and some medications can be changed to other medications without negative effects on bone metabolism.

The investigation should comprise a complete medical history with special focus on fractures, kidney stones, oligomenorrhea or other indications of estrogen deficiency, pregnancies and lactation periods, dietary habits, exercise and body weight over time. Furthermore, information about family history of fractures and other bone or calcium metabolic diseases, medical treatments including over-the-counter treatments and supplementations is important. The physical examination and the biochemical work-up should focus on signs of diseases associated with low bone mass or fractures. Imaging comprises Dualenergy X-ray Absorptiometry (DXA) and if vertebral fractures are suspected; spinal X-ray or vertebral fracture assessment using DXA. In premenopausal women with recurrent fractures without identifiable secondary causes, a bone biopsy may reveal osteogenesis imperfecta or other unusual causes such as mastocytosis and Gaucher's disease [35].

MANAGEMENT OF PREMENOPAUSAL WOMEN WITH OSTEOPOROSIS

Premenopausal women with low bone mass or fractures should be encouraged to embrace a bone-healthy lifestyle. This includes physical activity, preferentially weight baring exercise [36–37], nutrition securing a sufficient intake of protein, calcium and vitamin D, no smoking and avoidance of excess alcohol consumption. Peris *et al.* [38▪] performed a retrospective study of 16 premenopausal women with fragility fractures and BMD Z-scores less than –2 without secondary causes of osteoporosis. The women were treated with calcium and vitamin D to obtain a daily intake of 1500 mg calcium and 400–800 IU vitamin D and advised to increase physical activity. The women were followed for 1–6 years with annual DXA. BMD increased by 1.9 and 5.6% at the spine after 2 years and at the hip after 3 years, respectively. A metaanalysis of the effect of physical training on bone mass in premenopausal women demonstrated that exercise programs that combine odd-impact or high-impact activity with high magnitude-resistance training appear to be effective in improving BMD at the spine and hip, although with some heterogeneity between studies [39].

Although pharmacological treatment most likely will improve BMD in premenopausal women with low bone mass, there is no evidence that this will reduce fracture risk in neither the short term nor in the long term and is therefore generally not recommended [40–42]. As mentioned above, it may be beneficial to secure sufficient intake of calcium and vitamin D [38▪].

In women with estrogen deficiency and oligomenorrhea, estrogen substitution should be considered if there are no contraindications. If the estrogen deficiency is caused by anorexia nervosa,

weight gain is the most efficient treatment. Studies of the effect of estrogen substitution in premenopausal women with anorexia have shown conflicting results and meta-analyses have not found consistent improvements in BMD [43]. Most secondary causes of low bone mass or fractures can be corrected or treated with a beneficial effect on bone mass and fracture risk. Some secondary causes cannot be removed. Premenopausal women needing long-term glucocorticoid treatment may need pharmacological bone protection. Bisphosphonates; alendronate, risedronate and zoledronic acid have been investigated in patients with glucocorticoid-induced osteoporosis and have been shown to improve bone mineral density and prevent fractures [44–46]. The same studies also showed that the antifracture efficacy was seen exclusively in postmenopausal women and elderly men as no fractures were seen in premenopausal women despite glucocorticoid treatment. This may be because of the fact that most patients included in the trials received moderate glucocorticoid doses, but it does suggest that premenopausal women without fractures who are treated with moderate glucocorticoid doses can be supplemented with calcium and vitamin D and only premenopausal women requiring glucocorticoids in high doses, or who had a previous fragility fracture or bone loss during glucocorticoid treatment should be treated with a bisphosphonate. Teriparatide has also been investigated for the treatment of glucocorticoid-induced osteoporosis in comparison with alendronate. Bone mass increased more with teriparatide than with alendronate – also in premenopausal women. Very few fractures occurred during the trial, but significantly fewer vertebral fractures were seen in patients treated with teriparatide compared with patients treated with alendronate [47–48]. Teriparatide is therefore also a treatment option in premenopausal women with severe glucocorticoid-induced osteoporosis. However, as in the other studies, no vertebral fractures were seen in the premenopausal women in this study.

Another secondary cause of bone loss and fractures that cannot be removed is cancer and cancer treatment-induced bone loss. GnRH agonists, chemotherapy including the accompanying glucocorticoid treatment and treatment of premenopausal women with SERMs, often lead to bone loss and increased fracture risk [49▪]. If treatment is needed because of fractures, very low bone mass or bone loss during treatment, bisphosphonates are the treatment of choice [50]. Zoledronic acid is the best investigated bisphosphonate in premenopausal women with cancer treatment-induced bone loss and has been demonstrated not only to prevent bone loss, but also to improve bone mineral density significantly [51–52]. Oral clodronate has been demonstrated to prevent bone loss [53], whereas risedronate failed to do so [54]. There are no studies of the other oral bisphosphonates or denosumab in this patient group.

Occasionally, premenopausal women present with low bone mass and recurrent fragility fractures without any secondary causes. If the fractures are severe, for example hip or vertebral fractures, treatment may be indicated. In such cases, treatment with bisphosphonates or teriparatide is preferable as these treatments have been investigated in premenopausal women with osteogenesis imperfecta [55–56], anorexia nervosa [40–41] and pregnancy-associated osteoporosis [42] in addition to the conditions mentioned above. The outcome in these studies was change in BMD. Teriparatide has been investigated in 21 premenopausal women with fragility fractures and idiopathic osteoporosis. BMD increased substantially; however, the outcome seems to be dependent on baseline bone turnover as four women with low baseline bone turnover had no increase in BMD and a blunted delayed increase in markers of bone formation [57▪]. After stopping treatment, the women were followed without treatment for 2 years. In the 15 women completing the 2 years follow-up, BMD at the lumbar spine increased by $11.1 \pm 7.2\%$ during teriparatide treatment and decreased by $4.8 \pm 4.3\%$ over the 2 years of follow-up. At the total hip, BMD increased by $6.1 \pm 6.5\%$ during teriparatide treatment and a non-significant loss of $1.1 \pm 3.7\%$ was seen during the follow-up [58▪].

When starting pharmacological treatments in premenopausal women, a possible future pregnancy should always be discussed with the patient. Bisphosphonates adhere to bone and stay in the skeleton for a long time. Bisphosphonates can cross the placenta and affect the fetal skeleton [59]. There are animal studies suggesting a toxic effect of ongoing bisphosphonate therapy in pregnant rats [60]; however, there are no reports of any bone or teeth malformations in children born by mothers taking a bisphosphonate during pregnancy [61].

If the woman is planning a pregnancy within the next year, treatment with a bisphosphonate should not be initiated. If the women has no plans of becoming pregnant, treatment can be started, but the women should be informed to stop the treatment at least 6 months before trying to become pregnant and to stop treatment immediately should she become pregnant while on treatment. Premenopausal women treated with teriparatide should be very careful not to become pregnant.

CONCLUSION

Osteoporosis is very uncommon in healthy premenopausal women. Premenopausal women with (recurrent) fragility fractures and very low bone mass should be thoroughly investigated for secondary causes of low bone mass or fractures. Glucocorticoid use, cancer treatment-induced bone loss, anorexia nervosa, premenopausal estrogen deficiency and celiac disease are among the most commonly seen secondary causes. Correction or treatment of the secondary cause should be done if at all possible. A bone-healthy lifestyle including sufficient intake of calcium and vitamin D should be implemented. Pharmacological intervention is only indicated in premenopausal women with an ongoing cause of bone loss or recurrent clinically relevant fragility fractures. Treatment with bisphosphonates and teriparatide has been investigated in premenopausal women; however, no data on fracture prevention or long-term outcome are available.

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Conflicts of interest

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

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Fracture Liaison Services

Karine Briot

Purpose of review
The purpose of this review is to report the evidence of beneficial effects of Fracture Liaison Service (FLS) including data regarding their impact on subsequent fracture, mortality risk and cost-effectiveness. This review also discusses the limitations of these data and the challenges faced during the implementation of FLS.

Recent findings
Recent studies showed the beneficial impact of implementation of FLS on the prevention of subsequent fracture risk, reduced mortality and cost-effectiveness. However, heterogeneity of FLS models and small number of studies limited the conclusion about the impact of FLS on secondary fracture prevention.

Summary
Patients with osteoporosis-related fractures are at higher risk of subsequent refractures. These subsequent fractures are associated with increased morbidity and premature mortality. However, there is a gap between evidence-based recommendations for postfracture care and actual clinical practice. FLS care is recommended for the management of the prevention of secondary fracture. FLS implementation reduces the risk of subsequent fracture, but the level of evidence is low as the interpretation of data is limited by the number of studies and their heterogeneity. FLS care significantly reduces the postfracture mortality, especially in patients with hip fractures. FLS implementation is cost-effective compared with usual care. Additional studies (with large sample and long-term follow-up) are needed to assess the impact of FLS care on subsequent fracture risk.

Keywords
cost-effectiveness, fracture, Fracture Liaison Service, mortality, osteoporosis

INTRODUCTION

Osteoporotic fractures such as hip fractures are associated with increased morbidity and mortality and impose a large financial burden on healthcare systems. Patients with osteoporosis-related fractures are at higher risk of subsequent fractures, which are associated with increased morbidity and premature of mortality. Patients with a nonvertebral fracture (NVF) have a two-fold higher risk of refracture as compared to individuals without a fracture [1]. This subsequent fracture risk is highest within the first 2 years after a fracture [2,3]. Almost half of patients with hip fractures had a previous fracture before the hip fracture [4]. The estimated risk of a second hip fracture ranges from 2.3 to 10.6% [5]. The impact of hip fractures is major: 20% of mortality in the first year, 85% of patients need assistance to walk and 20% require nursing home care after 1 year [6].

Effective antiosteoporotic treatments are available to prevent future fracture. They have shown their efficacy to reduce the risk of subsequent fracture in patients with a previous fracture. However, there is a gap between evidence-based recommendations for postfracture care and actual clinical practice. An observational prospective study of more than 60 000 women ages at least 55 years reported that less than 20% of women with new fractures received a treatment [7]. Solomon *et al.* [8] reported that osteoporosis medication use rates in patients hospitalized with hip fracture have significantly declined between 2002 and 2011, from 40.2% in 2002 to 20.5% in 2011. One of the main reasons for the care gap existence is that postfracture management is considered as a low priority, because of the lack of awareness of the seriousness by physicians, policy makers, health administrators and the general public. Different models of care have emerged to prevent subsequent fractures. One model is a Fracture Liaison Service (FLS), which includes dedicated personnel to

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KEY POINTS

- FLS is the most successful approach for secondary fracture prevention.
- Implementation of an FLS reduces the risk of subsequent fracture, but the number of studies is limited.
- Introduction of an FLS significantly reduces the mortality risk in patients with hip fractures.
- FLSs are cost-effective compared with usual care for the prevention of further fractures in patients who have experienced a low trauma fracture.

facilitate bone health assessment. International Osteoporosis Foundation (IOF) and American Society for Bone and Mineral Research task force have proposed the FLS for the management of the prevention of secondary fracture [9,10], to close the care gap in secondary fracture prevention. There are several national and international initiatives for the improvement and implementation of the post-fracture management. The IOF website (www.capturethefracture.org) has listed 124 active FLS sites worldwide.

THE MODEL OF FRACTURE LIAISON SERVICE

FLS is a coordinated, multidisciplinary approach for secondary prevention of fractures. This care model ideally targets outpatients and inpatients (admitted to a hospital or rehabilitation center after fracture). The numerous healthcare system functions coordinated by the FLS include: identification of patients who suffer a first fracture (case finding), diagnosis screening with bone densitometry, laboratory tests (for causes of secondary osteoporosis and safety screening before therapy initiation), patient education, osteoporosis therapies initiation, falls prevention and improvement long-term adherence with therapy [9,10]. The organization of each FLS differs according to the local organization and is based on primary or secondary care. The implementation of an FLS needs a multidisciplinary team: a lead FLS physician champion (rheumatologist, orthopedic surgeon or endocrinologist) who approaches the administration (health system or hospital) and discusses the benefits of an FLS, a programme coordinator, referring physicians, easy access to bone densitometry, physiotherapists, nurses and so on. To support the implementation and for the promotion of FLS throughout the world, the IOF launched the Capture the Fracture Campaign which has developed internationally endorsed standards for best practice. The Best Practice Framework sets an international benchmark for FLS (Table 1) [10]. There is a consensus about the need for coordinator-based model of FLS with care coordinators at the center of the service. A qualitative study showed that health professionals' capacity to collaborate and coordinate their actions was achieved by using fracture prevention coordinators who organized important processes of care [11].

Table 1. Capture the Fracture best practice standards [10]

The 13 Capture the Fracture best practice standards
1. Patient identification standard
2. Patient evaluation standard
3. Postfracture assessment timing standard
4. Vertebral fracture standard
5. Assessment guidelines standard
6. Secondary causes of osteoporosis standard
7. Falls prevention services standard
8. Multifaceted health and lifestyle risk-factor assessment standard
9. Medication initiation standard
10. Medication review standard
11. Communication strategy standard
12. Long-term management standard
13. Database standard

Current models have demonstrated heterogeneity in terms of organization and structure. FLS can be classified by intensity, ranging from the less intensive, which only educates patients to the most intensive models that identifies, assesses and treats bone fragility [12]. A classification of FLS as one of four general types of care models based on intensity of care is proposed [12]. Type A is considered the most intensive and comprehensive model, consisting of a coordinated approach in which, following a fracture, the patient is identified, assessed and treated. In this model, the FLS coordinator is the key figure. Type B differs from type A in terms of treatment initiation, which is delegated to the primary care physician. Type C is a less intensive FLS model, in which fracture patients are identified and educated about the diagnosis and lifestyle modifications. Patients are informed that they need diagnosis, fracture risk assessment and possible pharmacologic and nonpharmacologic treatment. The primary physician is alerted about the patient's recent fracture and the need for fracture risk assessment, without recommendations. Type D is the less intensive model, in which fracture patients receive only education about osteoporosis, but there is no

diagnosis or treatment initiation and no communication with the primary care physician [12].

The efficacy of the FLS model is correlated with their intensity, and type A models demonstrating the best outcomes in terms of number of patients investigated, an increase in the diagnosis rates for osteoporosis and improvement of the number of prescription for osteoporosis medications [12]. In a systematic review, Sale *et al.* [13] found a significant increase in patients undergoing diagnostic investigation for osteoporosis (up to 71%). Studies showed that factors that impact on the effectiveness of an FLS care are the intensity of the intervention, the length of time between fracture and the intervention. The immediate period after a fracture seems to be 'a teachable moment' to instigate behavioral changes.

IMPACT OF FRACTURE LIAISON SERVICE ON SUBSEQUENT FRACTURE

The level of evidence of the impact of FLS on reducing the subsequent fractures is low as there are few prospective studies (Table 2) [14–16,17▪,18]. In a prospective controlled observational study, patients with NVF, followed up in an FLS, had significantly lower incidence of refracture comparatively to those with similar fractures who opted to follow up with primary care physicians (4.1 vs. 19.7%, $P < 0.01$) [14]. The incidence of refracture over 4 years was reduced by more than 80% [14]. In this study, 54.8% of the control group received no treatment, whereas 80.5% of patients attending FLS began an antiosteoporotic treatment. Using a historical cohort of patients aged at least 50 years followed up in an FLS hospital and compared with patients presenting to a similar hospital without FLS, there was a significant reduction of 40% of major refractures and of any refractures by 30% over 3 years in the patients of the FLS center. In this study, the cumulative incidence of any refracture was 16% in the non-FLS center, compared to 11% at the FLS hospital [15]. In this study, the treatment rate is not described. The comparison of 1412 patients at least 50 years followed up in an FLS hospital with patients who underwent standard fracture care in a hospital without an FLS (mean age of 71.1 years) showed that patients seen at the FLS had a significant lower risk of subsequent NVF over 2 years of follow-up [relative risk of 0.44, confidence interval (CI) 95% 0.25–0.79]. The effect was time-dependent with no significant differences in fracture rate in the first year. The time-dependent effect on subsequent NVF was mainly explained by the benefit in patients with baseline hip fractures [16]. In this study, the treatment rate is approximately 50% in the FLS groups with no available data for the non-FLS group. A minimal effort FLS without coordinator increased the proportion of patients assessed for fracture and the number of osteoporosis medication initiation (31.8 vs. 12.6%) [17▪]. In this study, the control group consisted of historical controls followed up in the same hospital before the implementation of FLS. There was no significant reduction of refracture risk in the entire group, except in patients with hip fractures and aged at least 80 years for whom the refracture risk is reduced of 30% [17▪]. The treatment rate after a minimal resource FLS increased from 12.6 to 31.8% [17▪].

IMPACT OF FRACTURE LIAISON SERVICE ON MORTALITY

FLSs have beneficial effects on mortality rates, especially in patients with hip fractures. In a study conducted in the Netherlands, Huntjens *et al.* [16] compared patients with an NVF who presented to a hospital with a FLS and those seen at a hospital without a FLS and reported that patients followed up in an FLS had a significant lower mortality risk of 35% over 2 years of follow up, after adjustment for age, sex and baseline fracture risk. A population-based longitudinal study in England where Hospital Episode Statistics databases were linked to National Statistics mortalirty records (11 hospitals admitting hip fracture patients) showed that the

Table 2. Refracture rates in longitudinal studies in Fracture Liaison Service and control groups

Studies	Duration of follow-up	Refractures in FLS	Refractures in control group
Lih *et al.* [14]	37.7 months	10/246 (4.1%)	31/157 (19.7%)
Nakayama *et al.* [15]	36 months	63/515 (12%)	70/416 (17%)
Huntjtens *et al.* [16]	24 months	95/1412 (6.7%)	130/1910 (6.8%)
Axelsson *et al.* [17▪]	344 days	216/2616 (8.3%)	228/2713 (8.4%)
Van der Kallen *et al.* [18]	48 months	14/214 (6.5%)	41/220 (18.6%)

FLS, Fracture Liaison Service.

implementation of FLS was associated with a reduced post hip fracture mortality at 30 days [Hazard Ratio (HR)= 0.80 (95% CI 0.71–0.91)] and 1 year [HR= 0.84 (95% CI 0.77–0.93)] [19▪]. In this study, the FLS model of post hip fracture care was not significantly associated with a reduction of second hip fracture [19▪]. One of the reasons for the reduction of mortality in FLS could be a better coordination because of the multidisciplinary post-fracture care, identification of secondary causes of osteoporosis, management of comorbidities and so on [17▪].

COST-EFFECTIVENESS OF FRACTURE LIAISON SERVICE

Barriers to the widespread implementation of FLSs may include uncertainty about their cost-effectiveness. Economic evaluations, using Markov models, reported secondary fracture prevention (hospital nurse-led FLS, hospital osteoporosis case manager, outpatient-based FLS and orthogeriatric-led service) to be cost-effective in patients with previous fractures. A study conducted in Australia showed that an FLS improved quality-adjusted life years (QALYs) by 0.089 years and led to increased costs of AUD (Australian Dollar) 1486 per patient vs. standard care over the 10-year simulation period [20]. Using a computer simulation to estimate the cost and benefits of FLS in the United States, Solomon *et al.* [21] showed that for every 10 000 postfracture patients, an FLS program would result in 152 fewer fractures, 37.4 more QALYs and $66 879 in cost-savings compared with usual care. McLellan *et al.* [22] performed an evaluation of the cost-effectiveness of FLS in the UK, using the 8 years of detailed audit data collected by the West Glasgow FLS. They found that the cost of assessment at a hospital with FLS was £98 000 vs. £14 000 at a non-FLS hospital, and of pharmacological treatment was £298 000 vs. £85 000 in the usual care group. For a hypothetical population of 1000 patients, 18 fractures were prevented (including 11 hip fractures), giving an overall saving of £21000 in the FLS cohort [22]. The cost-effectiveness of a less intensive FLS over 6 years in Ontario has been shown in a program that identifies, educates and refers patients to their primary care for BMD testing improved QALYs by 4.3 years and led to increased costs of CAD $ 83 000 pour 1000 patients screened and a cost of $ 19 132 per QALY gained [23]. The enhanced model which includes the order of BMD was more cost-effective ($ 55720) [23]. The use of a coordinator in an FLS who manages 500 patients with fragility fractures reduces annually the number of subsequent fractures from 34 to 31 in the first year. Hiring a coordinator is cost-saving if at least 350 patients with fractures are managed annually [24]. Using large healthcare data sets based on computerized records, with a detailed evaluation of hospital hip fracture services in a UK region, Leal *et al.* [25▪] showed that it was cost-effective to introduce an orthogeriatrician, or a nurse-led FLS for postfracture care of patients with a hip fracture as compared to usual care because of the effects of these postfracture care models on mortality (greater gains in life years) rather than on refracture, but considerable uncertainty remains.

All these data suggest that FLSs are cost-effective compared with usual care for the prevention of further fractures in patients who have experienced a low trauma fracture. However, there are many assumptions in all these economic evaluations and some important economic considerations for people with hip fracture and their families (home adaptation costs, home social care and unpaid care provided by family,) are excluded from the analyses.

LIMITATIONS OF INTERPRETATION OF FRACTURE LIAISON SERVICE STUDIES

The number of studies is limited with very few prospective studies and some methodological concerns. Studies differed regarding to the fracture types included: some studies assessed the risk of subsequent NVF after baseline NVF [16], hip fracture after hip fracture [19▪] and vertebral fracture and NVF after vertebral fracture and NVF [15]. Different control groups are used in these studies: a group of patients who refused to participate in the FLS [14], another hospital without FLS [15,16], causing several biases of interpretation. Some of the studies used questionnaires to record refractures, introducing an error, as self-reported fractures have been associated with 11–29% of false positive [26]. The effect of an FLS on subsequent fracture rate is time-dependent with a benefit after 2 years of follow up [16]. None of the study's results have been corrected for the immortal time bias. Patients have to be alive to attend the FLS; this point is relevant for the comparison of FLS vs. non-FLS centers, or prefracture vs. postfracture care. Moreover, the duration of follow-up is limited and there are no studies with a longer follow-up. Most of studies of FLS are available for younger patients and show that the long-term effect of an intervention is higher in younger than elderly individuals and there are finally few data in older individuals ($\geq$80 years). Adherence to osteoporosis therapies is an important surrogate outcome of the efficacy of FLS models. Boudou *et al.* [27] reported a self-reported adherence of 80% at 12 months of follow up. However, there are few studies that reported the adherence to osteoporosis

therapies using the pharmaceutical claims for patients enrolled in FLS.

KEY POINTS AND CHALLENGES FOR A SUCCESSFUL FRACTURE LIAISON SERVICE

Several important barriers to the implementation of FLS exist at different levels: individual, institutional and societal. They are the consequences of the lack of awareness of the gravity of fractures, current osteoporosis guidelines, insufficient time for physicians to address preventive care and lack of interest. One major barrier is the lack of funding for dedicated personnel. Developing business case for the implementation of FLS is recommended very early in the development of the FLS. Communication and cooperation between the stakeholders including providers and commissioners should be included in the discussion of the project of an FLS [11]. In an open system with multiple payers, cost-savings are not clear for the payers. In contrast, within a closed system, reduction in fracture rate directly results in cost-savings to the payers. Hospitals usually receive a single payment under for fracture repair during a hospitalization, which discourages the additional osteoporosis assessment, necessary for secondary fracture prevention. Moreover, in our fragmented systems, there is no salary support for such initiatives.

Another difficulty faced by the FLS is the coordination of care, especially when treating patients with multiple medical comorbidities. The main point for FLS is the inclusion of the largest number of patients with low trauma fracture, that is out and inpatients without any selection for age, or comorbidities. To make work flow efficient and to identify the largest number of patients, the functioning of an FLS should be standardized and the one-size-fits-all is not recommended.

Oldest frail patients with poor cognitive functions (30% of patients $\geq$85 years hospitalized for hip fractures [28]) should not be excluded of the postfracture care as their risk of subsequent fracture is high and imminent [29] and the consequences worse. On the basis of early clustering of subsequent fractures after a first fracture [3], early initiation of osteoporosis therapies is recommended in frail populations. Another challenge is to include falls prevention in the FLS with adaptive rehabilitation in the management of these frail patients. For these purposes, FLS and orthogeriatrics services are complementary as the geriatric expertise is essential for the medical management of frail patients. The efficacy of the FLS and orthogeriatric models is similar to reduce postfracture mortality, without efficacy on the reduction of the second hip fracture [19▪].

Finally, longitudinal care of patients enrolled in the FLS is necessary to ensure compliance to osteoporosis medication and falls prevention. Despite an increase in adherence to treatment after FLS implementation in previous studies, medication compliance remains an issue of critical importance. A study of patients included in an FLS with a 7-year prospective follow up available for 234 patients showed that low compliance to antiosteoporotic treatments is associated with an increased risk of subsequent fracture [30]. The continued follow up in an FLS needs a clear communication between the FLS and the primary physicians, which remains challenging [11]. A randomized study conducted in 102 patients enrolled in an FLS showed that the 2-year compliance and persistence to osteoporosis therapies was similar (64 vs. 61%) for patients followed up by the FLS or by their primary care physicians (64 vs. 61%) [31], illustrating that in terms of benefits to long-term compliance and persistence, patients should be followed up by primary care physicians. A fundamental requirement for FLS program coordination is the involvement of a robust network that facilitates identification of patients, capture of key information and follow up of fracture patients. A cloud-based application for the FLS has been proposed to coordinate postfracture care for osteoporotic patients [32▪]. Finally, one major challenge should be to convince patients to be enrolled in the FLS, to take an osteoporosis medication and to be followed up. Qualitative studies in patients with recent fracture showed that the concept of 'high risk of fracture' is misunderstood by patients and that physician's messages about fracture risk are confusing to patients and need to be modified [33▪,34].

CONCLUSION

FLS programs have the potential to effectively coordinate postfracture care and thus reduce morbidity, mortality and healthcare costs by preventing subsequent fractures. However, there are many challenges to solve and the interpretation of studies is limited by their small number, heterogeneity and several biases. Additional studies (with large sample and long-term follow-up) are needed to assess the impact of FLS care on subsequent fracture risk.

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Conflicts of interest

K.B. has no conflicts of interest to declare.

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